UNIVERSIDADE CATÓLICA PORTUGUESA

PHYSIOTHERAPY AND NEURO REHABILITATION ON STROKE EVIDENCE AND NEEDS

Tese apresentada à Universidade Católica Portuguesa para obtenção do

grau de Doutor em Ciências da Saúde - especialidade em Reabilitação Neurológica

por

Patrícia Maria Duarte de Almeida

Instituto de Ciências da Saúde

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Sob a orientação de Professor Doutor Alexandre Castro Caldas

2015

“Your body is a sophisticated machine
made up only of ATOMS,
63 percent of which are hydrogen,
and another 25,5 percent oxygen.
Carbon comes in third at 9,5 percent,
and nitrogen, phosphorous, and sulfur
make up almost of the rest.

You're nothing else!”

Jennifer Robbins
In Exploratorium magazine online
Volume 23, number 3
http://www.exploratorium.edu/

It’s then amazing how simplicity can generate such complexity of being human!

Patrícia Almeida, 2014

Acknowledgments

Though only my name appears on the cover of this thesis, a great many people have contributed to its production. I owe my gratitude to all those people who have made this thesis possible and because of whom my graduate experience has been one that I will cherish forever.

My deepest gratitude is to my advisor, Professor Alexandre Castro Caldas. I have been amazingly fortunate to have an advisor who gave me the freedom to explore on my own, and at the same time the guidance to recover when my steps faltered. His interest and trust on Physiotherapy was another motivation for the development of this research. Also his good connections gave the possibility to develop an experience with fMRI.

Many thanks to the team of Visual Neuroscience Laboratory, Institute for Biomedical Imaging in Life Sciences (IBILI), ICNAS, Faculty of Medicine, University of Coimbra, particularly to Professor Miguel Castelo Branco for the support and counseling during the development of the experimental paradigm and fMRI data analysis. Without the all team part of this thesis would not be possible.

I'm very grateful to Nádia Canário, a researcher from the Institute of Health Sciences - Catholic University of Portugal who gave me the entire support on the development of the fMRI paradigm, data processing and data analysis, without her commitment and dedication I would still be staring at Brain Voyager.

Also want to acknowledge the participants of the fMRI study, thanks for your kindness and ability to stay immobile inside the fMRI equipment.

A special thanks to Professor Roland van Peppen, programme manager at University of Applied Sciences Utrecht - The Hague Area, Netherlands, for the guidance and inspiration during the development of the systematic reviews and writing the scientific paper.

Also a grateful thanks to Professor Joaquim Ferreira, Professor of Neurology and Clinical Pharmacology at Faculty of Medicine, University of Lisbon that with his wisdom and experience gave me the fundamental advises on the starting of this adventure.

Many thanks to the co-authors of the systematic reviews, for your commitment and for not giving up.

A grateful thanks to all the experts who accepted to participate on the Delphi panel who collaborated with so much professionalism, dedication and "velocity".

Finally to Ana, for being my partner along this process, thank you very much for being "Yin" when I was "Yang".

Also appreciate the financial support of Alcoitão School of Health Sciences and of the Institute of Health Sciences - Catholic University of Portugal.

Despite of not being a scientific collaborator or a sponsor, I would like the thanks to the Câmara Municipal de Cascais, for the infinite hours waiting at their services giving me the time to read the long list of articles and the several versions of this thesis.

Finally to the ones who have not been directly involved on the development of this research, but have been my anchorage and locomotive:

To *Paul*, for being so patient and supportive. Thank you very much for all your attempts in giving me another view of life then the PhD in the last 4 years. Also thanks for the language review of my articles and the gathering process of so many literature.

To my parents who are eternally my supporters and the harbor in all my life events and a PhD thesis is a life event, a very special thanks.

To my co-workers and friends, many thanks for the support and understanding of the more stressing periods and absences.

At the end I dedicate this thesis and all my effort, dedication and persistence related to it, to my daughters. *Margarida* and *Júlia* thank you for giving me back an even bigger dedication and for standing by me in every moment!

Abstract

Scientific knowledge in the area of rehabilitation and physiotherapy for stroke is booming and leading to more sustainable models of practice. Several interventions show positive effects with strong scientific support. However, some issues remain to be clarified like what are the effects of PT on brain activity and what are the effects of hands on interventions. Also a general coherence of interventions and outcomes and outcomes measures need to improve.

With the intent to clarify these questions and to give an overview of Physiotherapy evidence and needs on stroke rehabilitation, this thesis will present the state of the art on a literature review and the four studies developed on the context of this PhD: Physiotherapy Hands-on Interventions and Stroke - Systematic Review; Physiotherapy and Brain Activity on Stroke - Systematic Review; Brain activity during lower limb movement with physiotherapy manual facilitation – an fMRI study; ICF Linking Process for Categorization of Interventions and Outcomes Measures on Stroke Physiotherapy - Delphi panel.

As innovative aspects of this thesis, we highlight: the organization within the ICF framework for the outcomes related with movement; the study of brain activity during a complex multijoint movement of lower limb; the study of immediate effects of manual facilitation of movement, as no similar studies was found on our literature search for this thesis.

Regardless the limitations encountered, the non-conclusive findings and some non-identified evidence, it seems still valid to conclude that Physiotherapy is no longer a “black box”, instead is a evidence-based profession.

Exists clear and evidence based information for clinical settings and scientific community, that hands off physiotherapy is relevant and has efficacy proved on the rehabilitation of stroke patients on the domains of Structure & Functions and Activities & Participation.

This efficacy is extended to the brain activity, which validates the idea that PT can influence neuroplasticity process and consequently contribute for a better recovery in a neurobiological perspective with impact on human performance and autonomy.

Resumo

O conhecimento científico na area da intervenção em utentes com sequelas após Acidente Vascular Cerebral (AVC) e especificamente na área da Fisioterapia, tem crescido nos últimos ano, conduzindo a modelos de prática mais sustentados. São várias as intervneções da Fisioterapia com eficácia comprovada. Contudo, alguns aspectos ainda necessitam de clarificação, como seja quais os efeitos da Fisioterapia na actividade cerebral e quais são os efeitos das intervenções baseadas na manualidade do Fisioterapeuta. É ainda necessária, uma maior coerência entre as intervenções, as variáveis em estudo e os instrumentos de avaliação utilizados.

Com o objectivo de contribuir para o esclarecimento destas questões e de oferecer uma visao global da evidência da intervenção da Fisioterapia e as necessidades de desenvolvimento na intervenção e utentes com AVC, esta tese apresenta um estado da arte na revisão de literature e os quarto estudos desenvolvidos no contexto deste doutoramento: Efeitos da Fisioterapia manual em utentes com AVC - revisão sistemática; Efeitos da Fisioterapia na actividade cerebral em utentes com AVC - revisão sistemática; Efeitos imediatos da facilitação manual na actividade cerebral - estudo com RMf; Processo de categorização de intervenções e intrumentos específicos da intervenção em utentes com AVC - Painel de Delphi.

Como aspectos inovadores, salientamos a organização de acordo com a estrutura da CIF, para as variaveis relacionadas com o movimento; o estudo a actividade cerebral durante um movimento complexo e multi-articular do membro inferior; o estudo dos efeitos imediatos da facilitação manual na actividade cerebral.

Independentemente das limitações encontradas, dos achados não conclusivos e alguns achados de não benefício de intervenções, parece-nos ser válido concluir que a Fisioterapia deixou de ser uma “caixa negra” sendo uma profissão científicamente suportada. Existe informação clara e suportada cientificamente, disponível para os locais de prática e para a comunidade científica, de que a Fisioterapia “hands off” é relevante e tem eficácia comprovada no contexto da intervenção em utentes com AVC, nos domínios da Estrutura e Função e da Actividade e Participação. Esta eficácia estende-se à actividade cerebral, validando a ideia de que a Fisioterapia pode influenciar a neuroplasticidade e consequentemente contribuir para uma recuperação neurobiológica mais adequada, com impacto no desempenho humano e autonomia.

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Abreviations

AFNI	*Analysis of Functional NeuroImages*
BC	*Bobath concept*
BICF-CSS	*Brief International Classification of Functioning - core set for stroke*
BOLD	*Blood oxygen level dependent*
BWS	*Body weight support*
CIMT	*Constraint induced movement therapy*
CNS	*Central nervous system*
EEG	*Electroencephalography*
fMRI	*Functional magnetic resonance image*
FOV	*Field of view*
ICF	*International Classification of Functioning*
ICF-CSS	*International Classification of Functioning - core set for stroke*
M1	*Brain primary motor area*
MEG	*Magnetoencephalography*
PETscan	*Positron emission tomography*
PNF	*Proprioceptive neuromuscular facilitation*
PT	*Physiotherapy*
RF	*Radiofrequency pulse*
S1	*Brain primary somatosensorial area*
S2	*Brain secondary somatosensorial area*
SNR	*Signal-to-noise ratio*
SPM	*Statistical Parametric Mapping*
T1	*Longitudinal relaxation of brain tissue*
T2	*Transversal relaxation of brain tissue*
TE	*Echo time*
TMS	*Transcranial magnetic stimulation*
TR	*Repetition time*
WCPT	*World confederation of physical therapy*

Introduction

As a clinician, an educator and a researcher in the field of physiotherapy and neuro-rehabilitation, a fundamental question remains not answered and in a need of clarification:

If physiotherapy is used to improve motor performance, but if motor performance depends on brain performance and brain performance depends on neuroplasticity, does physiotherapy promote brain activity and consequently plasticity?

Automatically this question leads to other two: *What do Physiotherapists exactly do?* and *What are the real effects and efficacy of Physiotherapy interventions?*

This was the trigger for the development of this thesis, aiming to support the professional fundaments of positive benefits of Physiotherapy in Neurological conditions.

What Physiotherapy is about

Physiotherapy (PT) dates back to Hippocrates in Ancient Greece who first developed it. At that time and during centuries was mainly characterized by massage and mobilizations. In the 18th century orthopedics was developed, with the invention of machines to help exercise joints. From 1950 a boom of development to other areas started leading to the nowadays profile of PT profession, regulated, with a specific body of knowledge and competences, as described by the World Confederation for Physical Therpy[1]:

"Physical therapy provides services to individuals and populations to develop, maintain and restore maximum movement and functional ability throughout the lifespan. This includes providing services in circumstances where movement and function are threatened by ageing, injury, pain, diseases, disorders, conditions or environmental factors. Functional movement is central to what it means to be healthy.

Physical therapy is concerned with identifying and maximizing quality of life and movement potential within the spheres of promotion, prevention, treatment/intervention, habilitation and rehabilitation. This encompasses physical, psychological, emotional, and social wellbeing. Physical therapy involves the interaction between the physical therapist, patients/clients, other health professionals, families, care givers and communities in a process where movement potential is assessed and goals are agreed upon, using knowledge and skills unique to physical therapists:

- Examination/assessment includes:
    - the examination of individuals or groups with actual or potential impairments, activity limitations, participation restrictions or abilities/disabilities by history-taking, screening and the use of specific tests and measures
    - the evaluation of the results of the examination and/or the environment through analysis and synthesis within a process of clinical reasoning to determine the facilitators and barriers to optimal human functioning
- Diagnosis and prognosis arise from the examination and evaluation and represent the outcome of the process of clinical reasoning and the incorporation of additional information from other professionals as needed. This may be expressed in terms of movement dysfunction or may encompass categories of impairments, activity limitations, participatory restrictions, environmental influences or abilities/disabilities.
- Prognosis (including plan of care and intervention/treatment) begins with determining the need for intervention/treatment and normally leads to the development of a plan, including measurable outcome goals negotiated in collaboration with the patient/client, family or caregiver. Alternatively it may lead to referral to another agency or health professional in cases that are inappropriate for physical therapy.
- Intervention/treatment is implemented and modified in order to reach agreed goals and may include:
    - therapeutic exercise
    - functional training in self-care
    - home management
    - work
    - community and leisure
    - manual therapy techniques (including mobilisation/manipulation)
    - prescription, application, and, as appropriate, fabrication of devices and equipment (assistive, adaptive, orthotic, protective, supportive and prosthetic)

- airway clearance techniques
    - integumentary repair and protection techniques
    - electrotherapeutic modalities
    - physical agents and mechanical modalities
    - patient-related instruction
    - coordination, communication and documentation
- Intervention/treatment may also be aimed at prevention of impairments, activity limitations, participatory restrictions, disability and injury including the promotion and maintenance of health, quality of life, workability and fitness in all ages and populations.
- Re-examination necessitates determining the outcomes.

The physical therapist's extensive knowledge of the body and its movement needs and potential is central to select strategies for diagnosis and intervention. The practice settings will vary according to whether the physical therapy is concerned with health promotion, prevention, treatment/intervention, habilitation or rehabilitation.

Physical therapy is an essential part of the health and community/welfare services delivery systems. Physical therapists practice independently of other health care/service providers and also within interdisciplinary rehabilitation/habilitation programs that aim to prevent movement disorders or maintain/restore optimal function and quality of life in individuals with movement disorders. Physical therapists practice in a wide variety of conditions: neurological rehabilitation, orthopedics, respiratory care, mental health, sports, occupational health, women health, etc".

Behind all PT procedures exists a complex, evaluative and scientific clinical decision process[2]. This process is based on several frameworks: International Classification of Functioning, Disability and Health (ICF), Normal movement, anatomy and physiology, evidence-based practice and specific models for each area.

PT and Hands On interventions

According to the presented above, PT treatment strategies are widely considered as "hands on" approaches or manual therapy or "hands off", on PT community. However its definition remains rather undefined. For the purpose of our research, we consider "Hands on" as the interventions where physiotherapists use their hands with direct contact on patient's body segments to: give sensorimotor input to guide movement or stability and promote proprioceptive awareness; promote muscular relaxation or activation; promote joint movement and task performance, soliciting rather active participation from the patient and not only passive mobilization as described before. "Hands off" interventions are all the others used by physiotherapists, without direct contact of physiotherapist's hands like: physical agents, robotics, exercise, verbal instructions, among others.

"Hands-on" or manual therapy techniques, usually considered as the conventional therapy, are still the most used approaches due to low cost and ease of implementation[3]. In fact, these are the brand image of PT, by the use of the hand of the physiotherapist to reeducate/facilitate the movement, joints or muscles or relief symptoms. Assumed as traditional interventions, their effects haven't been a target of research, particularly at the brain level.

Supponsingly, manual stimulation promotes activation of tactile and proprioceptive receptors which activates the somatosensorial areas (S1 and S2) creating a body map at the homunculus and insula region[4]. As the insula is also responsible for motor functions, by the activation of the anterior cingulate[5], is expected that the manual stimulation has effects on motor and somatosensorial activation. Also a good body perception and relation with space allows a better interaction with environment and better movement. Additionally, manual contact has positive effects on emotions, which it is an important variable on movement and pain perception[6]. These are the primordial basis for the use of manual techniques, regarding the control of movement.

The most common handling interventions used by physiotherapists are: Bobath Concept, Carr & Shepherd Approach, Proprioceptive Neuromuscular Facilitation (PNF), Hydrotherapy, Mobilization, Manipulation and Massage[7,8].

On the neurological rehabilitation context, Bobath Concept (BC) is one of the most commonly used of these approaches[9,10], and it offers therapists a framework for their clinical interventions[11]. It involves the whole patient, their sensory, perceptual and adaptive behaviors as well as their motor problems, with treatment tailored to the patient's individual needs[12] and is an interaction between therapist and patient where facilitation leads to improved function.

The BC is goal orientated and task specific, and seeks to alter and construct both the internal (proprioceptive) and external (exteroceptive) environment in which the nervous system and therefore the individual can function efficiently and effectively[12]. It relies on the statement of Mulder and Hostenbach that "without information (sensory input) there is no control, no learning, no change and no improvement[13]."

Motor output depends on sensoriomotor integration in the parietal lobe and on continuous input for comparison[14]. It has been identified that sensory input to muscles can potentiate the response of motor cortex[15], thus, the PT aims to be the afferent input and reeducate the internal modules of the task and sensoriomotor integration[12,16]. On BC, the use of afferent information to promote motor performance is called "Facilitation"[14] and is used during specific tasks aiming to reach the expected experience during normal movement[16].

Authors and followers do not like to provide specific description of the technical procedures, as it is considered as a concept and not a technique. However, in a general way, the physiotherapist can guide manually the movement and the postural control needed, regarding the specific task, sequence and it's temporal and spatial organization, using elongation, shortening, compression, support and directing the movement. For that, uses different points of sensory and proprioceptive input named "Key Areas"[14,16] or "Key Points" of control, together with visual, auditory and vestibular stimulus. Facilitation can also be the use of specific postures, positions or movements that automatically generates/facilitates other movements (ex: to promote trunk uprighting we can stimulate upper limb external rotation or to promote hip flexion we can stimulate foot dorsiflexion together with hip internal rotation[17]).

An important aspect of this method is that the patient needs to participate be active and attentive[9], even if there's no ability to perform the movement yet. Knowing that motivation, intention and imagination of motor task are also important forms of input to generate brain activity for motor performance[18], supports the principle that the treatment shouldn't be passive. The amount of facilitation will be given according to the level of autonomy of the patient.

This aspect brings a potential clinical advantage for BC compared with others techniques. It can be used in very initial phases of recovery[15], even when the patient needs to stay on the bed and/or has no active movement or very low grades and more dynamic interventions are not possible. However, this aspect hasn't been explored yet.

Despite of being one of the most popular interventions and assumed as conventional, this intervention together with the others "Hands On" interventions lack evidence and research.

PT and Neurological Rehabilitation and Evidence

As mentioned before, Physiotherapists practice in a wide variety of conditions and one of the specializations with larger development is the intervention of PT in neurological conditions integrated on Neurological Rehabilitation.

In the last decades, practitioners and researchers have been attempting to understand the mechanisms underlying the different interventions and effects of each one.

This work is mainly developed on stroke patients, as stroke remains one of the most devastating of all neurological conditions. Worldwide it accounts for approximately 5.5 million deaths annually, with 44 million disability-adjusted life-years lost, being part of the Global Burden of Disease study. From this report, there's a world recommendation for development of cost-effective interventions[20].

Thus, rehabilitation teams and researchers focus their attention on the effectiveness of best practices. Also this thesis focuses on PT for stroke patients.

The development of Neurosciences had a qualitative impact on PT intervention and understanding of the mechanisms behind it. From a reductionist intervention centered on structures and existing movement abilities, PT shifted to a more complete approach regarding the patient, the movement and all the factors that can influence it. With the better understanding of motor control, motor relearning and neuroplasticity (developed further), PT relies on conceptual framework of Task, Environment and Individual and all types of input can influence the brain activity and reeducation of movement[21,22].

Consequently, several interventions modalities emerged in the last decades, regarding these developments. In the last years, several studies have been attempting to present the evidence of these interventions in neurological rehabilitation.

The valid findings are pointing towards a better effectiveness of the "Hands-off" interventions of PT[3], namely: Constraint induced movement therapy (CIMT)[23,24], Treadmill and Body Weight Support System (BWS)[25,26], Mirror Therapy[27,28,29,30,31,32], Motor Imagery[33,34,35,36,37,38], Functional electrical stimulation[39,40], Task approach therapy[41], Bilateral Movements and Unilateral Movements[42], Mechanic orthotics[43,44], Virtual Reality[45], Dual-Task[46] and Cardiorespiratory Exercise[47,48]. A recent systematic review that analyzed 467 randomized controlled trials on stroke rehabilitation[49], synthetize the evidence for PT interventions favoring intensive high repetitive task-oriented and task-specific training in all phases post-stroke. The interventions with evidence are presented on table 1.

Effects are mostly restricted to the actually trained functions and activities. These results give clear and evidence based information for clinical and scientific community, that physiotherapy is relevant and has efficacy proved on the rehabilitation of stroke patients on the domains of functions and activities.

Some of these findings are applied to other neurological disorders then stroke, with similar results especially on movement reeducation.

Despite of these findings, in the clinical practice "Hands-on" interventions, are still the most used due to low cost and ease of implementation[3] as described above. Regarding BC, three systematic reviews[9,50,51] including the last one published so far, show no superiority to other interventions.

Under these findings several guidelines have been created and can be found on the International guideline network website[52], on Specific health related guidelines per country[53,54,55,56,57,58,59,60,61,62] and on Specific World and European Associations[63,64,65,66,67]. Regardless these results, many of these studies remain questionable and some are inconclusive due to methodological limitations[68,69,70,71], leading to qualitative syntheses of evidence[72,73] and recommendations[74] for practice, of moderate and low level.

For both "Hands Off" and "Hands On" the effectiveness of these interventions still need a deep investigation about their mechanisms and effects. Specificity and detailed interventions are the main weakness on research protocols, giving the general idea of PT as "black box"[75] due to poor description of procedures and doses[68].

Table 1. Evidence Based Physiotherapy Interventions for Stroke. Adapted from: Veerbeek JM, van Wegen E, van Peppen R, van der Wees PJ, Hendriks E, et al. (2014) What Is the Evidence for Physical

Therapy Poststroke? A Systematic Review and Meta-Analysis. PLoS ONE 9(2): e87987. doi:10.1371/journal.pone.0087987[49].

Body functions	
Motor function leg	NMS of the paretic leg 🟢 Mixed strength and cardiorespiratory exercises 🟢 High-intensity practice 🟢
Motor function arm	Low-intensity mCIMT 🟢 Bilateral elbow-wrist robotics 🟢 NMS wrist/finger flexors/extensors 🟢 EMG-NMS wrist/finger extensors 🟢 High-intensity practice 🟢
Motor function arm (prox.)	Unilateral shoulder-elbow robotics 🟢
Muscle strength leg	Water-based exercises 🟢 NMS of the paretic leg 🟢 TENS 🟢 Strength training paretic leg 🟢 Mixed strength and cardiorespiratory exercises 🟢 High-intensity practice 🟢
Muscle strength arm	Unilateral shoulder-elbow robotics 🟢 Bilateral elbow-wrist robotics 🟢 NMS wrist/finger flexors/extensors 🟢 High-intensity practice 🟢
Muscle tone leg	NMS of the paretic leg 🟢 Strength training paretic leg 🟢 High-intensity practice 🟢
Muscle tone arm	Interventions for somatosensory functions 🟢 High-intensity practice 🟢 Virtual reality training for the paretic arm 🔴
Pain	Unilateral shoulder-elbow robotics 🟢
Active range of motion	EMG-NMS wrist/finger extensors 🟢
Passive range of motion *	Therapeutic positioning of the paretic arm 🟢
Shoulder subluxation	NMS shoulder 🟢
Comfortable gait speed	BWSTT 🟢 Mixed strength and cardiorespiratory exercises 🟢 High-intensity practice 🟢
Maximum gait speed	Electromechanical-assisted gait training 🟢 ** Speed dependent treadmill training 🟢 Mixed strength and cardiorespiratory exercises 🟢 High-intensity practice 🟢
Walking distance	BWSTT 🟢 Electromechanical-assisted gait training 🟢 ** Circuit class training 🟢 Mixed strength and cardiorespiratory exercises 🟢
Spatiotemporal gait pattern parameters	Speed dependent treadmill training 🟢 Strength training paretic leg 🟢
Postural sway	Standing balance training with biofeedback 🟢
Aerobic capacity	Cardiorespiratoiry exercises 🟢 Mixed strength and cardiorespiratory exercises 🟢 Overground walking 🔴 △
Peak heart rate	Electromechanical-assisted gait training 🟢 **
Heart rate work	Mixed strength and cardiorespiratory exercises 🟢
Workload	Cardiorespiratory exercises 🟢
Respiratory functions	Cardiorespiratory exercises 🟢
Hand movement time	Sitting balance training 🟢
Anxiety	Overground walking 🟢 □ High-intensity practice 🟢
Depression	High-intensity practice 🟢
Gesture comprehension	Gestural training 🟢

Activities	
Sitting balance	Sitting balance training 🟢
Sitting and standing balance	Balance training during various activities 🟢 Electromechanical-assisted gait training with ES 🟢 Circuit class training 🟢 Mixed strength and cardiorespiratory exercises 🟢 High-intensity practice 🟢
Walking ability	Electromechanical-assisted gait training with ES 🟢 Circuit class training 🟢 TENS 🟢
Arm-hand activities	Original CIMT 🟢 High-intensity mCIMT 🟢 Low-intensity mCIMT 🟢 Mental practice with motor imagery 🟢 EMG-NMS wrist/finger extensors 🟢
Self-reported amount of arm-hand use in daily life	Original CIMT 🟢 High-intensity mCIMT 🟢 Low-intensity mCIMT 🟢 Trunk restraint 🔴
Self-reported quality of arm-hand movement in daily life	Original CIMT 🟢 High-intensity mCIMT 🟢 Low-intensity mCIMT 🟢
Basic ADL	Balance training during various activities 🟢 Electromechanical-assisted gait training 🟢 Caregiver-mediated exercises 🟢 Low-intensity mCIMT 🟢 Virtual reality training for the paretic arm 🟢 High-intensity practice 🟢
Physical activity	Circuit class training 🟢 Mixed strength and cardiorespiratory exercises 🟢

Participation	
Quality of life	Mixed strength and cardiorespiratory exercises 🟢 High-intensity practice 🟢
Leisure participation	Leisure therapy 🟢

Environmental factors	
Caregiver strain	Caregiver-mediated exercises 🟢

Legend: A green point indicates that the intervention has a significant positive effect on the outcome, while a red point indicates that the intervention has a significant negative effect on the outcome; *, shoulder external rotation; **, dependent walking patients in the early rehabilitation phase; △, dependent walking patients when compared to electromechanical-assisted gait training or BWSTT; □, independent walking patients; BWSTT, Body-weight supported treadmill training; CIMT, Constraint-induced movement therapy; EMG-NMS, Electromyography-triggered neuromuscular stimulation; ES, Electrostimulation; mCIMT, modified Constraint-induced movement therapy; NMS, Neuromuscular stimulation; prox., Proximal; TENS, Transcutaneous electrical nerve stimulation.

Research in the efficacy of physiotherapy with neurological patients is lacking methodological quality, specificity and is fragmentized. Treatment outcome research should be more critically designed in order to improve the understanding of the research findings and their usefulness in rehabilitation practice. This starts by basic methodological omissions noted by reviewers like no real randomization, blinding of participants, the complexity of the groups, a lack of (statistical) power and an integrated perspective on cost-effectiveness.

The underlying theories behind the interventions are limited, compromising the causal sequences connecting interventions and outcomes[76]. Comparing two techniques with each other doesn't show the efficacy of a treatment, it just point out the difference between two treatments in the light of the measurement instrument chosen. In order to measure the efficacy of a treatment it should always involve a group with no intervention or a placebo. Moreover when the theory behind the treatment is not sufficiently described researchers are likely to measure something else then the intervention intended[77].

Beside the specific treatment programs, intervention are often not measured within the process of rehabilitation thus ignoring the complexity of this process being a reiterative problem solving activity focused on disability, which includes also assessment, goal-planning and evaluation[78]. When relating interventions with the International Classification of Functioning, Disability and Health, it's clear that we have also to adequate the interventions according to the outcomes to address. Another missing aspect on research both for intervention and outcomes analysis is the appropriate instrument for the assessment of outcomes, leading to misinterpretation of results.

Also, most of the effectiveness studies addresses the external outcomes (functional recovery) related with body functions and structures and with activity and participation, but a better insight into the biological mechanisms underlying functional recovery became a need of the last years in research[70]. Only a few of them aim to determine the effects of PT on brain reorganization and activity as a biological mechanism.

Most research is only done in a certain phase of the rehabilitation process, however all phases play an important role on the rehabilitation process and certainly they demand different approaches. This variable can be a "key point" for the efficacy of an intervention or a combination of interventions. Clearly, Treadmill is not an intervention for a sub-acute phase but BC or Motor Imagery can be, so why not look for the best combination regarding the phase and the cost-efficacy dimension? This also implies that researchers and clinicians stop looking for a single "magic" intervention and shift to a mixed intervention, already proposed by Pollock et al.[3], according to phases and variables to be addressed.

More attention on these methodological and theoretical issues might lead to better understanding of research results and the therapeutic process[79,80].

Neurological Disorders and Demands for Rehabilitation

The interventions are directed to specific disorders. In neurological conditions most of the diseases lead to dysfunctions that reaches a plateau and then improves[81], not considering here the degenerative or progressive diseases.

The impact of these disorders is enormous, leading to motor, perceptive, cognitive, autonomy and quality of life disorders, with great impact on society. Thus the health care related with neuro-rehabilitation is significant and complex[82], as it has to address several variables. This complexity and needs it's very well integrated on the International Classification of Functioning, Disability and Health (ICF) conceptual framework and classification system, that will be described later.

Aware of this complexity, rehabilitation teams are multidisciplinary addressing several outcomes. As movement disorders and autonomy are the most visible damage, biomechanical and functional outcomes have been elected as priority of improvement and research. However it has been proved that it's not sufficient to fully understand and promote the best rehabilitation[70]. So in parallel, studies about the brain and it's mechanisms of normal functioning and with damage and it's re-organization have been developed in the last two decades.

Neuroplasticity

One of the most important findings is the understanding of the neurophysiological property of neural tissue - Neuroplasticity. It's role in formation and modification of cerebral maps has been studied and described for decades, and is a too large topic to treat comprehensively here. With respect to the main ideas that have impact and should be considered by PT interventions, a brief description will follow, according to the recent publications about this issue.

Neuroplasticity is a fundamental property of the central nervous system (CNS). It evolves throughout life and allows the brain to modify the properties of its neural circuits and to adapt to new conditions, such as a damage[83]. Thus, is the neurobiological basis for the ability to adapt and learn in an experience-dependent manner. At the structural level, neural plasticity could be defined in terms of dendritic and axonal arborization, spine density, synapse number and size, receptor density, and in some brain regions also the number of neurons. These structural constituents of neural plasticity jointly determine the complexity of neuronal networks and their activity and contribute to recovery of function after stroke and other CNS injury[84].

Loss of function attributable to stroke is caused by cell death in the infarcted region as well as cell dysfunction in the areas surrounding the infarct. In addition, the function of remote brain regions, including the contralateral areas that are connected to the area of tissue damage, is compromised because of hypometabolism, neurovascular uncoupling, and aberrant neurotransmission, jointly called diaschisis. Some recovery of function occurs spontaneously after stroke in humans and it is believed that this functional recovery involves 3 phases: (1) reversal of diaschisis, activation of cell genesis, and repair; (2) changing the properties of existing neuronal pathways; and (3) neuroanatomical plasticity leading to the formation of new neuronal connections[84]. According to Voytek *et al*[85]., many of these theories predate neuroimaging and were based on clinical observations of patients with brain damage and that recovery of function must be mediated by intact, undamaged brain regions.

It is proved that the brain, especially cerebral cortex, has a capacity to alter the structure and function of neurons and to reorganize its neural networks in response to the changes in input and output demands. Thus, when the normal input to a particular area of the primary somatosensory cortex is lost because of injury, rapid structural and functional reorganization results in this area being activated by sensory stimulation of the surrounding intact body regions[84].

When an injury occur in the motor cortex, this leads to the recruitment of motor areas that were not making significant contribution to the lost function before the injury. The notion that the activity of cortical areas recruited after injury plays a role in functional recovery in humans is supported by a study showing that in well-recovered stroke patients, the ipsilesional dorsal motor cortex shows increase in activity. The contralesional hemisphere also has the capacity to contribute to movement on the ipsilateral side because significant increases in contralesional motor cortex activity can be observed in stroke patients during movement of the affected foot or arm; however this activation is often reduced in the later stage of recovery[84]. In regard to recruitment of ipsilesional or contralesional secondary motor areas, this occurs when the outflow from primary motor cortex is disconnected from the spinal cord in large cortical, corticosubcortical or subcortical strokes, as well as in strokes that strategically damage the corticospinal tract[86].

In the adult human brain, neural stem cells keep producing new neurons, astrocytes, and oligodendrocytes in two defined regions, the dentate gyrus of the hippocampus and the subventricular zone[87]. Thus it is possible that newly formed neurons, astrocytes, or oligodendrocytes positively affect brain plasticity and functional recovery after stroke and also might protect the ischemic penumbra by a direct cell– cell transfer of signaling and other molecules[88,89,90,91].

The common features of mechanisms for recovery include: 1. importance of experience/activity, 2. Critical period immediately after neuronal/glial damage, 3. Importance of error in learning, and 4. Localization of function. Corollaries of 1 and 4 include: 1. Experience should change localization and 2. the more limited the area damaged, the greater the potential for recovery.

Numerous studies have shown that motor activity after brain damage plays an essential role in anatomo-physiological reorganization, which may occur in the areas adjacent to the damage[92]. Nevertheless, the building blocks with which the central nervous system constructs the motor patterns can be preserved in patients with neurological disorders. In particular, several studies highlighted a modular burst-like organization of muscle activity[82].

The last 20 years attest that, clinically useful improvement can be achieved after damage or diseases of the brain with non-invasive brain stimulations and rehabilitation training trials, presenting restored brain function with a combination of different treatments. This is an exciting time in the area of restoration of brain function with many new strategies aimed at helping recovering their impaired neurological functions[93,94].

There are many ways to examine changes of the network activity: external behavior, brain maps, metabolic and molecular changes, neuronal morphology[95]. Thus, successful functional recovery can be associated to neuroplasticity and also brain maps activation and reorganization.

Motor Control and Relearning Mechanisms

Another important development is the understanding of motor control and (re) learning, that it is intrinsically related with neuroplasticity. The variability of motor control, the repetition and the contextualization of a task will facilitate neuroplasticity[96] by activating and reorganizing brain activity[97].

Motor control theories attempt to explain how the brain controls the movement and motor tasks - motor performance. Contemporary theories, based on scientific studies, define a set of principles and properties, which may guide rehabilitation[98]:

- Actions are organized to achieve specific functions, being the result of complex movements with a specific purpose.
- Actions and complex movements result from an interaction of 3 different systems[21]: Individual: bones, soft tissues, neural networks; Environment: physical and social aspects; Task: goal, direction, speed, objects
- Motor control systems adapts quickly to both activity and non activity.
- If some components of the motor systems are unavailable, actions may configured in another way.
- Skilled actions are dependent on correct discrimination of environment features (ex: position and characteristics of an object), requiring a good perception and cognition system movement-related.
- Many neural networks participate in any action.
- Generation of actions can be simplified by activating stored rules like motor programs or the Central Pattern Generators (CPGs).

On the individual system, the major neural pathways of the motor control system are the cortex, basal ganglia, the diencephalon, the cerebellum, the brainstem and the spinal cord, which are organized in motor and sensitive circuits (systems), to promote skilled motor actions. Despite that many neural networks participate in every action, each neuronal system has a specific role. According to the task and the part of the body performing the major motor task, different brain areas are activated or deactivated[99].

Currently, it’s clear that both motor and sensitive system are activated during motor performance and that the brain organization for tasks of the upper limb is different for tasks of lower limb[100]. Although the expected activated areas for lower-limb movement have not been very precisely defined, it is however known that in addition to motor and pre-motor areas, other areas such as somatosensory and limbic areas, and basal nuclei and cerebellum structures are involved in the process of motor control[101,102]. Specifically, homunculus representations of the lower limb on motor and somatosensorial and cerebellum areas are activated[103]. However, most of the studies refer to single-joint movements, not reflecting the complexity of functional movements. Considering the need for synaptic selection of activations and inhibitions, for shaping patterns of activity in networks underlying complex skills, both activations and deactivations are important on brain activity analysis[104]. Deactivations are a controversial issue in brain imaging, as the interpretations are not yet clear or well established[104]. They appear to be associated with decreases in blood oxygen levels dependent signal (BOLD), usually associated with the inhibition of areas not involved in the specific task in order to facilitate task-relevant processing[105].

Another important remark from motor control is the biomechanical considerations for a fluid and low energy cost movement. The relation mobility-stability is of high importance for any type of movement and motor task aswell the body segments relation during actions[17].

Motivation and attention are also features that influence motor performance and neural activation for movement. This is the major basis for the development of imagetics approaches for movement either on non-lesioned or lesioned brain[28,29].

In short, brain (re)organization, specificity of brain activations, models of learning and influence factors for learning are major backgrounds to support physiotherapy interventions in neurological conditions.

ICF as patient management tool for health professionals

Besides the neurosciences knowledge, physiotherapists need to have a more broaden view of the patient, where the ICF is one of the models used as a framework. This framework helps physiotherapist in providing a client tailor-made intervention, regarding a client-centered approach[106], by contemplating all the variables.

ICF describes the functioning of a person and the influence factors[107] that can disturb a normal system. This classification system was created for provide a universal language understood by health professionals, researchers, policymakers, patients and patient organizations. Is based on an integrative model that provides a multidisciplinary understanding of health and health-related conditions, concerning the following components: *Body functions* & *Body structures* and the performance of *Activities* and *Participation* in life[108]. Health and health-related conditions are also influenced by contextual factors (components): *environmental* and *personal*. Thus ICF comprises 1,454 categories related with the components above.

These categories or outcomes are intrinsically related in a multidirectional way. It means that body functions or structures can influence the functioning on activity and participation and vice-versa. Also, that the environmental and personal factors have a role in the process of harmonization or disruption, so the diverse categories can have several combinations within the Core Set.

ICF is mainly used to facilitate interdisciplinary team communication, to structure the rehabilitation process, for goal setting and assessment and for documentation and reporting. In (electronic) clinical health care records the ICF can be used to register the findings of the patient, the findings of the therapists, the functional diagnosis, and, indirectly, the goals and the results of treatment. The ICF can also be used in the selection of outcomes[109] and development of the outcome measures instruments[110]. To distinguish that outcomes and outcomes measures are different issues.

Besides the clinical importance, ICF can also be used to formulate (in)dependent variables in research, to find literature in databases, to describe the health status or problems of patients in guidelines and in communication instruments or to select relevant assistive products for patients with problems in their functioning.

However, the ICF as a whole is not feasible and to facilitate its implementation, “ICF Core Sets” were developed[111,112]. These sets are directed to a specific health condition and/or intervention phase, comprising specific categories or outcomes.

Regarding the neurological conditions, ICF Core Sets for Acute and Post-acute phases were developed using a specific methodology of development and validation among health professionals and patients[113,114,115]. From these, specific Sets were created for specific conditions.

Regarding stroke patients, the “Comprehensive ICF Core Set for Stroke” (ICF-CSS) with 166 second level ICF categories (41+31 (extended acute and post-acute) categories of *body functions*; 5+5 (extended acute and post-acute) categories of *body structures*; 51 categories of *Activity and Participation*; 33 categories of *Environmental factors*) covers the typical spectrum of problems on acute, post-acute and chronic phases[113,116,117]. A practice-friendly tool with 18 categories was defined – “Brief ICF Core Set for stroke” (BICF-CSS)[116] that represent 14% of the categories from the Comprehensive Core Set and should account for the most striking aspects of stroke-related functioning according to experts[118]. As ICF is a tool for several health professionals, Starrost and colleagues studied the core competence categories for physical therapists, having identified 56 categories from the 166 of the ICF-CSS[119].

Considering the focus of PT and neurorehabilitation and specifically on movement related interventions, the 18 categories of the BICF-CSS are not enough. On the other hand the ICF-CSS 166 categories and the 56 categories related with physiotherapy, are to extended as framework for our research. Thus, a selection of 43 categories/outcomes of 2nd level related with movement is proposed (Table 2). This selection was based on the recommendations of PT experts for stroke patients management of movement disorders[106]. It almost corresponds to the goals of PT interventions for neurological conditions, found in the research of Mittrach R. et al.[120] However, this research was directed to acute phase so didn't include categories/outcomes related with Domestic Life and Community, social and civic life, which will be included in our research.

Table 2. Authors's selection of 43 ICF Core Set for Stroke Categories related with Movement

BODY FUNCTIONS	ACTIVITY & PARTICIPATION
Chapter 2: Sensory functions and pain	**Chapter 4: Mobility**
b260 Proprioceptive functions	d410 Changing basic body position
b265 Touch function	d415 Maintaining a body position
b280 Sensation of pain	d420 Transferring oneself
Chapter 4: Functions of the cardiovascular, hematological,	d430 Lifting and carrying objects
immunological and respiratory systems	d435 Moving objects with lower extremities
b455 Exercise tolerance function	d440 Fine hand use
	d445 Hand and arm use
Chapter 7: Neuromusculoskeletal and movement-related functions	d450 Walking
b710 Mobility of joint functions	d455 Moving around
b715 Stability of joint functions	d460 Moving around in different locations (d455)
b730 Muscle power functions	d465 Moving around using equipment
b735 Muscle tone functions	d470 Using transportation
b740 Muscle endurance functions	d475 Driving
b755 Involuntary movement reactions	**Chapter 5: Self-care**
b760 Control of voluntary movement functions	d510 Washing oneself
b770 Gait pattern functions	d520 Caring for body parts
b780 Sensations related to muscles and movement functions	d530 Toileting
	d540 Dressing
BODY STRUCTURES	d550 Eating
Chapter 1: Structures of the nervous system	d560 Drinking
s110 Structure of brain	**Chapter 6: Domestic life**
Chapter 7: Structures related to movement	d620 Acquisition of goods and services
s710 Structure of head and neck region	d630 Preparing meals
s720 Structure of shoulder region	d640 Doing housework
s730 Structure of upper extremity	**Chapter 9: Community, social and civic life**
s750 Structure of lower extremity	d910 Community life
s760 Structure of trunk	d920 Recreation and leisure

One of our critics to the ICF-CSS and to the BICF-CSS, is the limited inclusion of outcomes related with *Structure* and *Function* of the brain, regarding the importance of those in neurological conditions and stroke. Consequently, as a framework for our research, the categories/outcomes *b147* (specific mental functions of control over both motor and psychological events at the body level) and *b199* (mental functions, unspecified), which relate brain functions to movement, are added to the 43 categories/outcomes of Table 2. A panel of experts will validate this junction, and if relevant a proposal for change will be sent to the ICF working groups and managers.

For both clinical practice and research, one major barrier to analyze the intervention effects is the description of the intervention itself in a standardized way and the adequate relation with outcomes and outcomes measures[120]. This analysis of coherence should be developed to every intervention, outcomes and outcomes measures in order to improve rehabilitation programs and research conclusions.

ICF core sets can facilitate this organization and for that, ICF linking rules are developed to link ICF categories to the common intervention and outcomes used in practice and literature[121]. These rules were respected on the categorization of outcomes of this thesis.

Brain Activity Analysis Tools

Regarding the coherence needed with outcomes related with brain activity, it’s necessary to use appropriate outcome measures. Today's technology provides many useful tools for studying the brain. Some have their most important applications in medical diagnosis, and some are used manly for research.

There are two main groups of procedures. Structural analysis is used to analyze the anatomy of the brain, in order to find structural deviations. Functional analysis tries to measure and locate brain activity. This is useful for investigating the functioning of special structures, and to diagnose specific diseases affecting brain activity. Functional imaging is also used to aid surgical treatment of brain lesions when it becomes necessary to determine the locality of essential functional cortex to help guide the best surgical approach. Many times a structural and functional method is used in conjunction to better assess how the activity and region are related.

Considering the goals of analysis, the instrument to be used needs to be specific and adequate. To accurately detect activities from specific areas of the brain in real (near real) time during motor performance, instruments like electroencephalography (EEG), magnetoencephalography (MEG), transcranial magnetic stimulation (TMS), functional magnetic resonance (fMRI) and positron emission tomography (PETscan) are the most used[122]. The first ones, analyze the electromagnetic properties produced by brain neuronal firing and excitability and the last two ones derive their signal from regional blood flow (BOLD signal blood oxygen level dependent) and metabolic changes linked with function-related variations in neuronal firing level[123].

With the advantages of being non-invasive, no need of contrast injection and easy to access, fMRI also provides a good spatial resolution[123,124]. Thus, this instrument is widely used in diagnosis and research and considered one of the most adequate to analyze the brain activity during research about brain mapping areas[124] by showing which parts of the brain are involved in a particular mental process[125]. However, this method doesn't allow temporal sequences of activation and relation between areas, as its temporal resolution is low.

Functional Magnetic Resonance Imaging (fMRI)

In order to utilize fMRI techniques efficiently and interpret fMRI data accurately, it is important to understand underlying physiology and physics and get acquainted to experimental hardware and software for data acquisition, processing and analysis.

Physiology and Physics

fMRI analysis the Blood Oxygenation Level Dependence (BOLD process)[126]. The BOLD signal represents the changes of oxygenation after the onset of a neurone activity, being the contrast ratio of oxygenated - oxyhaemoglobin (do not have magnetic responses) and deoxygenated - deoxyhaemoglobin (have magnetic responses) haemoglobin (Hb). Immediately after the neuronal stimulus, O2 decreases and consequently deoxyhaemoglobin increases which gives an increase of inhomogeneity showing low contrast on T2* (described further). To regulate this lost of O2 and increase of deoxyhaemoglobin there is a massive influx of O2 rich blood, leading to a relative decrease of deoxyhaemoglobin and hence increase in the BOLD fMRI signal of that tissue. When this ratio returns to normal, the BOLD signal decays until it has reached its original baseline level (~24s)[127].

This signal is related with the neuronal tissue atoms behavior. The atoms that compose human tissues are: hydrogen, oxygen, carbon, calcium, phosphorus, fluor, sodium, potassium and nitrogen. The hydrogen has the higher sensibility to MRI because of its higher magnetic moment, thus the selected atom to analyze during MRI. The data collected is the result of an interaction between the magnetic field and the hydrogen protons that sends a radiofrequency through a coil and this signal is computerized to produce image or numeric data[128].

Hydrogen nucleus is only the proton. Protons are positively charged and have the spin property or angular moment that generates a spin around their own axis to maintain stability creating a magnetic field around, however this magnetic field is not sufficient for signal captation. To increase the signal, the nuclear spin can be manipulated by an external magnet, the basis for MRI imaging. Under an external magnetic field the spin increases and a higher magnetic field is created - magnetic moment with protons spins aligned with the direction of the external magnetic field and spinning around a longitudinal axis (Z axis) - precession movement. A perturbation of this alignment will lead to an increase of energy release and can be stimulated by a radiofrequency pulse (RF), that creates a negative charge and leads the proton to change its vector of alignment in the direction of transversal plan (Y, X axis).

After the emission of RF, the signal gradually decays with a relaxation time in a shape of a seno wave, bringing the force vector to the Z axis again with radio waves release, captured by the coil. This relaxation is characterized by two different times: longitudinal relaxation T1, related with the magnetization to the longitudinal axis (Z) and transversal relaxation T2, related with decrease of the transversal magnetization. Transversal relaxation is also influenced by the inhomogenization of the tissues that decrease the time of relaxation T2*. To remember that this inhomogeneity occurs when deoxyhaemoglobin increases on initial neuron activation, so as lower it is this inhomogeneity, longer it is the transversal relaxation T2 and T2*, increasing the possibility of signal detection.

A sequence of RF, generates a sequence of signal and it's echo, the time in between pulses and the echo peak is called the echo time (TE) and the time of overall repetitions is called repetition time (TR)[129], the value of these variables will determine the quality of the signal.

However, this signal needs to be codified to differentiate areas and create a map. This codification is obtained by the use of gradients that produce different frequencies allowing the specification of areas/tissues according to their frequency.

Imaging - Hardware and Software

According to the physiology and physics relation, the MRI equipment consists of a magnet, gradient and shim coil(s), a console, radiofrequency (RF) and gradient amplifiers, and RF coils[134], to create the external magnetic field and vectorial forces change on spins across a determined brain area (selected by the researcher or clinician) and a computer with specific software to transform this signals into image and numerical information.

The image and numerical data are possible by the use of the volumetric unit of signal information - Voxel. Each voxel represents one pixel and comprehends a 3D image regarding the matrix, the thickness and the field of view (FOV) of that point identified. Each image is composed by several pixels distributed on a matrix with lines and columns - more lines and more columns mean more pixels. Similarly to any other images, the resolution (how sharp the image is) will depend of the number of pixels on the matrix, but will also depend on the image field or Field of View (FOV), so the resolution will depend on the relation matrix vs FOV. As higher the matrix and smaller the FOV, smaller the pixel so better resolution of the image, but also increment of time to capture. Thus, with the increment of spatial resolution occurs a degradation of temporal resolution.

As the brain and its structures are volumes for image acquisition, and the resolution also depends on the thickness of the voxel, the imaging needs to be done in slices on different plans: transversal, sagittal and frontal. A pre-defined matrix composes each slice. Since repetitive images have to be obtained during fMRI, it is preferable to acquire images as fast as possible to improve temporal resolution and minimize motion (head and body) during data acquisition.

Considering that to collect fMRI data, the subject needs to lay down and stay immobile during the acquisition time inside the scanner, small movements are expected (even when very well stabilized head and body) producing noise. Also the magnet and coils and the image parameters contribute for noise production that can interfere with the signal processed. Thus, methods to decrease this noise variable are important to improve the reliability of the acquired image. The relation/ratio between the signal and the noise is the signal-to-noise ratio (SNR) and depends on[128]:

- Slice thickness and receiver bandwidth
- Field of view
- Size of the (image) matrix
- Number of acquisitions
- Scan parameters (TR, TE, flip angle)
- Magnetic field strength
- Selection of the transmit and receive coil (RF coil)

In a relation of 1:1, as higher the SNR better the reliability of the image. These aspects need to be defined when designing the paradigm parameters of the scanner, according to the goals of the imaging.

fMRI data processing requires specific software that can be obtained from various sources (Analyisis of Functional NeuroImages (AFNI), Brain Voyager, Statistical Parametric Mapping (SPM), etc). This software contains Pre-processing and Processing methods as well as visualization methods.

Imaging - Stimulus Paradigm

Typically, images are acquired during repeated control and stimulation periods. Depending on stimulation paradigms, the stimulation/task duration is a sub-second to a few minutes. Stimulation paradigms are the tasks analysed during fMRI acquisition[129], which can occur in blocks (task blocks intervealed with rest blocks), be event-related or mixed, depending on what is the goal of the observation[130]. For novel concepts or non explored phenomenons, “on and off” paradigms (block paradigm) are the most suitable[131].

The definition of the brain areas to be anlysed is also dependent of the previous knowledge of specific activations regarding specific tasks. When expected areas are not well defined, a whole-brain analysis is preferable[132]. Specific regions of interest (RoIs) analysis is applicable when studying specific regions known to be activated with a certain stimulus or when searching for validation of that area.

The identification of the area is then possible when the signal is transformed in an image, called map where specific coordinates localize specific brain areas[129]. Considering the nature of the signal and the process to transform it to an image, several steps are needed to guarantee the validity of the visual data.

Imaging - Pre-processing and Processing

Pre-processing attempts to improve SNR and comprehends the following steps:

1. Functional image alignment and co-registration to an anatomical reference
2. motion correction
3. slice-timming correction
4. spatial filtering
5. temporal filtering
6. global intensity normalization
7. registration

Processing attempts to generate a functional map from fMRI data set, using the signal intensities of images obtained during control and stimulation periods, which are compared on a voxel-by voxel basis. Voxels passing a statistical threshold are considered to be 'active', then color-coded based on statistical values such as t values. These values are always contrasted with another condition, usually the baseline (comparison). Color-coded functional map is overlaid on anatomic image for better visualization.

For both pre-processing and processing, several softwares can be used as presented above, specifically Brain Voyager uses the Talairach space with specific anatomical coordinates[129] and specific statistical tests.

On Talairach space coordinates for Brodmann areas are well defined but sub-cortical areas remain not specific yet, demanding specific landmark analysis[102]. The localization of the different body segments is very well localized on motor and somatosensorial areas, where lower limb has coordinates mostly at the middline (interhemispheric) regions of Brodmann area 4, 1,2 and 3 and on the lateral superior region of Brodmann area 5 and 7[133]. From a landrmark analysis and coordinates transformation[102], it's possible to identify that lower limb cerebellum representation is localized at the laminae IV, V, VI and IX, ipsilaterally.

Since no gold-standard method exists, defining activation of these areas is not straightforward and spatial localization demand specific statistic analysis regarding the values of activation. Common approaches use parametric statistical methods such as t test where a valid statistical threshold needs to be defined.

Since a statistical value is tightly related to SNR, functional maps generated using the same statistical threshold can give different maps if SNR varies. In animal studies, signal averaging can be performed extensively. Thus, it is less likely to encounter serious problems associated with low SNR. Nevertheless, voxels deemed active because they passed a threshold are likely not the only active areas, but represent a sub region of the actual active tissue. Especially, in high-resolution images with low SNR, less-active voxels may not pass a given statistical threshold. Researchers can evaluate this possibility by varying the statistical threshold. On the other hand, an active voxel may not necessarily mean that neuronal activity is present in that region, but may arise from hemodynamic signals that do not exactly co-localize with the neuronal activity. Rigorous studies of fMRI signal source are essential.

Another important test is reproducibility during repeated experiments. To determine reproducibility, data sets are separated in more than one group. Although many approaches can be feasible, one simple approach is to group odd and even data acquisition groups. Then, functional maps of odd and even data sets are computed separately.

Statistical values of two maps can be compared on a voxel-by-voxel basis. In an ideal case with extremely high SNR, a correlation value between the two statistical maps should be close to 1.0. Also, the percent overlap between two threshold functional maps can be determined. In the case that most voxels are active, this property is not a good indicator and its use should be avoided.

Functional Magnetic Resonance Imaging (fMRI) - Results analysis and translation into practice of physiotherapy

The results of and fMRI acquisition can have different value or interpretations depending on the professionals. For physiotherapists, the identification of specific brain activation or deactivation, need to be interpretated from a movement or task point of view. fMRI results in healthy subjects are important for identification of activated areas or specific sequences of activation during specific tasks, in order to promote them during rehabilitation. The results in patients are relevant to monitorize the progression and/or guide the intervention.

To respond specific questions, researchers or practitioners need to know the basics related with fMRI (or another instrument) acquisition, as described above. However certain specificities of paradigm, pre-processing and processing are sometimes to complex and need the experience of specialized teams to define the most adequate method as practitioners will focus on the practical translation of results.

Interest and Aims of the present Thesis

With respect to the summary of the "state of art" presented above, it's evident that scientific knowledge in the area of rehabilitation and physiotherapy for stroke is booming and leading to a more sustainable models of practice. Several interventions show positive effects with strong scientific support. However, some issues remain to be clarified like what are the effects of PT on brain activity and what are the effects of hands on interventions. Also a general coherence of interventions and outcomes and outcomes measures needs to improve for future research.

These issues fit the main questions that conducted to the development of this thesis:

If physiotherapy is used to improve motor performance, but if motor performance depends on brain performance and brain performance depends on neuroplasticity, does physiotherapy promote brain activity and consequently plasticity?

What do Physiotherapists exactly do?

What are the real effects and efficacy of Physiotherapy interventions?

To contribute to answer these questions, the aims of this thesis are:

- Aim 1 - to give an overall overview towards evidence and needs of PT and neuro-rehabilitation on stroke;
- Aim 2 - to understand the extent of effects of PT hands on interventions on Structures & Functions and Activity & Participation outcomes related with movement, on patients with stroke;
- Aim 3 - to observe and describe the effects of facilitation of movement (motor task) on brain activation;
- Aim 4 - understand the extent of effects of PT brain activity for patients with stroke;
- Aim 5 - to propose a categorization of PT interventions and outcome measures on stroke patients under the ICF model.

On the academic perspective of developing a PhD, according to the Dublin Descriptors, where students need to design, conceive, implement and adapt to research methods; develop scientific reflection about complex issues and contribute with original information to the scientific community, the challenge of this thesis is the exploration of such a complex issue by the use of different research methodologies. This approach permits the comprehension of different methods regarding benefits and limitations and also permits the analysis of the same phenomenon under different perspectives.

As innovative aspects of this thesis, we highlight:

- The organization within the ICF framework for the outcomes related with movement;
- The study of brain activity during a complex multijoint movement of lower limb (usually upper limb or single joints of toes are analyzed);
- The study of immediate effects of manual facilitation of movement, as no similar studies was found on our literature search for this thesis (usually long term effects are investigated);
- The proposal for PT interventions and outcome measures for stroke, ICF categorization.

Outline of the Thesis

In order to attain the aims and contribute to answer the main questions, an extensive literature review was performed and the following studies were implemented composing the content of this thesis, organized in the format of articles collection:

- **Physiotherapy Hands-on Interventions and Stroke: Systematic Review** - this study aims to collect the high level studies to present the evidence of what are the effects of “Hands On” PT interventions on the dimensions of Structure, Function, Activity and Participation of patients, what interventions are lacking evidence and what should be improved methodologically. We pretend to analyze the effects of one intervention and not the comparison with other interventions. This study contributes to achieve the aim 1, 2 and 5.

- **Physiotherapy and Brain Activity on Stroke: Systematic Review** - this study aims to collect the high level studies to present the evidence of what are the effects of a broad spectrum of PT interventions on the dimensions of Structure and Function, specifically on Brain activity of patients (and indirectly neuroplasticity), what interventions are lacking evidence and what should be improved methodologically. We pretend to analyze the effects of one intervention and not the comparison with other interventions. This study contributes to achieve the aims 1, 3 and 5.

- **Brain activity during lower limb movement with physiotherapy manual facilitation – an fMRI study** - this study aims to verify if facilitation provides brain activity and if the pattern of activation is similar to a non-manual facilitation stimulus of the task (autonomous performance). This study contributes to achieve the aim 1 and 4.

- **ICF Linking Process for Categorization of Interventions and Outcomes Measures on Stroke Physiotherapy - Delphi panel -** this study aims to propose a categorization of PT interventions and outcome measures on stroke patients under the ICF model, to increase the coherence or the appropriate relation of dimensions and categories among interventions, outcomes and outcomes measures. This study contributes to achieve the aim 5.

The results and reflections of the four studies, together with the literature review presented in the introduction regarding the PT and neurological rehabilitation and evidence, will contribute to achieve aim 1.

In the **Discussion** and **Conclusions**, the overall research and the specific methods will be critically appraised. Besides the limitations of this research, suggestions for the clinical significance and the translation to practice will be discussed. The impact of results of this study on patient management and future of research will conclude this chapter.

Considering the amount of extra paper, the appendices are provided only on digital version, organized in: Thesis Appendices and Articles Extra Appendices.

Studies Developed - Articles

Physiotherapy Hands-on Interventions and Stroke: Systematic Review

Authors: Patrícia Maria Duarte de Almeida, MSc, PT[1, 2]; Ana Santo, BSc, PT[1]; Beatriz Dias, BSc, PT[1]; Catarina Filipa Faria, BSc, PT[1]; Daniela Gonçalves BSc, PT[1]; Mónica Carvalho e Silva, BSc, PT[1] Alexandre Castro Caldas[2]

[1]Alcoitão School of Health Sciences, Rua Conde Barão, Alcoitão 2649-506 Alcabideche, Portugal

[2]Institute of Health Sciences - Catholic University of Portugal, Palma de Cima 1649-023 Lisbon, Portugal

Contacts: 00351214607459; patriciamdalmeida@gmail.com

Number of words in the Abstract – 199

Number of text characters - 24519

The authors have declared that there are no potential conflicts of interest with respect to the authorship and/or publication of this article.

This study has no funding resources.

This study and manuscript have not been previously presented or published elsewhere.

Publication accepted to European Journal of Physiotherapy - Manuscript ID SPHY-2014-0049-R2, 2015

European Journal of Physiotherapy

Preview

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Dear Dr Almeida:

Ref: Physiotherapy Hands-on Interventions and Stroke and ICF outcomes: Systematic Review

Our referees have now considered your revised paper once more and have recommended publication in European Journal of Physiotherapy. The comments can be found at the end of this message. We are therefore pleased to accept your paper in its current form.

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Thank you for your contribution to European Journal of Physiotherapy and we look forward to receiving further submissions from you.

Sincerely,
Professor Anne Söderlund
Editor in Chief, European Journal of Physiotherapy
anne.soderlund@mdh.se

Reviewer's Comments to Author:

Comments to the Author
I think that the authors have done the changes I have suggested, except for the Bobath Concept as hands on intervention. As I said before I do not agree with this categorization, however I understand that a great number of physiotherapists have this point of view and I that's why I accept its inclusion in the article.
I have just one more suggestion
Page 2
line 10: add "...the United States"

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Date Sent: 21-Apr-2015

Abstract

Aims: Effectiveness of "hands-on" physiotherapy for stroke is unclear. The objective here is to analyze the effectiveness of these interventions on movement-related ICF categories. **Methodology**: Systematic review of published RCT trials since 1980, using the following criteria: stroke, humans, >18 years, outcomes related to ICF movement-related categories, physiotherapeutic handling techniques, control group as Placebo or No intervention, including experiments where both groups have the same intervention and the experimental group has one extra intervention. **Major findings**: Nine studies were included and a best-evidence synthesis presented. Recommendations with limited evidence in favor of slow-stroke back massage for shoulder pain; ROM exercises for upper limb and lower limb structures and functions of muscles and joints; PNF on gait step and walking backwards with hip facilitation for gait parameters and performance and conventional physiotherapy with facilitation techniques for gait parameters. Recommendations with indicative findings in favor of PNF with trunk rhythmic stabilizations for function and mobility of upper limb. Recommendations with limited evidence for the non-efficacy of Bobath Therapy for upper-limb function and activity and facilitation of the step on body weight support treadmill training for gait parameters and performance. **Principal conclusion:** Some hands on interventions have limited evidence on stroke rehabilitation.

Keywords: Stroke, physiotherapy, hands-on interventions, handling techniques.

Introduction

Stroke is highly prevalent across the globe with a predicted increase of 4 million people suffering new cases in the period up to 2030, accounting for a rise of 21.9 % compared to 2013 levels in United States (1). In Europe the the cardiovascular diseases are responsible for over than 4 million deaths a year from which one third for women and one quarter for men is caused by stroke (2). For stroke survivors worldwide the levels of disability are high and of concern for health care systems (1, 2).

The levels of disability are related to the damage of specific brain structures and their function, and the impact of this on movement, activity performance and social participation. Considering these complex interactions, a “traditional” analysis of consequences related to body structures and body functions would not be appropriate (3), for either healthcare services or the scientific research that supports the healthcare.

In the interests of a more efficient and patient-centered approach, the International Classification of Functionality, Disability and Health (ICF) framework is the most suitable approach. The ICF framework provides a better understanding of the human dimensions and their relation to health and health-related events like stroke. It also provides a universal language and common framework of reasoning for clinical decisions and research. By using this framework, it is possible to identify which dimensions and categories (which will turn into outcomes) should be targets for intervention, improvement or attention for a specific health condition or event. At the same time, interventions and outcome measures should be tailored to those dimensions and categories. With regards to the specificities of each disease, several “ICF Core Sets” have been developed, namely the "Comprehensive ICF Core Set for Stroke" - ICF-CSS (4). Within this framework the objective of stroke rehabilitation is to enable individual patients to achieve their full potential and to maximize the benefits of training on physical and psychological performance (4, 5).

To fulfill this potential, rehabilitation teams, where the physiotherapist (PT) plays an important role, need to consider the relation between neuroplasticity and motor outcomes (6) as a basis of intervention. Generally, the framework of physiotherapy intervention on neurological conditions relies on motor control and learning theories, normal movement basis, neuroplasticity and functionality model (7). Most effective studies have pointed towards the greater effectiveness of “Hands-off” interventions of physiotherapy, and this has been validated by the most recent systematic review studying the evidence of post-stroke physiotherapy (8).

"Hands on" and "hands off" terms are widely used in the vocabulary of physiotherapists and researchers (9, 10, 11) and a regular topic of development on professional congresses and conferences (12). However a clear definition remains rather undefined. For the purpose of our research, we consider "Hands on" as the interventions where physiotherapists use their hands with direct contact on patient's body segments to: give sensorimotor input to guide movement or stability and promote proprioceptive awareness; promote muscular relaxation or activation; promote joint movement and task performance, soliciting rather active participation from the patient and not only passive mobilization as described before (13). "Hands off" interventions are all the others used by physiotherapists, without direct contact of physiotherapist's hands like: physical agents, robotics, exercise, verbal instructions, among others.

The most common hands on interventions used by physiotherapists in neurological context are (5, 14): Bobath concept, Proprioceptive Neuromuscular Facilitation (PNF), Hydrotherapy, Mobilization and Massage. Despite the fact that the Bobath concept is rather a problem-solving approach than a technique, its practical therapeutic skills involve the selective manipulation of sensory information, namely, manual facilitation, to positively affect motor control and perception in person's post-central nervous system lesion (15). This manipulation by the use of facilitation means the use of physiotherapist's hands on patient's specific body segments, called "key areas" (16), which is the main characteristic of this approach, considered then as a "hands-on" approach.

The use of these interventions isolated or in conjunction with each other, characterizes mostly the models of intervention of general rehabilitation services (17), and are usually considered as the conventional forms of therapy and still the most used approaches due to tradition of services and ease of implementation. This is observed on a systematic review (16) that analysed 20 randomized controlled trials (RCT) performed with stroke patients in several phases post-stroke (acute to rehabilitation and chronic). However, the effectiveness of these interventions remains unclear due to the lack of studies and to methodological issues (18), being important its clarification (19).

The objective of this study is to systematically review the published RCTs to examine the effectiveness of hands-on interventions on stroke patient categories/outcomes related to movement included on ICF-CSS, regarding the scope of physiotherapy (20) and based on the recommendations of PT experts for the management of movement disorders in stroke patients (21), used on the study "ICF Linking Process for Categorization of Interventions and Outcomes Measures on Stroke Physiotherapy" (22) and presented in Table 1.

Table 1. Selection of 43 categories related with movement, retrieved from ICF-CSS (22).

BODY FUNCTIONS	ACTIVITY & PARTICIPATION
Chapter 2: Sensory functions and pain	**Chapter 4: Mobility**
b260 Proprioceptive functions	d410 Changing basic body position
b265 Touch function	d415 Maintaining a body position
b280 Sensation of pain	d420 Transferring oneself
Chapter 4: Functions of the cardiovascular, hematological, immunological and respiratory systems	d430 Lifting and carrying objects
	d435 Moving objects with lower extremities
b455 Exercise tolerance function	d440 Fine hand use
	d445 Hand and arm use
Chapter 7: Neuromusculoskeletal and movement-related functions	d450 Walking
b710 Mobility of joint functions	d455 Moving around
b715 Stability of joint functions	d460 Moving around in different locations (d455)
b730 Muscle power functions	d465 Moving around using equipment
b735 Muscle tone functions	d470 Using transportation
b740 Muscle endurance functions	d475 Driving
b755 Involuntary movement reactions	**Chapter 5: Self-care**
b760 Control of voluntary movement functions	d510 Washing oneself
b770 Gait pattern functions	d520 Caring for body parts
b780 Sensations related to muscles and movement functions	d530 Toileting
	d540 Dressing
BODY STRUCTURES	d550 Eating
Chapter 1: Structures of the nervous system	d560 Drinking
s110 Structure of brain	**Chapter 6: Domestic life**
Chapter 7: Structures related to movement	d620 Acquisition of goods and services
s710 Structure of head and neck region	d630 Preparing meals
s720 Structure of shoulder region	d640 Doing housework
s730 Structure of upper extremity	**Chapter 9: Community, social and civic life**
s750 Structure of lower extremity	d910 Community life
s760 Structure of trunk	d920 Recreation and leisure

We also attempted to characterize the coherence of the outcomes studied and the interventions and outcome measures employed.

Methods

Search Strategy for study identification

A systematic search of the relevant literature was conducted, aiming for peer-reviewed published RCTs from the four most prominent databases for physiotherapy (23): PubMed, CENTRAL, PEDro and EMBASE. A bibliographical list analysis was performed of the articles selected for full-text reading,

The construction of the search expression (appendix 1) was based on the PICO question regarding stroke patients, the physiotherapeutic hands-on interventions and the 43 outcome categories related with movement (table 1) taken from the ICF-CSS. It includes the goals of PT interventions for neurological conditions, found in the research of Mittrach R. et al. (24) aimed at dealing with acute phases and also includes categories related to domestic life and the community, and social and civic life.

For these categories, we undertook a linking process with MeSH terms and common terms found in the relevant literature, in order to increase the spectrum of relevant RCTs. The same expression was applied to PubMed, CENTRAL and EMBASE databases without the insertion of any limits. A specific search expression was created in accordance with the search options of the PEDro database (appendix 1).

Inclusion and Exclusion Criteria

In order to be included in this review, studies had to meet the following criteria:

- Stroke patients including acute, post-acute and chronic phases,
- Adults ≥ 18 years old,
- Type of study: Randomized controlled trials (RCTs) are the only accurate way of determining a cause-effect relation between a treatment and its outcomes (25).
- Publications in English, Portuguese, French, Dutch and Spanish,
- Publications published after "1980" – from this date evidence-based medicine emerged, with the "best" interventions for stroke rehabilitation regarding the affected dimensions becoming a major concern (19).
- Control group characterized by Placebo; no intervention at all, or experiments where both groups are subject to one form of intervention while the experimental group has an additional intervention to be tested - most of the studies provide information that compares and contrasts varying interventions.

This methodology does not provide information regarding the effectiveness of the specific intervention (25). Instead, the intervention being tested should be compared with a placebo, or with an absence of treatment. As no treatment is ethically not approved, an additional intervention could be an option, as some evidence exists that extra-time therapy does not immediately lead to better results; rather, they are dependent on the content of the therapy (26).

- Intervention: any physiotherapeutic technique involving handling – Bobath Concept, Proprioceptive Neuromuscular Facilitation (PNF), Hydrotherapy, Mobilization or Massage performed by physiotherapists or by other professionals as long as the approach can also be used by physiotherapists,
- Outcomes related with movement and functioning linked with the categories presented in table 1.

Studies were excluded from this review if they did not investigate humans and if assistance was performed by robotics.

Data collection and analysis

After introduction to the citation manager EndNote® X5, which discounted duplicate references, two reviewers independently:

1. Selected the articles by title and abstract, according to the selection criteria
2. Selected the articles by full-text reading, according to the selection criteria
3. Categorized the methodological quality of the included RCTs using the Physiotherapy Evidence Database (PEDro) scale. The reviewers individually scored the studies, and did not use the database scores. There was no cut-off score for inclusion and all the studies were analyzed per item and their individual contributions interpreted.
4. Extracted the data according to the following model:
    - Qualitative features - Study identification, ICF Dimension(s), PEDro score, Non-accomplished items (PEDro) and Direction of results (positive or negative with respect to the experimental group or no difference).
    - Clinical features - N subjects, N control, N experimental, average Age, Stroke type, time since stroke, Control Approach, Tested approach, Length of treatment and Duration per session.

- Statistical features - Baseline scores/events, Final score/events, mean difference of scores/events and standard deviation.

In all the phases, panel consensus with the presence of a 3rd element (AS), was used to clarify doubts and to validate decisions.

As clinical and statistical features determine homogeneity, a quantitative analysis (meta-analysis) was not possible given the diversity of interventions and outcomes (18, 27).

In these situations, an alternative is to present a “best-evidence synthesis” (27, 29), taking into account the PEDro score and the amount of studies with the same characteristics and variables (30, 31). By the use of this method, results were classified by their level of evidence as: 1 - strong, 2 - moderate, 3 - limited evidence, 4 - indicative findings, 5 - no or insufficient evidence (31). Detailed information for the levels of evidence can be found on the annex 1. RCTs were classified as presenting a high quality when PEDro scores were >4 (30, 31).

With regard to the need to shift to an ICF language for universal homogenization (32), and the need for coherence in interventions and outcome measures for the target outcomes in clinical settings and research, an analysis of coherence will be attempted and discussed. One of the main methodological issues in a need of improvement on RCT’s (33) is a more logical explicit connection of intervention goals and outcomes expected. Different dimensions and outcomes have an intrinsic interaction with the capacity of multidirectional influences, the knowledge of such interactions and behavior is relevant for the knowledge of the real influence of each intervention.

A coherence analysis in our study refers to the ICF categories and dimensions logical correspondence between interventions and outcome measures or expected impact of one dimension into other dimension. For the purposes of this analysis we used the results of categorization of interventions and outcomes measures of the study “ICF Linking Process for Categorization of Interventions and Outcomes Measures on Stroke Physiotherapy” (22). This process followed a Delphi panel method with 7 experts and the ICF linking rules (34), where 43 interventions and 65 outcome measures in the context of stroke physiotherapy were categorized, according to 43 categories related with movement, retrieved from ICF-CSS (22) (Table 1).

Results

Study Identification

After a search of all the databases, we identified 1,756 trials, after selection process (Figure 1), nine studies (26, 35, 36, 37, 38, 39, 40, 41, 42) were included in this systematic review (Table 2).

In total, these nine studies evaluated 483 participants (mean age = 65.47 years) at different post-stroke stages (1 month – 60 months); 260 participants were assigned to an experimental group and the time of intervention ranged from 1 week to 6 weeks with the frequency per week ranging from 3 times a week to every day. Table 2 shows the main characteristics of the studies included.

Titles and abstracts screened (n=1756) EMBASE (n= 131) CENTRAL (n = 576) PUBMED (n = 371) PEDro (n = 678) After duplication elimination by Endnote (n= 1505)	
	Articles excluded after screening titles/abstracts (n=1368)
Potentially relevant articles retrieved for evaluation of full text (n=137)	
	Articles excluded after evaluation of full text (n=128)* • Intervention of the control group (n=22) • Non- "hands-on" therapy (n= 66) • No stroke (n=14) • Non-RCT (n=26)
Articles included in the review (n=9)	

Figure 1. Flow of articles through the review. * Papers may have been excluded for failing to meet more than one inclusion criteria.

Table 2. Characteristics of the included studies

Study	Objective study	n (E/C)	Mean age (E/C)	Mean time (months) since stroke (E/C)	Intervention - E	Intervention - C	Protocol period (weeks)	Outcome	Outcome Results/Conclusions	Methodological quality[2]
PNF-T (35)	Effect of **PNF** trunk exercises on limits of stability	40 (20/20)	51,4/53,5	22,9/26,8	General exercises of stretching and ROM + Trunk rhythmic stabilizations and stabilizing reversal (10 min)	General exercises of stretching and ROM	5 times a week / 4 weeks	FRT EMG (soleus, hamstrings, quadriceps, tibialis anterior)	**Significant** increase of the FRT score was found when compared with the C group. **Significant** increase of soleus and quadriceps activity was found on affected side, when compared with the C group. **No significant** differences were found on the other muscles activation, when compared with C group.	4 (3, 4, 5, 6, 7, 10)
ROM (36)	Effect of **ROM exercise** on joint flexibility, activity function, pain and depression	38 (21/17)[3]	75,05[4]	59,81[4]	Passive ROM exercises (10 to 20 min) of flexion, extension, adduction, abduction, external and internal rotation on shoulder, elbow, wrist, hip, knee and ankle.	No therapy	6 times a week / 4 weeks	FIM (ADL sub-scale) Goniometer Pain scale of 3 ratings	**Significant** differences for all the outcome measures, when compared with the C group, except for FIM: Increase of all joint angles Decrease of pain rating	6 (3, 5, 6, 9)

Table 2. Characteristics of the included studies (continued)

Study	Objective study	n (E/C)	Mean age (E/C)	Mean time (months) since stroke (E/C)	Intervention - E	Intervention - C	Protocol period (weeks)	Outcome	Outcome Results/Conclusions	Methodological quality[2]
BT (26)	Effects of augmented therapy with **Bobath** therapy for upper limb function	40 (20/20)[3]	60,6/60,9	1,5/1	Conventional Physical Therapy (CPT) + 45 min of Bobath approach for control of muscle tone and recruitment of arm activity during functional situations)	CPT	20 sessions during 4 weeks	Fugl-Meyer test ARAT	**No significant** differences were found at any outcome measures when compared with C group.	8 (5, 6)
PMTS (42)	Effects of MTS on upper limb function	76 (18/19/20/19)[5]	73,3/72,9/ 72,5/71,6	1/1/1/1	CPT + 30 min of MTS or + 60 min of MTS or + 120 min of MTS	CPT	Consecutive 14 working days	Motricity index ARAT	**No significant** differences were found at any outcome measures for all groups when compared with C group.	8 (5, 8)
SSBM (39)	Effects of **slow-stroke back massage** added to CPT, on anxiety and shoulder pain	102 (51/51)	73,1/73,3		10 min of slow back massage from the neck till lumbar region, before bed time.	No therapy	7days / 1week	VAS	**Significant** decrease on VAS, when compared with C group.	5 (3, 5, 6, 9)

Table 2. Characteristics of the included studies (continued)

Study	Objective study	n (E/C)	Mean age (E/C)	Mean time (months) since stroke (E/C)	Intervention - E	Intervention - C	Protocol period (weeks)	Outcome	Outcome Results/Conclusions	Methodological quality[2]
FT'-BWSTT (38)	Assess the benefit of **facilitation technique** coupled with BWSTT	49 (23/26)	62,9/59,3	2/2	CTP + Continous sensoriomotor stimulation on the hip and pelvic region to facilitate swing on treadmill (20 min)	CTP + treadmill (20 min) with no handling	3 times a week / 6 weeks	FIM Fugl-Meyer Gait velocity Gait cadence	**No significant** differences were found at any outcome measures when compared with C group.	6 (5, 6, 7 9)
PNF-G (37)	How **PNF**-based exercise affects gait performance	40 (20/20)	61,5/61,5	5,1/6,1	Walking with PNF on the lower limb on a 10º ramp- 30 min.	Walking on a 10º ramp - 30 min	5 times a week / 4 weeks	Gait temporal parameters (velocity, phase time) Gait spatial parameters (step length) FAP	**Significant** decrease of phase time with increase of velocity and **significant** increase of spatial parameters and of FAP score, for the E.	6 (3, 5, 6, 7)
CPT (40)	Effects of additional Functional Strenght Training (FST) or additional **CPT** on functionality and gait	73 (35/38)[3]	67,5/66,4	1-3	CPT + CPT (physiotherapist hands on therapy with joints and muscles preparation for activity and activity trainning)	CPT (physiotherapist hands on therapy with joints and muscles preparation for activity and activity trainning)	4 times a week / 6 weeks	Rivermed index Gait velocity Gait cadence Step length Knee peak torque	**Significant** increase of gait velocity (p= 0,031) and knee peak torque (p= 0,016), when compared with C. **No significant** differences were found to the other outcome measures when compared with C group.	8 (5, 6)

Table 2. Characteristics of the included studies (continued)

Study	Objective study	n (E/C)	Mean age (E/C)	Mean time (months) since stroke (E/C)	Intervention - E	Intervention - C	Protocol period (weeks)	Outcome	Outcome Results/Conclusions	Methodological quality[2]
BWFT (41)	Effectiveness of additional **backward walking with facilitation technique (BWTFT)** to CPT on gait	25 (13/12)	63,4/63,4	7/7	CPT + 30 min of facilitation according to Bobath concept of walking backwards	CPT	3 times a week / 3 weeks	Gait velocity Step length Symmetry index	**Significant** increase found at any outcome measures when compared with C group.	7 (5, 6, 7)

[1] Only outcomes relevant for this systematic review are presented;

[2] Quality assessment using PEDro-scale, presenting external validity, quality score and criteria not satisfied;

[3]Only one experimental group was selected to compare with control;

[4] Mean values given for all subjects;

[5] The experimental groups differ only on duration of application

Abbreviations: n = number of patients; E – experimental group; C = control group; PNF = proprioceptive neuromuscular facilitation; FRT = functional reach test; FAP = functional ambulance performance; ROM = range-of-motion; FIM = functional independence measure; ADL = activities of daily life; GDS-15 = geriatric depression scale short-form; ARAT = action research arm test; MTS = Mobilisation and Tactile Stimulation; STAI = state-trait anxiety inventory; VAS = visual analogue scale; BWSTT = body weight support treadmill training;

Interventions and Outcomes

Nine interventions were identified, having four directed to the upper limb, four directed to the lower limb and one directed for both. A more detailed description of each is presented on table 3. Thirteen outcome measures were found (see table 4).

Methodological quality assessment

PEDro scores had an average of 6.4 where only one study (35) scored < 4 and the other 8 studies (26, 36, 37, 38, 39, 40, 41, 42) ranged from 5 to 8 (see table 2).

All the studies have issues with blinding; in none of them were the subjects blinded regarding treatment allocation; in 8 studies (26, 35, 36, 37, 38, 39, 40, 41) there was no PT blinding and in 4 (35, 37, 38, 41) there was also no blinding of the assessor. Four studies (35, 36, 37, 39) did not use concealed allocation on randomization; one study (42) had less than 85% of the measures of at least one key outcome, of the subjects initially allocated to groups; in three studies (36, 38, 39) not all of the subjects for whom outcome measures were available received the treatment or control condition as allocated or used the "intention to treat" method, and one study (35) did not include inter-group statistical comparisons. The sample sizes were small in all of the studies.

Best-evidence synthesis

Limited evidence (based on one high-quality RCT for each) was found for the non-efficacy of (see table 2 and 3):

- Facilitation technique coupled with body weight support treadmill training (FT-BWSTT) (38) - on gait parameters and walking functionality,
- Bobath therapy (BT) (26) - on function and activity of the upper limb,
- Passive mobilization with tactitle stimulation (PMTS) (42) - on function and activity of the upper limb,
- Conventional Physiotherapy with manual facilitation (CPT) (40) - gait functionality,
- Passive range of motion exercises (ROM) (36) - on upper and lower limb functional Independence.

Limited evidence (based on one high-quality RCT for each) was found for the efficacy of (see table 2 and 3):

- Slow-stroke back massage (SSBM) (39) - on shoulder pain relief,
- Proprioceptive Neuromuscular Facilitation for Gait performance (PNF-G) (37) - on gait parameters and gait performance,
- Conventional Physiotherapy with manual facilitation (CPT) (40) - gait velocity and knee peak torque,
- Backward walking with facilitation technique (BWFT) (41) - on gait parameters and gait performance,
- Passive range of motion exercises (ROM) (36) - on upper and lower limb joint movement and decrease of pain.

Indicative fndings (based on one low-quality RCT) was found for the efficacy of (see table 2 and 3):

- Proprioceptive Neuromuscular Facilitation for Trunk Stability (PNF-T) (35) - on upper limb function and mobility.

Coherence between outcomes and interventions

In a general analysis of linkage with ICF domains (table 5): five interventions are related to *Body Functions* and *Activity & Participation* and three are related to *Body Structures* and *Functions*. SBM was not linked to any category related with movement. Four outcome measures are related to *Body Functions* and *Activity & Participation;* one is related to *Body Structures* and *Functions*; three are solely related to *Body Structures* and two are solely related to *Activity & Participation.*

In a specific analysis of category coherence between interventions and outcome measures, we found in general a good relation on ICF dimensions. It seems also, that by the use of outcome measures on the activity dimension, researchers are looking for the impact of some interventions applied to body structures and functions on activity. A more detailed analysis is found on table 5.

Table 3. Interventions used in the included studies, descriptions and best evidence synthesis

	Aimed at the upper limb	
Strategy	**Description**	**Best evidence synthesis**
Proprioceptive Neuromuscular Facilitation for Trunk Stability (PNF-T) (35)	Rhythmic stabilizations and stabilizing reversal, stimulated by the manual contact of the PT, are stimulated on the trunk in sitting position.	Significant efficacy with upper-limb function and mobility related to stability - “indicative findings” supported by one low-quality RCT.
Bobath Therapy (BT) (26)	Handling facilitation for control of muscle tone and recruitment of arm activity in functional situations with various positions (i.e., lying, sitting, standing, walking, both with and without objects and during unilateral or bilateral tasks	No efficacy with function and activity of the upper limb - “limited evidence” supported by one high-quality RCT.
Passive mobilization and tactile stimulation (PMTS) (42)	Conjunction of strategies: massage, passive mobilization, acessory movements, compression and tactile stimulation on body parts.	No efficacy with function and activity of the upper limb - “limited evidence” supported by one high-quality RCT.
Slow-stroke back Massage (SSBM) (39)	Slow rhythmic stroking with the hands on the region of neck and shoulders, following specific steps.	Significant efficacy with shoulder pain relief - “limited evidence” supported by one high-quality RCT.
	Aimed at the upper limb	
Interventions	**Description**	**Best evidence synthesis**
Facilitation technique coupled with BWSTT (FT-BWSTT) (38)	Swinging and stance of the paretic leg were assisted using the FT or mechanically (control) during BWSTT.	No efficacy with gait parameters and walking functionality - “limited evidence” supported by one high-quality RCT.
Proprioceptive Neuromuscular Facilitation for Gait performance (PNF-G) (37)	The therapist held the leg above the ankle in the experimental group with one hand and the anterior medial region with the other hand. Then, the therapist issued an oral instruction saying, “Raise your ankle and bend your lower extremity over the diagonal line.” Throughout the movement, the therapist continuously applied resistance against the movement. The patient performed a walking	Significant efficacy with gait parameters and gait performance - “limited evidence” supported by one high-quality RCT.

	exercise on the ramp in opposition to the therapist's pressure.	
Conventional Physiotherapy with manual facilitation (CPT) (40)	Soft tissue mobilization, facilitation of muscle activity, facilitation of coordinated multijoint movement, tactile and proprioceptive input, resistive exercise, and functional retraining.	Significant efficacy with gait velocity and knee peak torque but no impact on gait functionality - "limited evidence" supported by one high-quality RCT.
Backward walking with facilitation technique (BWFT) (41)	First, the subject is asked to take a step backwards within parallel bars and the therapist provides assistance to move the subject's leg in the correct pattern; Secondly, as the movement components have been practised, and the subject has taken over actively with only slight help, the therapist facilitates walking backwards within parallel bars. Thirdly, the subject walks backwards actively away from the parallel bars.	Significant efficacy with gait parameters and gait performance - "limited evidence" supported by one high-quality RCT.

Aimed at both upper and lower limb

Strategy	**Description**	**Best evidence synthesis**
Passive range of motion exercises (ROM) (36)	Full ROM movements in six joints (shoulder, elbow, wrist, hip, knee and ankle) were included in the protocol, including flexion, extension, adduction, abduction, internal and external rotations, and dorsal and plantar flexions.	Significant efficacy with upper and lower-limb joints functions and pain but no impact on functional independence - "limited evidence" supported by one high-quality RCT.

Table 4. Outcome measures used in the included studies

Outcome Measures
Functional Reach Test (FRT) (35)
Electromiography (EMG) (35)
Functional Independence Measure (FIM) (36, 38)
Goniometer (GMT) (36)
Pain Scale (PS) (36)
Fugl-Meyer test (F-MT) (26, 38)
Action Research Arm Test (ARAT) (26, 42)
Motricity Index (MI) (42)
Visual Analogue Scale (VAS) (39)
Gait parameters (velocity, cadence, length, symmetry) (GP) (37, 38, 40, 41)
Functional Ambulatory Performance (FAP) (37)
Rivermed Index (RI) (40)
Knee Peak Torque (KPT) (40)

Discussion

As with the other systematic review of hands-on interventions for the upper limb (18), only a few studies were included due to methodological limitations related to the control group, performing different types of treatment and not being a placebo or no-treatment. Considering the findings on neuroplasticity , where new synapses are established and brain re-mapping is observed after stroke in chronic phases (6) it is possible that the usual avoidance to placebo or non-treatment control groups, can be minimized in further research, as patients have gains over a longer period. From the included studies, only two (ROM and SSBM) had a real control group with no intervention. The other 7 had a common intervention for both groups and an extra therapy to be tested on the experimental group. This option is controversial as the results can be attributed to the extra time involved (43, 44, 45). However, it may also be argued that improved results are somewhat dependent on the content of the therapy (26) and this is supported by the studies of BT (26) and FT-BWSTT (38), which show no efficacy.

Furthermore, the descriptions of interventions limited the number of studies for inclusion. This limitation also influenced the conclusiveness of our results, judged to be moderate, as they are based on single high-quality RCTs. This only goes to highlight the need for high-quality studies into hands-on approaches.

With regards to our results, ICF coherence is a complex issue that needs to be taken into account when devising interventions programs and research. If in some cases the lack of coherence between interventions and outcome measures might influence the lack of efficacy in results, which is the case of PMTS (42), in other cases, such as PNF-T (35), PNF-G (37) and ROM (36), it can help to elucidate the way in which these interventions may or may not have an impact on other categories.

The results of PMTS (42) with no efficacy on function and upper-limb activity, are consistent with the neuroplasticity theories that re-learning needs to be task-meaningful and active in all subjects (5, 6, 14). However, these results do not indicate that PMTS (42) is not applicable to stroke rehabilitation, only that the outcome measures need to be consistent with the intervention (46). The positive impact on activity and participation of PNF-T (35) and PNF-G (37) are interesting results given the background of PNF, initially developed for movement patterns of functional tasks with the active participation of the patient. Its non-meaningful tasks might be the reason for ROM's lack of impact on activity and participation (36).

Good levels of coherence were verified for the studies of BT (26), CPT (40), FT-BWSTT (38) and BWFT (41) which, in addition to the high PEDro scores, contributes to the validation of the results. The non-efficacy of BT (26) and FT-BWSTT (38) are according to the results of previous studies into the Bobath concept (47), probably justified by the patient's phase of learning requiring more dynamic approaches. The use of CPT (40) where facilitation techniques are also used shows efficacy with gait parameters but not with gait functionality, which reinforces what was said about the need for more dynamic approaches for functional results. The benefits of facilitation added to a more dynamic strategy like walking backwards might justify the efficacy of BWFT (41).

Curiously SSBM has no linkage with the selected ICF categories related to movement. However, the efficacy is important with regard to how frequent the shoulder pain occurs in stroke patients.

Despite ICF coherence and the high quality provided by the PEDro scores, the results call for cautious interpretation with regard to the absence of certain methodological internal validity items in all of the studies.

As explained in the methodology, the number of studies and the heterogeneity of interventions and outcome measures did not allow for a meta-analysis, diminishing the level of validity of the results and recommendations. However, this systematic review identifies the needs for research in this field and its methodological considerations. It also corroborates the opinion of several researchers (15, 48) and clinicians regarding the effects of physiotherapy as a “black box”, stressing the need for consistency between interventions and measurements and the understanding of interventions individually.

Most of the studies we found were published after 2000 and the ones selected for full-text reading were from after 2003. Interestingly, the most recent ones are also the ones with the greatest methodological quality, displaying knowledge of the latest research critics. There is, however, still room for improvement.

Limitations of this review

The major limitations of this systematic review are the following: the limited number of studies that describe the effectiveness of handling physiotherapy techniques and the sole use of peer-reviewed published studies, which had an impact on the number of studies we found; the heterogeneity of interventions and outcome measures did not allow for the pooling of meta-analysis and the possible phenomenon of extra therapy time and the eventual benefits of intense therapy (42, 43, 44) in seven of the studies.

Conclusions

The conclusions of this review are limited regarding the nine studies included with high level of heterogeneity, leading to recommendations of limited level of evidence.

Practical Implications

Recommendations with limited levels of evidence call for the use of the following: slow-stroke back massage for shoulder pain; ROM exercises for upper-limb and lower-limb structures and the functions of muscles and joints; PNF during gait step and walking backwards with hip facilitation for gait parameters and gait performance and conventional physiotherapy with facilitation techniques for gait parameters. Recommendations with indicative findings in favor of the use of PNF with trunk rhythmic stabilizations, for the function and mobility of the upper limb.

Recommendations with limited evidence for the non-efficacy of the use of Bobath Therapy for upper-limb functions and the activity and step facilitation during body weight support treadmill training for gait parameters and performance.

With regard to other interventions mentioned in the introduction as hands-on interventions, we did not find any eligible studies that dealt with them, and as such we are unable to make any recommendations concerning their use (or not).

Research Implications:

There is a need for RCTs that compare hands-on interventions with placebos, or with no treatment at all, or treatment in both groups with the addition of some other intervention in the experimental group. In addition, research on different post-stroke phases is relevant in order to specify the benefits of each intervention. The use of ICF categories to ensure consistency between interventions and outcome measures would also make a contribution to the specification of each intervention. After attaining clear findings concerning individual intervention efficacy, research on comparisons, mixed interventions and efficiency studies would be core to analyzing the economical and societal impact of each intervention.

Acknowledgements

We would like to thank Professor Roland van Peppen, Program manager at the University of Applied Sciences Utrecht - The Hague Area, Netherlands, for his guidance and support during the development of our study and paper.

Conflict of interest and funding

The authors have declared that there are no potential conflicts of interest with respect to the authorship and/or publication of this article.

This study had no funding resources.

Table 5. Hands on interventions identified and respective outcome measures and link with ICF categories

Intervention	ICF link to the intervention			ICF link to the outcome measure			Outcome measures	Coherence
	Structure	Function	Activity & Participation	Structure	Function	Activity & Participation		
Proprioceptive Neuromuscular Facilitation (PNF-T) trunk exercises (35)	-	b260 b715 b730 b735 b740	d415	-	b710 b730 b760	d440 d445	Functional Reach Test	Good relation on the domains of body function and activity. However, intervention is centered on trunk function and control and the outcome measures focus on the function and activity of upper limb mobility.
					b730		EMG (soleus, hamstrings, quadriceps, tibialis anterior)	
Range Of Motion (ROM) exercises (36)	s730 s750	b710	-	-	-	d420 d450 d460 d510 d520 d530 d540 d550 d630 d640 d910 d920	FIM (ADL sub-scale)	Intervention centered on the domain of body structures and functions, related with mobility of the limbs. The outcomes measures comprise these domains and specific categories but also look on the sensation of pain and on impact on activities: mobility, self-care, domestic life and community, social and civic life.
				s730 s750	b710	-	Goniometer	
					b280	-	Pain scale of 3 ratings	

Bobath therapy for upper limb function (BT) (26)	-	b260 b265 b710 b715 b730 b760 b770	d410 d415 d420 d430 d435 d440 d445 d450 d455 d510 d520 d530 d540 d550 d560	- -	b260 b265 b280 b710 b715 b730 b780 b710 b730 b760	d415 d440 d445	Fugl-Meyer test ARAT	Good relation on the domains and categories on the body functions, centered on proprioceptive and touch, mobility, stability and control of voluntary movements. The domain of Activity is wider for the intervention when compared with the outcome measure, aiming for integration of upper limb on specific activities of mobility and self-care.
Mobilization and Tactile Stimulation (PMTS) on upper limb function (42)	s730 s750	b265 b710 b735	-	- -	b730 b710 b730 b760	- d440 d445	Motricity index ARAT	Intervention centered on the domain of Body structures of upper limb and functions of touch, mobility and muscle tone. The outcome measures differ on the categories of the body functions, focused on muscle power and control of voluntary movements; have no structures and look for the impact on the domain of activity of upper limb mobility.
Slow-stroke back massage (SSBM) (39)	-	-	-	-	b280	-	VAS	Intervention has no codification on the selected categories related with movement. Outcome measures related with movement are only on the domain of body functions and the category of pain.
Facilitation technique coupled with treadmill (FT-BWSTT) (38)	-	b260 b265 b760 b770	d450	-	-	d420 d450 d460 d510	FIM	Intervention is centered on body functions related with proprioception and control of movement and activity of walking. The outcome measures, assess these categories and

						d520 d530 d540 d550 d630 d640 d910 d920		also activities where walking is integrated related with mobility, self-care, domestic life and community, social and civic life.
				-	b260 b265 b280 b710 b715 b730 b780	d415	Fugl-Meyer	
				-	b770	d450	Gait velocity	
				-	b770	d450	Gait cadence	
PNF-based exercise for gait (PNF-G) (37)	-	b260 b730 b735 b740	-	-	b770	d450	Gait temporal parameters (velocity, phase time)	No direct relation between the intervention and the outcome measures. Intervention is centered on the domain of functions of muscles and outcomes measures are focused on gait pattern functions and activity of walking.
				-	b770	d450	Gait spatial parameters (step length)	
				-	-	d450	FAP	
Conventional Physical Therapy (CPT) (40)	-	b260 b265	d410 d415	-	-	d410 d420	Rivermed index	Intervention is centered on body functions related with proprioception, muscle and control of

		b710	d420			d450		movement and on activities related with mobility,
		b715	d430			d455		self-care and domestic life.
		b730	d435			d460		Outcome measures are centered on gait pattern
		b735	d440			d510		functions and activities related with mobility only.
		b760	d445					
			d450	-	b770	d450	Gait velocity	
			d455					
			d510	-	b770	d450	Gait cadence	
			d520					
			d530	-	b770	d450	Step length	
			d540					
			d550	-	b770	-	Knee peak torque	
			d560					
Backward walking with facilitation technique (BWTFT) (41)	-	b260 b265 b760 b770 b780	d450	- - -	b770 b770 b770	d450 d450 -	Gait velocity Step length Symmetry index	Good relation between intervention and outcome measures. Intervention is centered on body functions related with proprioception, muscle, control of movement and gait pattern functions, and with walking activity. Outcome measures focus on gait pattern functions and walking activity.

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Appendix 1 - Final search expression

PUBMED, EMBASE and CENTRAL

(Stroke OR “Cerebrovascular accident” OR “Cerebrovascular disorders” OR CVA) AND (“Physical therapy” OR Physiotherapy OR “Physiotherapy modalities” OR “Bobath concept” OR “Carr and Shepherd” OR “Neurodevelopmental approach” OR “Motor relearning” OR “Proprioceptive neuromuscular facilitation” OR “Neuromuscular facilitation” OR “Aquatic therapy” OR “Hydrotherapy” OR Mobilization “Manipulation” OR Massage) AND (“Proprioceptive function” OR Proprioception OR “Sense of Touch” OR “Tactile Sense” OR Taction OR Handling OR Manipulation OR Feel OR Sensation OR “Sensory Function” OR Sensibility OR Feeling OR Pain OR Analgesia OR Hyperalgesia OR Joints OR Stability OR Instability OR Laxity OR Hypermobility OR Muscle OR Strength OR Power OR Weakness OR Lack OR Flexibility OR “Muscle Hypertonia” OR Hypertonicity OR Spasticity OR “Muscle tone increase” OR “Muscle tonus” OR “Muscle Hypotonia” OR Hypotony OR Flaccidity OR “Muscle tone poor” OR “Decreased Muscle Tone” OR Tone OR Hypotonia OR Hypotonic OR Flaccid OR “Involuntary Movements” OR Control OR Manipulate OR Harmony OR Gait OR Walking OR Locomotion OR Balance OR Speed OR Instability OR Imbalance OR Move OR Mobility OR Equilibrium OR Transfer OR Shift OR Move OR Lifting OR Raise OR Carrying OR Bear OR Transport OR “Fine hand use” OR Writing OR “Operating tools” OR Manipulate OR Grasp OR Reach OR Dexterity OR Moving OR Driving OR “Task Performance” OR “Acquiring skills” OR Perform OR Task OR Exercise OR Writing OR Dexterity OR “Carrying out daily routine” OR “Daily life activities” OR “Activities of Daily Living” OR “Domestic life” OR “Acquisition of goods and services” OR “Preparing meals” OR Meal OR “Meal Time” OR Housekeeping OR Housework OR Self care OR Washing OR Wash up OR Hygiene OR Bathing OR “Caring for body parts” OR Toileting OR Dressing OR Eating OR Feeding OR Food Intake OR Ingestion OR “Community life” OR “Social life” OR Recreation OR Leisure OR Work OR Hobbies).

PEDro

Subdiscipline: Neurology

Method: Clinical trial

Combination of each Therapy with each Problem (available on PEDro database):

- Therapy: Hydrotherapy and Neurodevelopmental Therapy and Skill training and Strenght training and Stretching
- Problem: Motor incoordination and Muscle shortening and Muscle weakness and Reduced exercise tolerance and Reduced work and Pain

Annex 1 Criteria list best evidence synthesis

Best-evidence synthesis

Strong evidence:	provided by consistent, statistically significant findings in outcome measures in at least two high quality RCTs*
Moderate evidence:	provided by consistent, statistically significant findings in outcome measures in at least one high quality RCT and at least one low quality RCT or high quality CCT*
Limited evidence:	provided by statistically significant findings in outcome measures in at least one high quality RCT*
or:	provided by consistent, statistically significant findings in outcome measures in at least two high quality CCTs* (in the absence of high quality RCTs)
Indicative findings:	provided by statistically significant findings in outcome and/or process measures in at least one high quality CCT or low quality RCT* (in the absence of high quality RCTs)
or:	provided by consistent, statistically significant findings in outcome and/or process measures in at least two ODs with sufficient quality (in absence of RCTs and CCTs)*
No or insufficient evidence:	in the case that results of eligible studies do not meet the criteria for one of the above stated levels of evidence
or:	in the case of conflicting (statistically significant positive and statistically significant negative) results among RCTs and CCTs
or:	in the case of no eligible studies

Best-evidence synthesis. *If the number of studies that show evidence is <50% of the total number of studies found within the same category of methodological quality and study design (RCTs, CCTs, or ODs), we will state no evidence.

Retrieved from: Steultjens EM, Dekker J, Bouter LM, van de Nes JC, Cup EH, van den Ende CH. Occupational Therapy for Stroke Patients A Systematic Review. Stroke. 2003; 34:676-687 (31).

Physiotherapy Interventions and Brain Activity on Stroke: Systematic Review

Authors:

1. Patrícia Maria Duarte de Almeida, MSc, PT, Alcoitão School of Health Sciences, Portugal; Institute of Health Sciences - Catholic University of Portugal, Portugal, patriciamdalmeida@gmail.com
2. Ana Florinda Granada Simões, BSc, PT, Alcoitão School of Health Sciences, Portugal; ana_florinda_9@hotmail.com
3. António Pedro Lóio Oliveira, BSc, PT, Alcoitão School of Health Sciences, Portugal; antonioloio@hotmail.com
4. Joana de Sousa Alves, BSc, PT, Alcoitão School of Health Sciences, Portugal; joanadesousaalves@gmail.com
5. Joana Filipa de Brito Beleza, BSc, PT, Alcoitão School of Health Sciences, Portugal; joanna.beleza@gmail.com
6. Mariana Travassos Manaças de Almeida Batista, BSc, PT, Alcoitão School of Health Sciences, Portugal; mariana.tmbatista@gmail.com
7. Alexandre Castro Caldas, PhD, Institute of Health Sciences - Catholic University of Portugal, Portugal, acastrocaldas@ics.lisboa.ucp.pt

Correspondence (for review):

Name	Patrícia Maria Duarte de Almeida
Department	Physiotherapy
Institution	Alcoitão School of Health Sciences,
Country	Portugal
Tel	00351214607450
Mob	00351 916102233
Fax	00351214607459
Email	patriciamdalmeida@gmail.com

Correspondence (for publication)

Name	Patrícia Maria Duarte de Almeida
Department	Physiotherapy
Institution	Alcoitão School of Health Sciences,
Country	Portugal
Email	patriciamdalmeida@gmail.com

Abbreviated title: PIBAS - SR

Key words: stroke, physiotherapy, brain activity

Word Count: 225 words (Abstract)

2539 words (Introduction, Method, Results, Discussion)

References: 37

Tables: 2

Boxes: 1

Ethics approval: No ethics approval needed regarding the non experiments or involvement of subjects to be analysed.

Source(s) of support: This study has no funding resources.

Acknowledgements: We would like to thank to Professor Roland van Peppen, Programme Manager at the University of Applied Sciences Utrecht, The Hague Area, Netherlands, for his guidance and support during the development of our study and paper.

Competing interests: The authors declared no potential conflicts of interest with respect to the authorship and/or publication of this article.

Submission to Journal of Physiohterapy - JPHYS-D-15-00086

http://www.journals.elsevier.com/journal-of-physiotherapy/

ABSTRACT

Question: Scientific knowledge in the area of rehabilitation and physiotherapy (PT) for stroke is booming and leading to more sustainable models of practice. Several interventions show positive effects with strong scientific support, however, the effects on brain activity remains unclear. The objective is to analyze the impact of physiotherapy on the brain activity of stroke patients. **Design**: Systematic review of published RCT in PubMed, CENTRAL, PEDro and EMBASE, since 2006: **Participants**: stroke, humans, >18 years, **Intervention**: any physiotherapy technique **Outcome measures**: outcomes related to brain activity. **Results**: Seven studies were included, evaluating 148 participants in different post-stroke stages. Heterogeneity of interventions and outcome measures only permitted a best-evidence synthesis. Limited evidence was found for strategies that require the involvement of the patient and goal-orientated interventions such assistance with robotics for the realization of computer tasks, mirror therapy, mental imagery for upper limb tasks and treadmill training for gait improvement with positive impact on brain activity. There are growing benefits from areas of activation both on the ipsilesional and the contralesional hemisphere; decreases in thresholds of excitability of synapses and increase in the metabolism of cerebral glucose. These findings are verified in motor, somatosensorial and sub-cortical areas. **Conclusions**: Despite the limitations regarding the inclusion of only seven studies with high level of heterogeneity, this review concludes with that physiotherapy has a positive impact on brain activity.

INTRODUCTION

Stroke represent the main cause of disability worldwide and are responsible for about 5.5 million deaths per year.[1,2] The major consequences are functional limitations of upper limb[3] and gait performance.[4] Several forms of intervention have been developed in order to minimize these consequences. However, their neurobiological support and understanding is limited.[5] A successful intervention can influence movement organization at brain level, depending on the experience of meaningful tasks.[6] Neuroplasticity after lesion can be modulated by the correct input,[7] where physiotherapy can play an important role. Consequently, research on rehabilitation and neurological conditions is increasing[8,9,10] in terms of both human autonomy and brain reorganization.

Studies showed that after motor training, mental imagery[11] or constraint-induced[12] therapy, electrical changes occur at the cortical level and the areas of activation increase in both the contra and the ipsilesional brain. In spite of these findings, some authors also refer to spontaneous reorganization in the first few months after the stroke[13]. This puts the efficacy of interventions in perspective and emphasises the need for more research in this field.

Most intervention studies focus on areas related to bodily functions, specifically the categories of movement, activity and participation. These outcome measures are more easily accessible in relative terms. The improvement of neuroimage, metabolic and electrical analysis instruments allows the neuronal reorganization during interventions to be monitored,[14,15,16] affording the possibility of new information about the neurobiological effects of interventions and the way in which they are related to other outcomes.

Regarding the neurobiological support and understanding of PT on neurorehabilitation and the advances of instruments to analyze brain activity, the research question of this systematic review is to know the impact of physiotherapy on the brain activity of stroke patients.

METHOD

Identification and selection of studies

A systematic literature search was conducted, aiming for peer-reviewed published Randomized Controlled Trials (RCTs) on the 4 most relevant databases for physiotherapy:[17] PubMed, CENTRAL, PEDro and EMBASE. A bibliography list analysis was performed on the articles selected for full text reading.

The construction of the search expression (Appendix 1), was based on the PICO question relating to stroke patients at any phase[19], physiotherapy interventions and outcome measures related to brain activity. The same expression was applied to the PubMed, CENTRAL and EMBASE databases without any limits insertion. A specific search expression was created according to the search options of the PEDro database.

Inclusion and exclusion criteria

In order to be included in this review, studies had to meet the criteria presented on box 1. RCTs (randomized controlled trials) are the only accurate way of determining a cause-effect relation between a treatment and its outcomes, as they guarantee the internal validity of studies and randomization without any influence from the research team or the subjects[20] the reason why only RCT are included. Regarding the control group most of the studies are providing information about the effectiveness of one intervention compared to another. This methodology does not provide information about the effectiveness of the specific intervention.[21] In order to prove effectiveness, an intervention should be compared to a placebo, or to no treatment. The latter case raises ethical questions and is therefore rarely used. Given the opinion and results of several studies that show evidence that extra time in therapy does not always lead to better results, but rather that these are dependent on the content of the therapy,[22] we included studies where both groups receive the same treatment (equal conditions) and the experimental group receives an extra treatment. This way the control group will be considered as receiving no treatment.

Studies were excluded from this review if they did not investigate humans, if patients had a previous neurological incident, or involved patients with dementia and cognitive disorders.

After running the articles through the citation manager EndNote® X5, where duplicates were eliminated automatically, two reviewers independently:

- Selected the articles by title and abstract, according to the selection criteria
- Selected the articles by full text reading, according to the selection criteria

Box 1 Inclusion criteria

Design
- Randomised controlled trial

Participants
- Adults ≥ 18 years old
- Stroke

Intervention
- Any physiotherapy intervention

Outcome measures
- magnetic resonance imaging (MRI),
- electroencephalography (EEG),
- magnetoencefalography (MEG),
- transcranial magnetic stimulation (TMS),
- tomography emission-computed single photon (SPECT),
- positron emission tomography (PET), positron emission tomography imaging (PETI),
- spectroscopy near infrared (NIRS),
- near infrared imaging (NIR),
- transcranial doppler brain (TCD) and
- ultrasonography doppler transcranial (uTCD)

Comparisons
- Control group characterized by the use of a placebo, No intervention or experiments where both groups have a common intervention and the experimental group has an additional intervention are to be tested

Assessment of characteristics of the studies

The valued characteristics of the studies were the type of intervention and its impact on brain activity. Also a correlation of brain activity improvement with secondary outcomes was analyzed.

Methodological quality analysis was performed by the use of Physiotherapy Evidence Database (PEDro) scale. The reviewers independently scored the studies, not using the database scores. A cut-off score for inclusion was not used and all the studies were analyzed on their own merits and their individual contributions interpreted.

In all the phases, panel consensus with the presence of a 3rd element (PA) was used to clarify doubts and validate decisions.

Data Analysis

The data was extracted, with the following organization:

- Qualitative features: study identification, PEDro score, not accomplished items (PEDro) and direction of results (positive or negative in relation to the experimental group, or no differences).
- Clinical features: N subjects, N control, N experimental, average age, stroke type, time since stroke, control approach, tested approach, length of treatment and duration per session.
- Statistical features: baseline scores/events, final score/events, mean difference of scores/events and standard deviation.

Given the clinical and statistical features as determinant for homogeneity among studies, a quantitative analysis (meta-analysis) was not possible. The difficulty in comparing the wide diversity of interventions did not permit it.[23]

A best-evidence synthesis[24] was then applied, taking the PEDro score and the amount of studies with the same characteristics and variables [25, 26]. The results were classified on the basis of on their level of evidence as follows: (1) strong, (2) moderate, (3) limited evidence, (4) indicative findings, (5) no or insufficient evidence.[26]. Detailed information for the levels of evidence can be found on the annex 1. RCTs were classified as high quality when their PEDro scores where above 4[26].

RESULTS

Flow of studies

Due to technical problems and difficulties with the search expression, the PEDro database was ruled out. After searching the other databases, 276 trials were identified (EMBASE = 12; CENTRAL = 63; PUBMED = 201), which decreased to 244 after automatic duplicate elimination by Endnote. After the first selection phases, 107 were included for full text reading. Seven studies[27,28,29,30,31,32,33] were included in this systematic review (Figure 1).

The most common reasons for exclusion during full text reading were as follows: a type of study that was different from RCTs (n=46); the intervention of the control group (n=9); non-existence of brain activity analysis (n=5); and a lack of physiotherapy-based intervention (n=2).

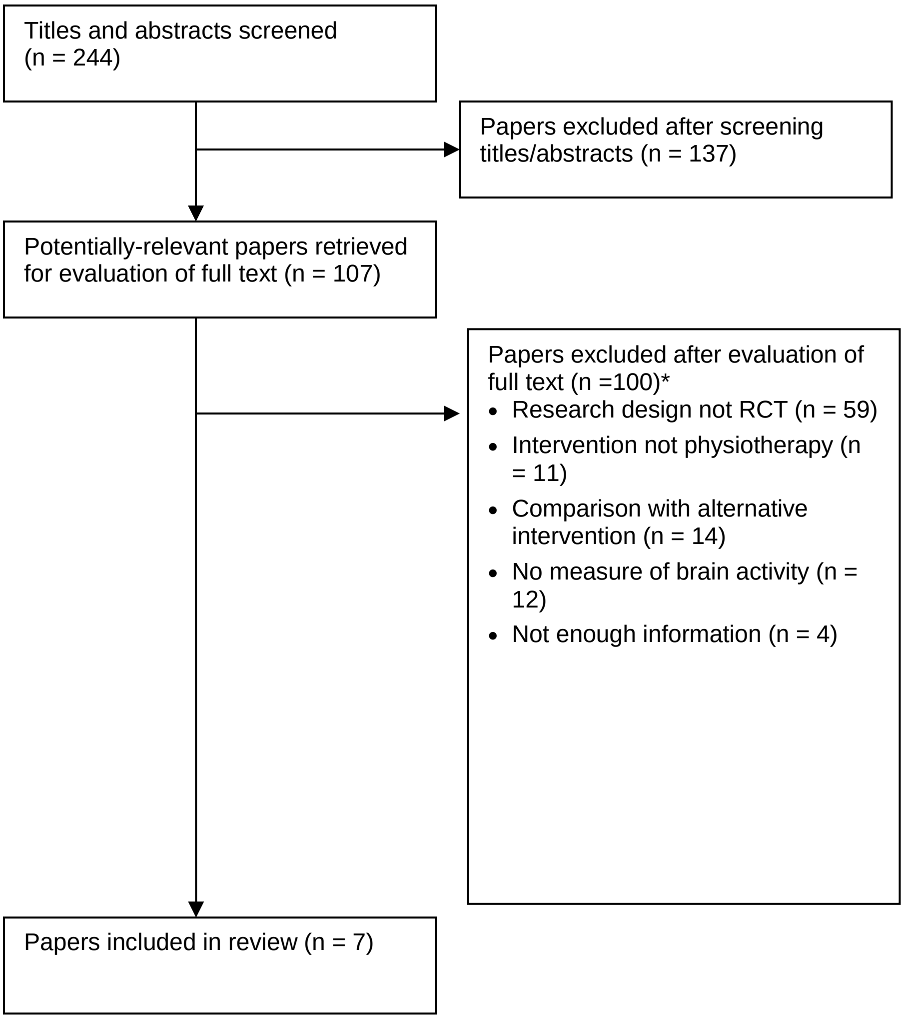

Figure 1. Flow of studies through the review. * Papers may have been excluded for failing to meet more than one inclusion criteria.

Characteristics of the studies

In total, these seven studies evaluated 148 participants (mean age = 57.5 years) in different post-stroke stages; 77 participants were assigned to an experimental group (17 for lower limb experiments and 60 for upper limb experiments).

For the studies related to upper limb recovery, the time of intervention ranged from 2 weeks to 6 weeks, while the frequency varied between 3 times a week and every day of every week. Table 1 shows the main characteristics of the studies included. The studies related to lower limb recovery showed a time of intervention of 4 weeks, with a frequency of every day per week. Table 2 shows the main characteristics of the studies included.

Study	Objective study	Participants (E/C)	Mean age (E/C)	Mean months stroke (E/C)	Intervention - E	Intervention - C	Protocol period (weeks)	Outcome measures	Results/Conclusions
Dechaumont-Palacin at al 2008	The aim of the study was to characterize the impact of 4 weeks of passive proprioceptive training of the wrist on brain sensorimotor activation after stroke.	13(7/6)	58/64	<1/<1	Bobath Therapy + Proprioception passive trainning (20 min)	Bobath Therapy	5 times a week / 4 weeks	fMRI NIH Stroke Scale barthel Index Motricity Index Score Dynamometer	Standard rehabilitation along with natural recovery mainly led to increases in ipsilesional activation and decreases in contralesional activation. On the contrary, standard rehabilitation and paretic wrist proprioceptive training increased contralesional activation. Proprioceptive training produced change in the supplementary motor area (SMA), pre-frontal cortex, and a contralesional network including inferior parietal cortex (lower part of BA 40), secondary sensory cortex, and ventral premotor cortex (PMv). No Significant results for the other outcome measures.

Study	Objective study	Participants (E/C)	Mean age (E/C)	Mean months stroke (E/C)	Intervention - E	Intervention - C	Protocol period (weeks)	Outcome measures	Results/Conclusions
Hong et al 2012	The aim of this study was to investigate whether MITEMG improved paretic extremity motor function. We also tested whether the intervention induced cortical reorganization in patients with chronic stroke through brain.	14 (7/7)[3]	53,43/51,29	29,71/31,71	Electrical stimulation + Mental imagery (20 min)	Electrical Stimulation	5 times a week / 4 weeks	Positron Emission Tomography Motor Activity Log Modified Barthel Index Modified Ashworth Scale	The mental imagery training combined with electromyogram-triggered electric stimulation group showed significantly increased metabolism in the contralesional supplementary motor, precentral, and postcentral gyri (P uncorrected0.001) after the intervention, but the functional electric stimulation group showed no significant differences. Significant improvements in the upper extremity component of the Fugl-Meyer Motor Assessment
Michielen et al 2010	To evaluate for any clinical effects of home-based mirror therapy and subsequent cortical reorganization in patients with chronic stroke with moderate upper extremity paresis	40 (20/20)[3]	55,3/58,7	56,4/54	Bimanual exercises + Mirror Therapy	Bimanual exercises	5 times a week / 6 weeks	fMRI Fugl-Meyer test ARAT Tardieu Scale Visual Analogue Scale Abilhand Questionnaire Stroke ULAM EuroQol EQ-5D	fMRI results showed a shift in activation balance within the primary motor cortex toward the affected hemisphere in the mirror group only (weighted laterality index difference 0.40 ± 0.39, P < .05). FMA improved more in the mirror than in the control group (3.6 ± 1.5, P < .05)

Study	Objective study	Participants (E/C)	Mean age (E/C)	Mean months stroke (E/C)	Intervention - E	Intervention - C	Protocol period (weeks)	Outcome measures	Results/Conclusions
Takahashi et al 2008	The goal of this study is to determine the efficacy of robot assistance for hand activities.	13 (6/7)	67,3/58,6	54/14,4	Active Robot assistance during hand activities (computer games) during 15 days	Non Active Robot assistance during hand activities (computer games) during 7,5 days + Active Robot assistance during hand activities (computer games) during 7,5 days	15 days during 3 weeks	fMRI Fugl-Meyer Assessment - arm Action Research Arm Test Stroke Impact Scale Goniometer Dynamometer Box/Blocks test Electromiography Notthingam Sensoru Assessment NIH Stroke Scale Geriatric Depression Scale Peg Test Modified Ashworth Scale	Results suggest greater gains for subjects receiving robotic assistance in all sessions as compared to those receiving robotic assistance in half of sessions. Significant efficacy on the increase of ispsilesional brain activity at the primary somatosensorial cortex
Gauthier et al 2008	To investigate the effects of a transfer package added to constraint induced therapy, on brain activity and activities of daily life.	36 (20/16)	63,3	43,2	Constraint induced movement therapy + transfer package to daily life activities (30 min)	Constraint induced movement therapy (2,5 hours)	3 hours/10 consecutive days	fMRI Motor Activity Log Wolf Motor Test	Experimental group exhibited far greater improvement in use of the more affected arm in the life situation than the comparison therapy group. Structural brain changes paralleled these improvements in spontaneous use of the more impaired arm for activities of daily living. There were

									profuse increases in gray matter in sensory and motor areas both contralateral and ipsilateral to the affected arm that were bilaterally symmetrical, as well as bilaterally in the hippocampus. In contrast, the comparison therapy group failed to show gray matter increases. Importantly, the magnitude of the observed gray matter increases was significantly correlated with amount of improvement in real-world arm use.
Yang et al 2010	To investigate corticomotor changes induced by body weight–supported treadmill training (BWSTT) in patients with short or long poststroke duration.	18 Short duration of stroke (5/4) Long duration of stroke (5/4)	Short duration of stroke (56,8/61, 8) Long duration of stroke (57,5/48, 1)	Short duration of stroke (4/4) Long duration of stroke (24/36)	Exercise programe (20 min) + BWSST (30 min)	Exercise programe (50 min)	3 days week/4 weeks	TMS (Transcranial magnetic stimulation) Fugl-Meyer Assessment	The 4-week BWSTT resulted in a decrease of motor threshold and an increase of map size in subjects with hemiparesis of short duration, whereas only the expansion of the map size was noted in subjects with hemiparesis of long duration. Improvement of motor control occurred in subjects with hemiparesis of both short and long duration after BWSTT.

Study	Objective study	Participants (E/C)	Mean age (E/C)	Mean months stroke (E/C)	Intervention - E	Intervention - C	Protocol period (weeks)	Outcome measures	Results/Conclusions
Yen et al 2008	To investigate the effects of additional gait training on motor performance and corticomotor excitability and to demonstrate the relationship between motor improvement and corticomotor excitability change in patients with chronic stroke.	14 (7/7)	57,30/56, 05	24/24	Exercise programe (50 min) + BWSST (30 min)	Exercise programe (50 min)	3 days week/4 weeks	TMS (Transcranial magnetic stimulation) Berg Scale GAITRite System for gait parameters	After general physical therapy, we noted that the patients showed an improvement only in walking speed and cadence, and there were no significant changes in corticomotor excitability. After additional gait training, participants improved significantly on BBS score, walking speed, and step length. Moreover, the motor threshold for TA decreased significantly in the unaffected hemisphere. The map size for TA was increased in both hemispheres, whereas that for AH was increased only in the affected hemisphere.

E = experimental group, C = control group

Table 2. PEDro scores of included studies.

Study	Random allocation	Concealed allocation	Groups similar at baseline	Participant blinding	Therapist blinding	Assessor blinding	< 15% dropouts	Intention -to-treat analysis	Between-group difference reported	Point estimate and variability reported	Total (0 to 10)
Dechaumont-Palacin et al, 2008	Y	N	Y	N	N	N	N	Y	Y	N	4
Gauthier et al, 2008	Y	N	N	N	N	N	Y	N	Y	Y	4
Hong et al, 2012	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Michielsen et al, 2010	Y	Y	Y	N	N	Y	N	Y	Y	Y	7
Takahashi et al, 2008	N	N	Y	N	N	N	Y	Y	Y	Y	5
Yang et al, 2010	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Yen et al, 2008	Y	Y	Y	N	N	N	Y	Y	Y	Y	7

Interventions and outcomes

Six interventions, three primary outcomes related to brain activity and 23 secondary outcome measures related to movement and functionality were identified:

Interventions

- Directed at upper limb
  - Proprioceptive passive training (PST)[27]
  - Mental imagery (MI)[28]
  - Mirror therapy (MT)[29]
  - Robotics[30]
  - Constraint-induced movement therapy transfer package (CMIT)[31]
- Directed at lower limb
  - Treadmill training with body weight support (TTBWS)[32,33]

Outcome Measures

- Primary outcomes
  - Functional magnetic resonance (fMRI)[27,29,30,31]
  - Positron emission tomography (PET)[28]
  - Transmagnetic stimulation (TMS)[32,33]
- Secondary outcomes
  - Barthel index (BI)[27,28]
  - Motricity index (MI)[27]
  - NIH stroke scale (NIHSS)[27]
  - Dynamometer[27,29,30]
  - Motor activity log (MAL)[28,31]
  - Modified Ashworth scale (MAS)[28,30]
  - Fugl-Meyer assessment (FMA)[28,29,30,32]
  - Tardieu scale (TS)[29]
  - Visual analogue scale (VAS)[29]
  - Action research arm test (ARAT)[29,30]
  - Abilhand questionnaire (AQ)[29]
  - Stroke ULAM (SULAM)[29]
  - EuroQol health questionnaire (EQ-5D)[29]
  - Stroke impact scale (SIS)[30]

- Goniometer (Gn)[30]
- Box&Blocks test (B&BT)[30]
- Electromiography (EMG)[30]
- Nothingham sensory assessment (NSA)[30]
- Geriatric depression scale (GDS)[30]
- Peg test (PT)[30]
- Wolf motor test (WMT)[31]
- Berg scale (BS)[32,33]
- GAITRite System for Gait Parameters (GAITRite-GP)[33]

Methodological quality assessment

The PEDro scores give a mean of 6.1, with two studies[27,31] scoring < 5 and the other 5 studies[28,29,30,32,33] ranging from 5 to 8 (see Table 2).

All the studies have issues with blinding: in none of them were the subjects and therapists blinded regarding the treatment allocation; in four[27,30,31,33] the additional blinding of the assessor did not occur.

Three studies[27,30,31] did not use concealed allocation on randomization; two studies[29,30] had less than 85% of measures of at least one key outcome, of the subjects initially allocated to groups; and in one study[31] not all subjects for whom outcome measures were available received the treatment or control condition as allocated or used the "intention to treat" method, while one study[27] did not present variability values.

All of the studies have a small sample size.

Best-evidence synthesis

- Directed at an upper limb
  - Proprioceptive passive training (PST)[27] – significant efficacy in terms of the increase of the ipsilesional pre-frontal cortex and the contra-lateral ventral pre-frontal cortex, and primary and secondary somatosensorial cortices on fMRI. No significant efficacy was found in relation to the secondary outcome measures – "indicative findings" supported by one low-quality RCT.

- Mental imagery (MI)[28] – significant efficacy in terms of the increase of the metabolism of cerebral glucose in the ipsilesional supplementary motor, motor and somatosensorial areas on PET scan. Also, significant efficacy on the FMA scores for upper limbs; "limited evidence" supported by one high-quality RCT.
- Mirror therapy (MT)[29] – significant efficacy in terms of the increase of bilateral brain activity at the primary motor cortex on fMRI. Also, significant efficacy in relation to the FMA – "limited evidence" supported by one high-quality RCT.
- Robotics[30] – significant efficacy in terms of the increase of ispsilesional brain activity at the primary somatosensorial cortex on fMRI. Also, significant efficacy in relation to the FMA – "limited evidence" supported by one high-quality RCT.
- Constraint-induced movement therapy transfer package (CMIT)[31] – significant efficacy in terms of the increase of bilateral brain activity at the motor and somatosensorial areas and hippocampus, and the ipsilateral supplementary motor area on fMRI. Also, significant efficacy in relation to the MAL scores for movement quality – "indicative findings" supported by one low-quality RCT.

- Directed at an lower limb
    - Treadmill training with body weight support (TTBWS)[32,33] shows significant efficacy in terms of increases on ipsilesional brain map representation of the big toe in both studies on TMS. Also, significant efficacy in relation to the FMA and BS scores – "strong evidence" supported by two high-quality RCTs.

DISCUSSION

After an initial find of 244 articles, the number of studies included is satisfactory. However, this number is not enough for a high level of recommendations and the conclusions lack power. We have no comparison with previous systematic reviews on the topic, but the results with only a few studies included are similar to other studies in the field of physiotherapy interventions[34]. We mainly attribute the reduced amount of studies to the rigorous inclusion criteria related with the comparison group[21]. Aware of this risk, the methodological option was kept to guarantee the inclusion of only valid RCTs for efficacy of a strategy[21,23].

Researchers should promote research of commonly used rehabilitation techniques, and conduct better RCTs and consequently systematic reviews.

The results relating to the extent of effects of PT on brain activity for patients with stroke (even with limited evidence) supports the models of practice based on the assumption that functional outcomes of physiotherapy (movement and autonomy), already scientifically proven[35] are related to brain reorganization[27,28,29,30,31,32,33,36,37,38]. This relation leans of the fact that recovery depends on brain reorganization[6] and brain reorganization depends on the stimulus[7]. What the interventions used in the selected articles have in common is that they focus on the patient and goal-orientated interventions like assistance with robotics for the realization of computer tasks, mirror therapy, mental imagery for upper limb tasks and treadmill training for gait improvement. Their positive impact on brain activity corroborate the learning theories regarding experience-dependent learning, motivation and meaningful tasks for long term potentiation of neuroplasticity[37,38,39] and validate the importance of specialized physiotherapy.

The benefits are the increase of areas of activation on the ipsilesional and the contralesional hemisphere; decreases in thresholds of excitability of synapses and increase of the metabolism of cerebral glucose. These findings are verified on motor, somatosensorial and sub-cortical areas. These results are of importance for physiotherapists, rehabilitation teams and researchers to better plan treatment programs and develop specific researches.

Other approaches might also be effective for brain activity, but they were not included in our analysis due to the specific criteria aimed at finding high quality studies. This exclusion of much-used interventions in physiotherapy should be critically debated in the scientific community. RCTs are the standard for intervention research methodology. Apparently this methodology is hard to implement for these interventions, making it difficult to develop scientific evidence for mainstream physiotherapy interventions in stroke cases.

This systematic review reveals a need for more research towards high-level evidence for the effect of physiotherapy interventions on brain activation. Also a need for scientific reflection on RCT methodologies for stroke patients seems to be urgent in order to make it possible or adequate to the complexity of this population.

Limitations of this review

The major limitation of this systematic review is the fact that there are very few studies that describe the effectiveness of physiotherapy interventions, and the RCTs included were heterogeneous when it came to interventions, outcome measures and results, which prevented a meta-analysis. The quality of studies was compromised. The consistency of some results was compromised by the quality of the studies and the fact that in 4 of the studies the results can be influenced by extra therapy time, in view of the ultimate benefits of intense therapy.

The search method did not include other article resources such as other databases, finding manuals and consulting reference lists, which may affect the number of found studies.

Despite the limitations regarding the inclusion of only seven studies with high level of heterogeneity, this review concludes with that physiotherapy has a positive impact on brain activity.

Implications for Practice: Recommendations with indicative findings for the use of proprioceptive passive training (PST) and the constraint-induced movement therapy transfer package (CMIT) for upper limb rehabilitation; recommendations with limited evidence for the use of mental imagery (MI), mirror therapy (MT) and robotics for upper limb rehabilitation; and recommendations with strong evidence for the use of treadmill training with body weight support (TTBWS). Moreover, the other interventions mentioned in the introduction have no or insufficient research evidence as we did not find any eligible studies. Consequently, we cannot make any recommendations for the use or non-use of them.

Research Implications: We consider that further studies should be carried out, specifically RCTs comparing interventions with placebos, or no treatment, or treatment in both groups with the addition of some other intervention in the experimental group. These studies should be performed during different post-stroke stages, and focused on the wide range of interventions used in physiotherapy.

Alongside the RCT, an economic evaluation should be conducted to determine the economical and societal impact of the intervention.

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APPENDIX 1: SEARCH STRATEGY

Databases: MEDLINE, EMBASE, CENTRAL

The search of MEDLINE, EMBASE and CENTRAL databases was optimised by using the MESH terms and using the terms used in previous reviews and books of the speciality for the intervention (physiotherapy) and outcomes (brain activity).

Common terms	Mesh Terms	Other Terms
Patients		
• Stroke	Stroke (includes brain infarction, lacunar stroke).	cerebrovascular disorders CVA
Intervention		
• Physiotherapy	Physical Therapy Modalities (include electric stimulation therapy, exercise therapy, hydrotherapy)	Physiotherapy Physiotherapy modalities Physical Therapy Passive mobilization
• Conventional – Bobath Concept and Motor Re-learning Program	No results	Neurodevelopmental approach Carr & Sheppard Motor relearning
• Innovative		
○ Robotics – treadmill, lokomat, hand robotics, mechanic orthotics	Robotics	treadmill, lokomat, hand robotics, mechanic orthotics
○ Task oriented approach	No results	
○ Bilateral movements	No results	
○ Unilateral movements	No results	
○ Mental imagery	Imagery (Psychotherapy)	Motor imagery Visual mental imagery Mental imaging
○ Mirror therapy	No results	
○ Constraint-induced Therapy	No results	Constraint induced movement therapy
○ Proprioceptive neuromuscular facilitation	Included on physical therapy modalities	Neuromuscular facilitation
○ Virtual reality	Virtual Reality Exposure Therapy	
• Electrical Modalities – electrical stimulation, functional electrical stimulation	Included on physical therapy modalities, except for Functional Electric Stimulation	
• Exercise therapy	Included on physical therapy modalities	
○ Strengthening	Included on physical therapy modalities	

○ Exercise training	Included on physical therapy modalities	
○ Cardiovascular training	No results	
○ Home exercises	No results	
Outcomes		
Functional magnetic resonance imaging (fMRI)	Magnetic Resonance Imaging(includes Cholangiopancreatography, Magnetic Resonance; Diffusion Magnetic Resonance Imaging; Echo-Planar Imaging; Magnetic Resonance Angiography; Magnetic Resonance Imaging, Cine; Magnetic Resonance Imaging, Interventional)	Functional magnetic resonance
Electroencephalography (EEG)	Electroencephalography (includes Electroencephalography Phase Synchronization; Brain Waves)	Electroencephalography
Magnetoencephalography (MEG)	Magnetoencephalography	Magnetoencephalography
Transcranial magnetic stimulation (TMS)	Transcranial magnetic stimulation (TMS)	Transcranial Magnetic Stimulation
Single-photon emission computed tomography (SPECT)	Tomography, Emission-Computed, Single-Photon	
Positron emission tomography (PET)	Positron-Emission Tomography	Positron-emission tomography imaging
Near-infrared spectroscopy (NIRS)	Spectroscopy, Near- Infrared	Near infrared imaging
Transcranial Doppler ultrasonography (TCD)	Ultrasonography, Doppler, Transcranial	Transcranial Doppler brain

ANNEX 1 CRITERIA LIST BEST EVIDENCE SYNTHESIS

Best-evidence synthesis

Strong evidence:	provided by consistent, statistically significant findings in outcome measures in at least two high quality RCTs*
Moderate evidence:	provided by consistent, statistically significant findings in outcome measures in at least one high quality RCT and at least one low quality RCT or high quality CCT*
Limited evidence:	provided by statistically significant findings in outcome measures in at least one high quality RCT*
or:	provided by consistent, statistically significant findings in outcome measures in at least two high quality CCTs* (in the absence of high quality RCTs)
Indicative findings:	provided by statistically significant findings in outcome and/or process measures in at least one high quality CCT or low quality RCT* (in the absence of high quality RCTs)
or:	provided by consistent, statistically significant findings in outcome and/or process measures in at least two ODs with sufficient quality (in absence of RCTs and CCTs)*
No or insufficient evidence:	in the case that results of eligible studies do not meet the criteria for one of the above stated levels of evidence
or:	in the case of conflicting (statistically significant positive and statistically significant negative) results among RCTs and CCTs
or:	in the case of no eligible studies

Best-evidence synthesis. *If the number of studies that show evidence is <50% of the total number of studies found within the same category of methodological quality and study design (RCTs, CCTs, or ODs), we will state no evidence.

Retrieved from: Steultjens EM, Dekker J, Bouter LM, van de Nes JC, Cup EH, van den Ende CH. Occupational Therapy for Stroke Patients A Systematic Review. Stroke. 2003; 34:676-687[26]

Brain activity during lower limb movement with manual facilitation – an fMRI study

Authors: Patrícia Maria Duarte de Almeida[1,2], Ana Isabel Correia Matos de Ferreira Vieira[1,2], Nádia Isabel Silva Canário[2, 3], Miguel Castelo-Branco[3] and Alexandre Castro Caldas[2]

[1]Alcoitão School of Health Sciences, Rua Conde Barão, Alcoitão 2649-506 Alcabideche, Portugal

[2]Institute of Health Sciences - Catholic University of Portugal, Palma de Cima

1649-023 Lisbon, Portugal

[3]Visual Neuroscience Laboratory, Institute for Biomedical Imaging in Life Sciences (IBILI), ICNAS, Faculty of Medicine, University of Coimbra, Azinhaga de Santa Comba, 3000-548 Coimbra, Portugal

Contacts: 00351214607459; patriciamdalmeida@gmail.com

Number of words in the Abstract – 198

The authors have declared that there are no potential conflicts of interest with respect to the authorship and/or publication of this article.

This study had funding resources from the Institute of Health Sciences - Catholic University of Portugal for the use of the fMRI equipment and team.

This study and manuscript have not been previously presented or published elsewhere.

Almeida P, Vieira A, Canário N, Castelo-Branco M, Castro-Caldas A. Brain activity during lower limb movement with manual facilitation – an fMRI study. Neurology Research International 2015, Volume 2015, Article ID 701452. Received 4 September 2014; Revised 11 November 2014; Accepted 17 December 2014

Abstract

Brain activity knowledge of healthy subjects is an important reference on the context of motor control and reeducation. While the normal brain behavior for upper limb motor control, has been widely explored, the same is not true for lower limb control. Also the effects that different stimulus can evoke on movement and respective brain activity are important in the context of motor potentialization and reeducation. For a better understanding of these processes a functional magnetic resonance imaging (fMRI) was used to collect data of 10 healthy subjects performing lower-limb multi-joint functional movement under three stimuli: verbal; manual facilitation and verbal+manual facilitation. Results showed that with verbal stimulus, both lower limbs elicit bilateral cortical brain activation; with manual facilitation only the left lower limb (LLL) elicits bilateral activation while the right lower limb (RLL) elicits contra-lateral activation; verbal+manual facilitation elicits bilateral activation for the LLL and contralateral activation for the RLL. Manual facilitation also elicits sub-cortical activation in white matter, the thalamus, pons and cerebellum. Deactivations were also found for lower-limb movement. Manual facilitation is stimulus capable to generate brain activity in healthy subjects. Stimulus need to be specific for bilateral activation and regarding which brain areas we aim to activate.

Keywords: brain activity, lower-limb movement, manual facilitation.

Introduction

The knowledge of normal brain activity during several task gives insight for both normal and abnormal behavior [1], Brain activity knowledge of healthy subjects is an important reference on the context of motor control. This understanding of mechanisms underlying motor control and re-learning is the basis for neurosciences development of frameworks for motor performance potentialization or reeducation. In the context of neurorehabilitation this is shown in the recovery of disturbances which tend to present similar brain networks to those of healthy subjects [2, 3, 4] as the result of neuroplasticity [5].

Brain behavior is a complex task, being related with several aspects like: somatotopic identification, activations and deactivations [6] sequences and differenttiations of activations, interconnectivity, metabolic changes, synaptic transmissions, among others.

While the normal brain behavior for upper limb motor control, has been widely explored, the same is not true for lower limb control. It is however known that in addition to motor and pre-motor areas, other areas such as somatosensory and limbic areas, and basal nuclei and cerebellum structures are involved in the process of motor control [7, 8] of healthy subjects. Specifically, homunculus representations of the lower limb on motor and somatosensorial and cerebellum areas are activated [9]. However, most of the studies refer to single-joint movements, not reflecting the complexity of functional movements. Thus the identification of somatotopic maps of brain activity during complex movements of lower limbs on healthy subjects are still needed for the understanding of mechanisms underlying motor control of lower limb.

Considering the need for synaptic selection of activations and inhibitions, for shaping patterns of activity in networks underlying complex skills, both activations and deactivations are important on brain activity analysis [6]. Deactivations are a controversial issue in brain imaging, as the interpretations are not yet clear or well established [6]. They appear to be associated with decreases in blood oxygen levels dependent signal (BOLD), usually associated with the inhibition of areas not involved in the specific task in order to facilitate task-relevant processing [2].

As movement can be triggered by different stimulus like: cognition, motivation, verbal orders, vision, external manual guidance, environment and task demands, other areas then motor-related areas are expected to be involved on the process of neural connections. Also the experience-dependent process of the dominant or non dominant limb [10] will influence the localization, the intensity and pattern of brain activity.

On the perspective of movement potentialization or reeducation, the understanding of the impact of the different stimulus on motor-related areas is relevant for a selection of the closest to normal autonomous movement and the scientific base for professions like physiotherapy.

The latest research studies already show some evidence for brain activation through several physiotherapeutic approaches both in healthy subjects or neurological patients [11, 12, 13, 14, 15]. However, none of the studies focused on external manual guidance or "manual facilitation", the most frequently used stimulus and considered as the conventional physiotherapy treatment [16]. The underlying neurophysiological processes that are elicited by motor-related sensoric stimuli during manual facilitation have not been previously investigated. It's empirical use relies on the assumptions that activation of tactile and proprioceptive receptors will activate the somatosensorial areas (S1 and S2) creating a body map at the homunculus and insula region [17]. As the insula is also responsible for motor functions, by the activation of the anterior cingulate [18], is expected that the manual stimulation has effects on motor and somatosensorial activation.

With regard to these considerations concerning brain activity, physiotherapeutic stimuli and the complex movements of lower limbs, the goal of this whole-brain functional MRI study is to analyse the somatotopic map of brain activity for lower limbs during multi-joint functional movement (simultaneous movement of the hip, knee and ankle), and to investigate the effects of the manual facilitation of lower-limb functional movements on brain activity in healthy subjects.

To that end, we analysed brain activity through three different stimuli for movement performance: a) verbal stimulus; b) manual stimulus (physiotherapeutic manual facilitation) and c) verbal+manual stimulus.

In contrast with other studies, we analysed: multi-joint movement of the lower limb during complex functional tasks and not single-joint movements; the brain activity during the performance of manual facilitation of movement using a specific physiotherapeutic approach and not after a period of intervention; the white matter activity and attempted to analyse deactivations.

Methods

Participants

A sample of 10 healthy subjects (5 male/5 female; Mean age of 60.6 ± 9.1 years), right-handedness and footedness assessed by the Portuguese-language translation of the Waterloo Handedness Questionnaire - Revised (WHQ-R) and Waterloo Footedness Questionnaire - Revised (WFQ-R) [19], participated in this study. They presented no relevant medical history and no indicators of anxiety on the State Trait Anxiety Inventory (STAI) [20] scale, or mental disorders on the Saint Louis University Mental Status (SLUMS) [21] scale or negative social touch reaction according to the Social Touch Questionnaire (STQ) [22] (table 1.). The experimental procedures were approved by the Ethics Committee of Health Sciences Institute at the Portuguese Catholic University and all participants gave their informed consent in accordance with the Declaration of Helsinki prior to their participation.

Table 1. Subjects Characteristics

Subjects	Age	Gender	STAI Y1	SLUMS	STQ	Lateralization
1	84	F	34	25	23	Right
2	57	M	28	26	24	Right
3	60	M	32	30	14	Right
4	63	F	26	28	18	Right
5	56	F	28	25	19	Right
6	55	M	25	30	9	Right
7	52	F	43	25	15	Right
8	64	F	34	27	14	Right
9	56	M	25	30	17	Right
10	56	M	41	30	20	Right
Average	60,6	-	31,6	27,6	17,3	-

STAI Y1- State-Trait Anxiety Inventory (min. 20; max. 80); STQ - Social Touch Questionnaire (min. 0; max. 80); SLUMS - Saint Louis University Mental Status (min 1; max. 30).

Procedures for Brain Activity Acquisition

Functional Magnetic Resonance Imaging Scanning

Data acquisition was performed on a 3 Tesla scan Siemens Magnetom Trio at the Portuguese Brain Imaging Network. A whole-brain approach, starting with one 3D anatomical MPRAGE sequence T1-weighted, 1x1x1 voxel size, repetition time (TR): 2,530 ms, echo time (TE): 3.42 ms, field of view (FOV): 256 x 256 mm, and a matrix size of 256 x 256. The anatomical sequence comprised of 176 slices. Functional MRI experiment was acquired in 2 functional runs: RUN 1 - right lower limb (RLL) and RUN 2 - left lower limb (LLL), in the same session, sensitive to BOLD signal sequences, a TR: 2500 ms, TE: 30 ms, voxel size 3x3x3 mm, FOV: 256 x 256, and a matrix size of 86 x 86. For each run, 45 slices were acquired with 200 volumes.

Experimental Paradigms / Motor Testing

All participants underwent a single session comprising of one structural scan and one functional scan with two runs. Both runs consisted of 3 stimulation blocks and 1 fixation block (Figure 1.). The stimulation blocks aimed to induce the movement of lower limbs in a pattern of hip flexion, knee flexion and dorsiflexion, requiring multi-joint movement and a stabilization of the contra-lateral side, with the following stimuli:

- *Block 1 - Verbal stimulus* - “bring your leg up to the table”, recorded on a sound recorder with a female voice and translated into audio windows media format and listened to by the subjects - to be used as a trigger for autonomous movement performance and consequentelly create an expected the somatotopic map of activation closed to the voluntary autonomous movement;
- *Block 2 - Physiotherapeutic manual facilitation stimulus* based on Bobath Concept key points [23], performed by a specialized physiotherapist, encouraging the movement of the leg up to the table, with one hand on the dosal face of the foot, stimulating manually the movement of dorsiflexion and another hand on the external superior extremity of lower leg stimulating knee elevation, leading to hip flexion - to verify the effects of manual stimulus;
- *Block 3 - Mixed stimuli* including both verbal and physiotherapeutic manual facilitation - to verify if any stimulus is predominant over the other.

Each stimulation block included 5 trials each lasting 7 seconds, totalling 35 seconds per stimulation block with a total of 105 seconds of stimulation per run. Resting periods of 15 seconds were used after each trial for the repositioning of the LL. The fixation block lasted 30 seconds, being applied before the first stimulation trial and after the last stimulation trial. The fixation block served for baseline purposes and the participants were asked to rest and make no intentional movement. The sum of this time came to 322 seconds. The overall functional acquisition lasted 990 seconds for each subject. The functional acquisition always started with the RLL and the sequence of the following stimulation blocks was the same to all subjects and previously randomised on Matlab R 2013a, for preparation of the physiotherapist performing the stimulus but no anticipation of the subject. Three different image codes displayed on a computer screen for each block only for the physiotherapist. This procedure allowed the physiotherapist to identify the blocks when his participation was needed and showed the necessary duration.

Figure 1 - Experimental paradigm

	322 seconds - aprox. 5 min per RUN				
	Fixation Block Baseline 1	Block 1 	Block 2 	Block 3 	Fixation Block Baseline 2
RUN 1 - Right Lower Limb Movement	30 seconds	Pseudo-randomized sequence, with 5 repetions of each block and 15 seconds of rest for replacing the lower limb to the initial position, in between each repetition			30 seconds
RUN 2 - Left Lower Limb Movement	30 seconds	Pseudo-randomized sequence, with 5 repetions of each block and 15 seconds of rest for replacing the lower limb to the initial position, in between each repetition			30 seconds

Image Processing and Data Analysis

Functional imaging analysis was carried out using BrainVoyager^{TM} QX version 2.3 software (Brain Innovation B.V., The Netherlands; http://www.brainvoyager.com). Anatomical images were re-oriented into a space where the anterior and the posterior commissure lie on the same plane (AC-PC) and then transformed to the Talairach reference system. Functional images were intensity-adjusted and all slice scans were time- and 3D motion-corrected, temporal-filtered and subsequently coregistered to the structural image. The first three functional volumes were discarded in order to attain signal equilibrium.

The effects of stimulation blocks vs baseline were determined by performing, for each functional run, a one-way repeated ANOVA measure for the identification of significant clusters for each contrast. Due to the presence of substancial head movements caused by the design of the experience itself, it was deemed necessary to include 6 motion confound predictors (x, y, z, rotation, translation) into the whole-brain Random Effects - General Linear Model Analysis (RFX-GLM). This allowed for the possibility for generalization to the population [24]. In addition, a whole-brain mask was included in order to eliminate voxels located outside of the boundaries of the brain. We considered the presence of significant clusters at the 0.05 threshold, corrected for multiple comparisons using a cluster threshold estimator (based on Monte Carlo simulations [1,000 interactions]). The cluster-size thresholding allowed us to define multi-subject volumes of interest (VOIs), according to the clusters's center of mass (CoM), and measure its activation volume. We also examined the surrounding areas that were included in the identified clusters using the Brain Voyager Brain Tutor atlas. These areas were properly identified according to the location of their center of mass and peak voxel, but no activation volume was recorded due to the intrinsic limitations of using a brain atlas in order to segment these areas. The VOIS were obtained using particular contrasts. The contrast of *verbal stimulus* with the baseline would be used to provide a somatotopic map of reference for the lower-limb multi-joint movement of healthy subjects; the contrast of the *manual stimulus* with the baseline would be used to verify the effects of manual facilitation on brain activity; and the contrast of the manual+verbal with the baseline would be used to identify if there is any advantage in giving simultaneous stimuli. Specific predictors from the stimulation blocks were compared: *verbal stimulus* > *manual stimulus; manual stimulus* > *verbal stimulus*.

Results

Brain activity during verbal stimulus for the multi-joint movement of lower limbs

For both lower limbs, verbal stimulus for movement elicits a statisticaly significant (RFX, $p = 0.05$, corrected) bilateral midline cortical brain activation in the M1, S1, S2 and cingulate cortex.

For the RLL, the cluster with the greatest volume of activation has both its Center of Mass and Peak Voxel level at S2-BA7 (No. voxels = 16,655; $t(0.36)=6.58$; $p<0.00$ for the right hemisphere and No. voxels = 2080; $t(0,36)=5.60$; $p<0.00$ for the left hemisphere) and includes primary somatosensory (BA 1, 2 and 3), motor areas (BA 4) and cingulate cortex (BA 24, 30, 31 and 32), (see Figure 2a, Table 2 and Appendix 1).

For the LLL (see Figure 2a, Table 2 and Appendix 1), the cluster with the greatest volume has both its Center of Mass and Peak Voxel level at M1-BA4 (No. voxels = 7,153; $t(0.36)=5.02$; $p<0.00$ for the right and left hemisphere) and includes the same areas as the RLL.

We also found activation in SMA - BA6, in the left hemisphere for both lower-limb stimulations included in the clusters presented above.

In the areas BA 1, 2, 3, 4, 5 and 7 activation is located in the lower-limb representation (homunculus).

Deactivation is found in the interhemispheric connectivity region and occipital area (see Table 3).

Compared with *manual stimulus, verbal stimulus* elicits activity in language (BA 21 and 22) and auditory (BA 42) areas bilaterally for both lower limbs (see Figure 2c, Table 2 and Appendix 1). Deactivations are found for the RLL, in ispsilateral auditory, visual, language, memory and sub-cortical areas and for the LLL in the cerebellum (see Table 3).

Brain activity during manual facilitation of lower-limb multijoint movement of lower limbs

For the RLL, manual facilitation of movement elicits a statisticaly significant (RFX, p = 0.05, corrected) level of contra-lateral cortical brain activation. The cluster with the greatest volume of activation has both its Center of Mass and Peak Voxel level at BA1 (No. voxels = 4,784; t $t(0.36)=4.98$; $p<0.00$) and includes the primary somatosensory areas (BA 2, and 3, the secondary somatosensory area homunculus (BA5 and 7) and the motor area (BA 4), (see Figure 2b, Table 2 and Appendix 1). In areas BA 1, 2, 3, 4, 5 and 7, activations are located in the lower limb representation (homunculus).

For the LLL, manual facilitation of movement elicits a statisticaly significant (RFX, p = 0.05, corrected) bilateral cortical brain activation. The cluster with the greatest volume of activation has both its Center of Mass and Peak Voxel level at BA5 (No. voxels = 11,004; t $t(0.36)=5.29$; $p<0.00$) and includes the primary somatosensory area (BA 1, 2 and 3), the secondary somatosensory area (BA5 and 7) and the motor area (BA 4), (see Figure 2b, Table 2 and Appendix 1). Deactivations are found in auditory and linguistic areas as well as in ipsilateral motor, executive, memory and cognitive areas and upper limb representation is found in the cerebellum (see Table 3).

Compared with *verbal stimulus*, *manual stimulus* elicits bilateral activity in the white matter of somatosensorial areas (both the Center of Mass and Peak Voxel), with a volume of 42,725 voxels ($t(0.36)=5.44$; $p<0.00$) (see Figure 2d, Table 2 and Appendix 1).

For the same contrast, when the LLL is stimulated, bilateral activation is found in SMA - BA6, BA24 and cerebellum (lobes XI and VIIIb). Ipsilateral activation of sub-cortical areas (thalamus, pons and amygdala) is also observed (see Figure 2e, Table 2 and Appendix 1). In this comparison, deactivations are found in linguistic and auditory areas for both lower limbs (see Table 3).

Brain activity during manual + Verbal stimuli for the multi-joint movement of lower limbs

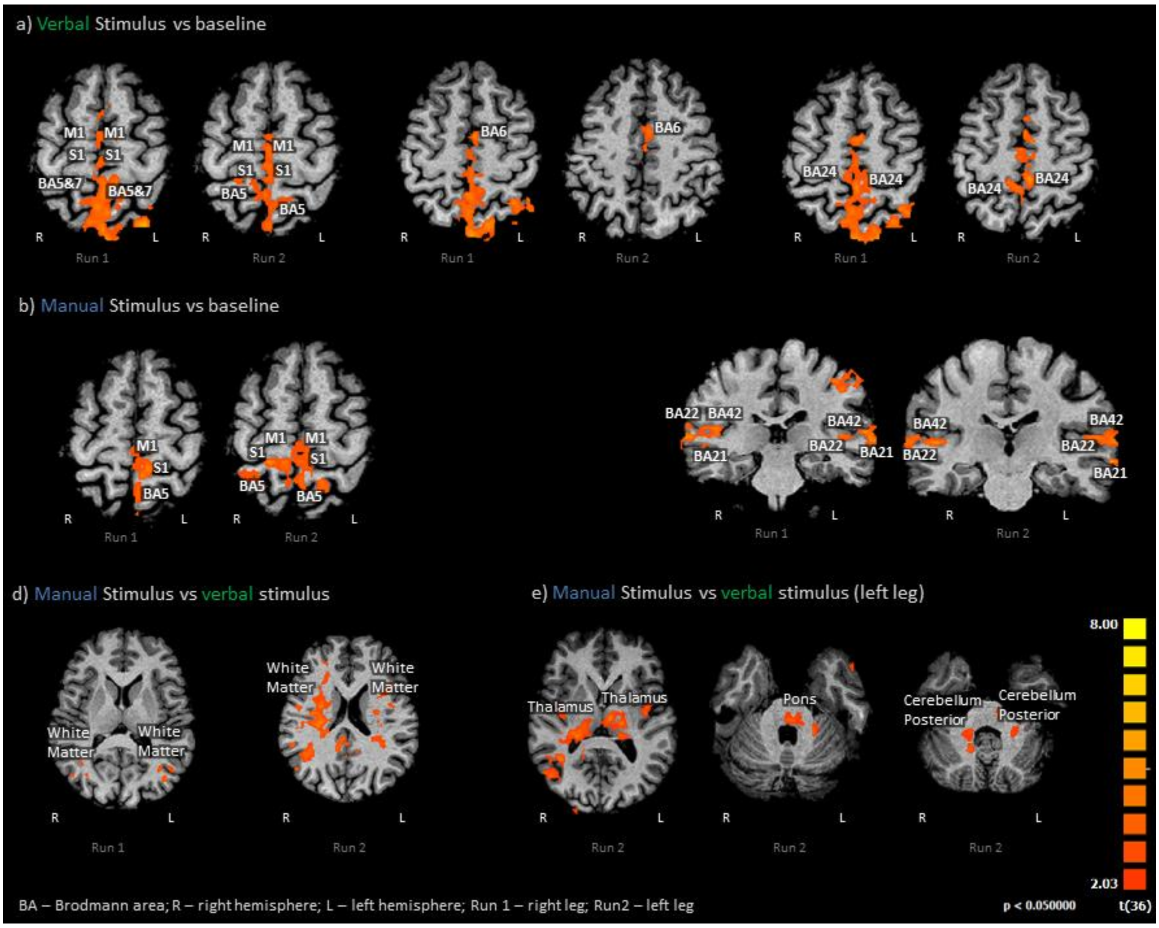
The clusters with the greatest volume of activation are related to auditory areas bilaterally.

For the RLL the Center of Mass is at BA42 (No. voxels = 5,054 in the right hemisphere and 4,276 in the left hemisphere) with the Peak Voxel at BA22 ($t(0.36)=5.50$; $p<0.00$ for the right hemisphere and $t(0.36)=6.01$; $p<0.00$ for the left hemisphere).

For the LLL the Center of Mass is at BA42 (No. voxels = 9,426) with the Peak Voxel level at BA52 ($t(0.36)=6.61$; $p<0.00$) in the right hemisphere and at BA22 (No. voxels = 4,829) with the Peak Voxel level at BA22 ($t(0.36)=5.59$; $p<0.00$) in the left hemisphere). For the LLL, bilateral activation was also found in the primary somatosensory (BA 1.3 and 2), secondary somatosensory area homunculus (BA5 and 7), ventral cingulate cortex (BA 24) and motor areas (BA 4). Contra-lateral activation was found in the same areas for RLL.

For the RLL, deactivation of cerebellum and sub-cortical areas. For the LLL, deactivation of motor planning and somatosensory areas.

Figure 2 – Statistical maps of activation for lower limb movement



Discussion

Coherently, the manual stimulus of RLL elicits contra-lateral cortical activation, requiring less connectivity, probably related with automated mechanisms for the dominant limb and hemisphere.

Despite the analysis of white matter activation being unusual in fMRI studies, we valued it as it represents the cluster with the highest volume of activation. Its localization in the frontal and parietal lobes is coherent with the connectivity of pre-motor, motor and somatosensory areas, showing greater activity for the manual stimuli and consequently descending motor information.

The activation of sub-cortical areas for the LLL manual stimuli may be related with the phenomenon that the non-verbal stimuli do not generate motivation and free-will, requiring more proprioceptive feedback and spatial references for adequate motor programming. This idea is emphasized by the results of the mixed stimulus, where the verbal stimuli do not appear to elicit the sub-cortical areas and maintain the same activated areas as in the verbal stimulus alone.

The activation of auditory and visual areas must be related with the processing of the sound information and the interpretation of the words related with movement and body segments, generating a more cognitive process for movement performance.

Despite the lack of consensus regarding their interpretation, the deactivations found are coherent with the activations and results of previous findings, mainly dealing with the upper limbs. In a motor system, lateral inhibition can result in the selection of one movement pattern with the suppression of others in the interests of specificity of movement. In upper-limb activity it is common to observe a significant deactivation (i.e., decreased blood flow) in the ipsilateral sensorimotor cortex and subcortical regions, and when present, the contralateral cerebellum. Conjunction analysis demonstrated regions that are activated by one hand and deactivated by the contralateral hand [33]. However this behavior has not yet been explored for the lower limb.

Implications for Practice

Lower-limb activity generates specific brain activity, confirming that motor control mechanisms differ between the upper and lower limb. From the findings with healthy subjects, (re)learning strategies, specifically physiotherapy, need to promote the specific mechanisms for the movement control: the bilateral brain activation and the bilateral interconnectivity and function of the lower limbs, indicating the need for a bilateral approach to lower-limb movements and tasks coordination movement with contra-lateral stabilization. Despite the harmful impact of excessive activation of the unaffected hemisphere on stroke patients [34], the bilateral brain activation is important for normal brain behavior. Eventually control of symmetric levels of activity of lower limbs are required to not stimulate the overuse of the unaffected limb and consequently of the unaffected hemisphere.

The type of stimulus also seems to be relevant when designing an intervention plan. Manual stimuli elicit cortical and sub-cortical brain activity in healthy subjects, while verbal stimuli only elicit cortical activation, implying that when we need to stimulate the sub-cortical areas then manual stimulus without any verbal support might be appropriate. However, when looking for more cognitive stimuli, verbal or mixed stimuli would be more suitable. The presence of cingulate areas shows the importance of meaningful tasks for motor control in order to stimulate motivation and willingness for movement. These findings are important to validate the impact of manual therapeutic strategies and to develop physiological understanding for patients with neurological disorders. However, this needs further validation.

Research Implications

Considering the limited research of lower-limb and brain activity, our results can contribute to future development. However, maps alone are not sufficient for an understanding of cerebral processes. Remapping is neuronal functionally-driven, however the proficiency of functional output can be constrained, if the map user does not use the newly remapped area correctly [35] applied to repeated meaningful tasks. Thus, specific regions of interest and connectivity studies are required to understand the mechanisms of motor control. The fine structure of the motor map appears not to be map-like at all, meaning that recovery processes within small areas may not be best interpreted as remapping. In fact, the characterization of changes in activity and connectivity that appear to support recovery as "reorganization" or "remapping" often seem overblown in situations in which synaptic strength and the excitability of preexisting circuits are adjusted [35]. Thus the brain analysis of patients with neurological disorders is also of great importance in different phases of recovery.

With regards to the methods used in this study, we recommend fMRI procedures for functional sequences in the same run to minimize instrumental bias and to allow for direct comparisons between right and left limbs and to strengthen the validity of the results.

Conclusions

With regards to the goals of our study, we conclude that the brain somatotopic map for lower-limb multi-joint movement is in line with previous findings on bilateral brain activation and the activation of cortical and sub-cortical areas. Furthermore, the activation of white matter is an important feature. Concerning the effects of the physiotherapeutic manual facilitation of lower-limb functional movements, we conclude that for healthy subjects manual facilitation promotes brain activity and that this activation is similar from one activated area to another. As has been seen in other studies, the valid interpretation and signficance of deactivations still require further investigation and clarification. However, the level of deactivations found reveals how important this physiological event might be for the understanding of the neurophysiological processes of motor tasks.

Conflict of Interests

The authors have declared that there is no potential conflict of interests with respect to the authorship and/or publicationof this paper.

Acknowledgment

This study had funding resources fromthe Institute of HealthSciences, Catholic University of Portugal, for the use of the fMRI equipment and team.

Table 2. Cluster Analysis of Activations

			Center of Mass*					Peak Voxel*									
Contrast	**Run**	**Cluster**	**x**	**y**	**z**	**Region Area**	**BA**	**x**	**y**	**z**	**Region Area**	**BA**	**Other BA included in the cluster**	**Nº Voxels**	**t-test**	**p-value**	**Function**
Verbal vs Baseline	Right	1	56,72	-16,26	6,09	Temporal Lobe; Superior Temporal Gyrus	42 R	47	-14	6	Temporal Lobe; Superior Temporal Gyrus	42 R	-	4425	6,30	0,000	Processing auditory information
		2	-2,3	-50,54	50,26	Parietal Lobe; Precuneus	S2 - 7 R	-1	-80	46	Parietal Lobe; Precuneus	S2 - 7 R	1,2,3,4,24 R	16655	6,59	0,000	Processing Somatosensorial and motor information (motivation and execution)
		3	-0,34	-55,52	3,8	Lingual Gyrus	NA	-4	-62	3	Lingual Gyrus	NA	-	3480	5,41	0,000	Visual recognition of words
		4	-34,97	-59,22	47,28	Parietal Lobe, Inferior Parietal Lobule	S2 - 7 L	-28	-65	55	Parietal Lobe, Superior Parietal Lobule	S2 - 7 L	1,2,3,4,6,24 L	2080	5,60	0,000	Processing Somatosensorial and motor information (motivation, planning and execution)
		5	-59,17	-21,42	6,55	Temporal Lobe; Superior Temporal Gyrus	42 L	-58	1	9	Temporal Lobe; Superior Temporal Gyrus	42 L	-	5177	6,10	0,000	Processing auditory information

Table 2. Cluster Analysis of Activations (continued)

			Center of Mass*					Peak Voxel*									
Contrast	**Run**	**Cluster**	**x**	**y**	**z**	**Region Area**	**BA**	**x**	**y**	**z**	**Region Area**	**BA**	**Other BA included in the cluster**	**Nº Voxels**	**t-test**	**p-value**	**Function**
Verbal vs Baseline	Left	1	51,8	-17,84	7,86	Temporal Lobe; Superior Temporal Gyrus	42 R	47	-20	6	Temporal Lobe; Superior Temporal Gyrus	42 R	-	3541	5,63	0,000	Processing auditory information
		2	1,71	-31,33	54,31	Frontal Lobe, Precentral Gyrus	M1 - 4 R/L	-1	-32	60	Frontal Lobe, Precentral Gyrus	M1 - 4 R/L	1,2,3,5, 24 (R/L), 6 (L)	7153	5,03	0,000	Processing Somatosensorial and motor information (motivation, planning and execution)
		3	-57,16	-13,99	5,48	Temporal Lobe; Superior Temporal Gyrus	42 L	-49	-23	9	Temporal Lobe; Superior Temporal Gyrus	42 L	-	3830	5,25	0,000	Processing auditory information
Manual vs Baseline	Right	1	-5,04	-36,5	58,66	Parietal Lobe, Central Gyrus	S1 - 1L	-4	-41	57	Parietal Lobe, Central Gyrus	S1 - 1L	2,3,4, 5 L	2784	4,99	0,000	Processing Somatosensorial and motor information (execution)
		2	-5,06	-75,24	43,24	Parietal Lobe; Precuneus	S2 - 7L	-10	-71	48	Parietal Lobe; Precuneus	S2 - 7L	-	1064	4,48	0,000	Processing visuo-motor coordination information
	Left	1	9,16	-37,59	55,61	Ventral Cingulate Cortex	24 R	38	-41	51	Superior Parietal Lobe	S2 - 5L	1,2,3,4, 24 (R/L)	11004	5,30	0,000	Processing Somatosensorial and motor information (motivation, planning and execution)

Table 2. Cluster Analysis of Activations (continued)

			Center of Mass*					Peak Voxel*									
Contrast	**Run**	**Cluster**	**x**	**y**	**z**	**Region Area**	**BA**	**x**	**y**	**z**	**Region Area**	**BA**	**Other BA included in the cluster**	**Nº Voxels**	**t-test**	**p-value**	**Function**
Verbal vs Manual	Right	1	56,55	-17,03	6,34	Temporal Lobe; Primary Auditory Cortex	42 R	47	-14	6	Temporal Lobe; Primary Auditory Cortex	42 R	-	4802	6,30	0,000	Processing auditory information
		2	18,82	-67,3	26,33	Parietal Lobe; Precuneus	31 R	14	-62	15	Limbic Lobe	31 R	-	1308	4,18	0,000	Processing emotions and recognition
		3	-0,84	-59,71	31,8	Parietal Lobe; Precuneus	S2 - 7 L	2	-44	39	Limbic Lobe; Cingulate Gyrus	31 R	1,5, 7 L	17222	6,67	0,000	Processing somatosensorial information and emotions
		4	-23,82	-76,38	25,78	Occipital Lobe	19 L	-19	-89	28	Occipital Lobe	19 L	-	1429	3,89	0,000	Processing visual information
		5	-38,57	-48,11	46,84	Parietal Lobe, Inferior Parietal Lobule	40 L	-28	-65	54	Superior Parietal Lobe	S2 - 7 L	-	5018	5,85	0,000	Processing somatosensorial information
		6	-60,01	-25,59	6,95	Temporal Lobe	22 L	-61	-14	6	Temporal Lobe	22 L	21	4892	6,12	0,000	Language comprehension
		7	-59,29	-0,49	-2,26	Temporal Lobe	22 L	-62	4	0	Temporal Lobe	22 L	21	1205	5,82	0,000	Language comprehension

Table 2. Cluster Analysis of Activations (continued)

			Center of Mass*					Peak Voxel*									
Contrast	**Run**	**Cluster**	**x**	**y**	**z**	**Region Area**	**BA**	**x**	**y**	**z**	**Region Area**	**BA**	**Other BA included in the cluster**	**Nº Voxels**	**t-test**	**p-value**	**Function**
Verbal vs Manual	Left	1	54,79	-16,53	6,88	Temporal Lobe; Superior Temporal Gyrus	42 R	50	-8	3	Temporal Lobe	22 R	-	3243	4,86	0,000	Processing auditory information and language comprehension
		2	-59,34	-11,55	4,06	Temporal Lobe; Superior Temporal Gyrus	22 L	-64	-20	-6	Temporal Lobe; Superior Temporal Gyrus	22 L	-	3350	5,35	0,000	Language comprehension
Manual vs Verbal	Right	1	39,08	-64,17	12,73	Occipital Lobe; Middle Occipital Gyrus	19 R	35	-56	3	White matter; Occipital Lobe	NA	-	2701	4,38	0,000	Processing visual information
		2	9,92	30,9	-1,26	White matter; Frontal Lobe; Prefrontal Cortex R	NA	17	31	-3	White matter; Frontal Lobe; Prefrontal Cortex R	NA	-	1037	4,27	0,000	Executive functions
		3	-40,24	-61,92	9,41	Occipital Lobe	19 L	-46	-59	6	Occipital Lobe	19 L	-	958	5,04	0,000	Processing visual information

Table 2. Cluster Analysis of Activations (continued)

			Center of Mass*					Peak Voxel*									
Contrast	**Run**	**Cluster**	**x**	**y**	**z**	**Region Area**	**BA**	**x**	**y**	**z**	**Region Area**	**BA**	**Other BA included in the cluster**	**Nº Voxels**	**t-test**	**p-value**	**Function**
Manual vs Verbal	Left	1	28,71	-22,78	30,62	Parietal Lobe, Sub-Central Gyrus; Whitte matter R	NA	48	-35	51	Parietal Lobe, Sub-PostCentral Gyrus; White matter R	NA	-	42752	5,44	0,000	Processing somatosensorial information; Conectivity with M1
		2	44,94	-46,16	-4,1	Temporal Lobe; Lateral Occipitotemporal Gyrus	37 R	44	-38	-3	Temporal Lobe; Lateral Occipitotemporal Gyrus	37 R	-	1604	4,41	0,000	Processing multi-modal information
		3	34,57	-70,21	-0,07	Occipital Lobe	19 R	38	-50	6	Occipital Lobe	19 R	-	2835	4,89	0,000	Processing visual information
		4	21,29	-5,92	-8,72	Limbic Lobe; Amygdala R	NA	26	-2	-15	Limbic Lobe; Amygdala R	NA	-	1389	4,07	0,000	Processing emotional and motivational information
		5	15,83	-48,26	-35,17	Cerebellum Posterior; Lobes VIIIb and IX R	NA	14	-53	-33	Cerebellum Posterior; Lobes VIIIb and IX R	NA	-	1164	5,26	0,000	Processing somatosensorial information
		6	-6,06	-29,09	-22,44	Brainstem; Superior Dorsal Pons L	NA	-1	-29	-24	Brainstem; Superior Dorsal Pons L	NA	-	1789	4,78	0,000	Comunication with the Cerebellum

Table 2. Cluster Analysis of Activations (continued)

Contrast	Run	Cluster	Center of Mass* x	y	z	Region Area	BA	Peak Voxel* x	y	z	Region Area	BA	Other BA included in the cluster	Nº Voxels	t-test	p-value	Function
Manual vs Verbal (cont.)	Left (cont.)	7	-15,6	-20,15	5,25	Thallamus; Ventroposterol lateral nucleus L	NA	-7	-14	9	Thallamus; Ventroposterol lateral nucleus L	NA	-	2291	4,91	0,000	Processing somatosensorial information
		8	-25,32	-19,4	32,93	Parietal Lobe, Sub-Central Gyrus; Whitte matter L	NA	-25	-20	30	Parietal Lobe, Sub-Central Gyrus; Whitte matter L	NA	-	13258	4,76	0,000	Processing somatosensorial information; Conectivity with M1
		9	-20,93	-41	-33	Cerebellum Posterior; Lobes VIIIb and IX R	NA	-19	-38	-27	Cerebellum Posterior; Lobes VIIIb and IX R	NA	-	1485	5,13	0,000	Processing somatosensorial information
		10	-33,53	4,33	-7,23	Insula Lobe L	NA	-34	-5	-3	Insula Lobe L	NA	-	1601	3,55	0,001	Processing emotions
		11	-47,05	-13,71	-13,92	Temporal Lobe; Sub Gyral L	21	-49	-29	-9	Temporal Lobe; Sub Gyral L	21	-	1521	5,46	0,000	Processing auditory and language information

Table 2. Cluster Analysis of Activations (continued)

			Center of Mass*					Peak Voxel*									
Contrast	**Run**	**Cluster**	**x**	**y**	**z**	**Region Area**	**BA**	**x**	**y**	**z**	**Region Area**	**BA**	**Other BA included in the cluster**	**Nº Voxels**	**t-test**	**p-value**	**Function**
Manual + Verbal vs Baseline	Right	1	53,52	-17,26	7,23	Temporal Lobe; Superior Temporal Gyrus	42 R	59	-17	0	Temporal Lobe; Superior Temporal Gyrus	22 R	-	5054	5,50	0,000	Processing auditory information and language comprehension
		2	-3,88	-37,85	59,07	Parietal Lobe, PostCentral Gyrus	1 L	-4	-41	57	Parietal Lobe, PostCentral Gyrus	2 L	-	2343	5,00	0,000	Processing somatosensorial information
		3	57,75	-23,57	7,35	Temporal Lobe; Superior Temporal Gyrus	42 L	-64	-32	6	Temporal Lobe; Superior Temporal Gyrus	22 L	-	4276	6,02	0,000	Processing auditory information and language comprehension
	Left	1	50,65	-20,25	9,91	Temporal Lobe; Superior Temporal Gyrus	42 R	50	5	3	Temporal Lobe; Superior Temporal Gyrus	22 R	-	9426	6,61	0,000	Processing auditory information and language comprehension
		2	4,01	-32,12	54,61	Frontal Lobe; Cingulate Cortex Ventral	24 R	20	-35	57	Parietal Lobe; Prepyriform cortex	5 R	-	6161	4,61	0,000	Processing Somatosensorial and motivation information
		3	-55,53	-19,25	7,6	Temporal Lobe	22 L	-52	-17	6	Temporal Lobe	22 L	-	4829	5,60	0,000	Language comprehension

* Talairach Coordinates; BA - Brodmann Area; R - Right hemisphere; L - Left hemisphere; S2 - Secondary somatosensorial area; S1 - Primary somatosensorial area; M1 - Primary motor area

Table 3. Cluster Analysis of Deactivations

			Center of Mass*					Peak Voxel*								
Contrast	**Run**	**Cluster**	**x**	**y**	**z**	**Region Area**	**BA**	**x**	**y**	**z**	**Region Area**	**BA**	**Nº Voxels**	**t-test**	**p-value**	**Function**
Verbal vs Baseline	Right	1	0,36	-6,54	6,8	Ventral Inter-hemispheric region; comissures	NA	44	-8	-18	Temporal Lobe; Inferior Temporal Gyrus	20 R	246561	-6,96	0,000	Processing Interhemispheric conectivity; visual object recognition
	Left	1	-3,43	-31,28	0,21	Parahippocampal Gyrus	27 L	29	-86	15	Occipital Lobe; Middle Occipital Gyrus	18 L	307282	-8,60	0,000	Processing memory and visual information
Manual vs Baseline	Right	1	27,76	-6,41	25,44	Frontal Lobe; Sub-Precentral Gyrus; White matter R	NA	50	-8	30	Frontal Lobe; Precentral Gyrus	4 R	13466	-5,39	0,000	Processing motor information
		2	33,56	-17,33	-14,22	Limbic Lobe; Parahippocampal Gyrus; White matter R	NA	26	-20	-15	Limbic Lobe; Parahippocampal Gyrus; White matter R	NA	2347	-5,57	0,000	Processing complex aspects of learning and memory
		3	29,23	-79,82	14,5	Occipital Lobe	18 R	29	-71	21	Occipital Lobe	19 R	2161	-4,21	0,000	Processing visual information
		4	-22,84	16,07	22,1	Frontal Lobe; Sub-Superior Frontal Gyrus White matter L	NA	-25	43	30	Frontal Lobe; Superior Frontal Gyrus	9 L	29285	-6,16	0,000	Processing executive information
		5	7,37	45,45	40,41	Frontal Lobe; Medial Frontal Gyrus	9 R	5	52	36	Frontal Lobe; Medial Frontal Gyrus	9 R	1057	-4,09	0,000	Processing executive information

Table 3. Cluster Analysis of Deactivations (continued)

			Center of Mass*					Peak Voxel*								
Contrast	**Run**	**Cluster**	**x**	**y**	**z**	**Region Area**	**BA**	**x**	**y**	**z**	**Region Area**	**BA**	**Nº Voxels**	**t-test**	**p-value**	**Function**
Manual vs Baseline (cont.)	Right (cont.)	6	-17,48	-44,53	-21,06	Cerebellum Anterior; Lobe V L	NA	-16	-41	-21	Cerebellum Anterior; Lobe V L	NA	3574	-5,20	0,000	Processing upper limb motor information
		7	-25,33	-87,28	5,79	Occipital Lobe, Middle Occipital Gyrus	17 L	-28	-86	6	Occipital Lobe, Middle Occipital Gyrus	17 L	2314	-4,02	0,000	Processing visual information
		8	-36,44	-1,44	-29,22	Temporal Lobe; Inferior Temporal Gyrus; White matter L	NA	-43	-11	-21	Temporal Lobe; Inferior Temporal Gyrus; White matter L	White matter L - temporal	2547	-4,37	0,000	Processing auditory and language information
		9	-46,5	-35,55	-6,36	Temporal Lobe; Inferior Temporal Gyrus; White matter L	NA	-25	-44	-6	Temporal Lobe; Inferior Temporal Gyrus; White matter L	37 L	1103	-4,16	0,000	Multi-modal integration, faces and object recognition
		10	-41,74	8,28	-18,05	Temporal Lobe; Inferior Temporal Gyrus; White matter L	37 L	-49	7	-12	Temporal Lobe; Inferior Temporal Gyrus; White matter L	37 L	2016	-4,49	0,000	Multi-modal integration, faces and object recognition
		11	-43	-51,96	-36,83	Cerebellum Posterior; Lobe Crus I L	NA	-40	-44	-30	Cerebellum Posterior; Lobe Crus I L	NA	1732	-5,49	0,000	Processing language and memory information

Table 3. Cluster Analysis of Deactivations (continued)

			Center of Mass*					Peak Voxel*								
Contrast	**Run**	**Cluster**	**x**	**y**	**z**	**Region Area**	**BA**	**x**	**y**	**z**	**Region Area**	**BA**	**Nº Voxels**	**t-test**	**p-value**	**Function**
Manual vs Baseline (cont.)	Left	1	2,52	-70,52	-13,26	Cerebellum Posterior; Lobe VI proximal R	NA	-7	-98	3	Occipital Lobe, Middle Occipital Gyrus	17 R	34619	-5,36	0,000	Processing upper limb movement and visual information
		2	33,08	3,74	-28,17	Temporal Lobe; Medial Temporal Gyrus	38 R	32	19	-33	Temporal Lobe; Medial Temporal Gyrus	38 R	5782	-6,05	0,000	Processing emotional and memory information
		3	4,67	49,87	38,23	Frontal Lobe	9 R	20	49	36	Frontal Lobe	9 R	2230	-4,70	0,000	Processing cognitive and execution information
		4	-13,68	43,68	5,96	Frontal Lobe; Sub-Superior Frontal Gyrus White matter L	NA	-16	37	6	Frontal Lobe; Sub-Superior Frontal Gyrus White matter L	NA	5707	-4,73	0,000	Processing executive information
		5	-39,05	44,1	18,74	Frontal Lobe	9 L	-40	43	21	Frontal Lobe	9 L	1367	-4,24	0,000	Processing cognitive and execution information
Verbal vs Manual	Right	1	41,3	-2,06	-23,03	Temporal Lobe; Inferior Temporal Gyrus; White matter R	NA	44	-8	-18	Temporal Lobe; Inferior Temporal Gyrus; White matter R	NA	5003	-5,89	0,000	Processing auditory and language information
		2	39,65	-57,88	-5,58	Occipital Lobe, Inferior Occipital Gyrus R	NA	44	-59	-3	Occipital Lobe, Inferior Occipital Gyrus R	NA	3409	-4,70	0,000	Processing visual information

Table 3. Cluster Analysis of Deactivations (continued)

			Center of Mass*					Peak Voxel*								
Contrast	**Run**	**Cluster**	**x**	**y**	**z**	**Region Area**	**BA**	**x**	**y**	**z**	**Region Area**	**BA**	**Nº Voxels**	**t-test**	**p-value**	**Function**
Verbal vs Manual (cont.)	Right (cont.)	3	30,17	-27,48	-7,28	Limbic Lobe; Hippocampus gray matter R	NA	32	-26	-9	Limbic Lobe; Hippocampus gray matter R	NA	1053	-5,57	0,000	Processing memory information
		4	26,52	3,62	-10,78	Insula Lobe R	NA	32	13	-6	Insula Lobe R	NA	1369	-4,57	0,000	Processing auditory somesthesic skelomotor function
		5	27,49	-8,38	20,28	Frontal Lobe; Sub-Precentral Gyrus White matter R	NA	23	-14	27	Frontal Lobe; Sub-Precentral Gyrus White matter R	NA	1260	-4,01	0,000	Processing motor information
		6	8,85	33,23	14,28	Frontal Lobe; Cingulate Gyrus; White matter R	NA	14	19	9	Sub cortical area; Caudate neuclei R	NA	8392	-4,57	0,000	Processing motor information (planning)
		5	-39,05	44,1	18,74	Frontal Lobe	9 L	-40	43	21	Frontal Lobe	9 L	1367	-4,24	0,000	Processing cognitive and execution information
		7	-33,91	5,07	-7,05	Insula Lobe L	NA	-40	7	-6	Temporal Lobe; Superior Temporal Gyrus; White matter L	NA	1260	-5,95	0,000	Processing auditory somesthesic skelomotor function
		8	-33,58	-0,63	-30,26	Temporal Lobe; Inferior Temporal Gyrus; White matter L	White matter L - temporal	-28	4	-30	Temporal Lobe; Inferior Temporal Gyrus; White matter L	NA	2632	-5,14	0,000	Multi-modal integration, faces and object recognition

Table 3. Cluster Analysis of Deactivations (continued)

			Center of Mass*					Peak Voxel*								
Contrast	**Run**	**Cluster**	**x**	**y**	**z**	**Region Area**	**BA**	**x**	**y**	**z**	**Region Area**	**BA**	**Nº Voxels**	**t-test**	**p-value**	**Function**
Verbal vs Manual (cont.)	Left	1	0,79	-42,06	-5,38	Cerebellum Anterior; Lobe III R	NA	-7	-20	-21	Pons L	NA	57558	-6,53	0,000	Processing upper limb function
		2	29,44	-5,55	25,09	Frontal Lobe; Sub-Precentral Gyrus White matter R	NA	26	-5	33	Frontal Lobe; Sub-Precentral Gyrus White matter R	NA	2564	-4,60	0,000	Processing motor information
		3	14,41	-45,97	21,39	Occipital Lobe R	18 R	14	-59	27	Occipital Lobe, Precuneus R	31 R	1717	-4,58	0,000	Processing visual information
		4	-15,2	57,39	22,01	Frontal Lobe; Sub-Superior Frontal Gyrus White matter L	NA	-16	61	21	Frontal Lobe; Sub-Superior Frontal Gyrus White matter L	NA	1103	-4,03	0,000	Processing motor information
		5	-21,81	-66,95	-36,32	Cerebellum Posterior; Lobe Crus II / VIIb L	NA	-7	-65	-39	Cerebellum Posterior; Lobe VIIIb L	NA	3873	-4,73	0,000	Processing somatosensory information
		6	-25,89	-88,88	3,86	Occipital Lobe, Middle Occipital Gyrus	17 L	-37	-90	6	Occipital Lobe, Middle Occipital Gyrus	19 L	1834	-5,14	0,000	Processing visual information
		7	-41,05	-45,4	-31,01	Cerebellum Anterior Lobe Crus I L	NA	-37	-44	-30	Cerebellum Anterior Lobe Crus I L	NA	1130	-5,41	0,000	Processing emotions

Table 3. Cluster Analysis of Deactivations (continued)

				Center of Mass*					Peak Voxel*							
Contrast	**Run**	**Cluster**	**x**	**y**	**z**	**Region Area**	**BA**	**x**	**y**	**z**	**Region Area**	**BA**	**Nº Voxels**	**t-test**	**p-value**	**Function**
Manual vs Verbal	Right	1	58,72	-15,02	6,52	Temporal Lobe; Superior Temporal Gyrus	42 R	56	-11	3	Temporal Lobe; Superior Temporal Gyrus	42 R	3128	-4,97	0,000	Processing auditory information
		2	-44,06	-24,24	45,7	Parietal Lobe; Precuneus	S2 - 7 L	-52	-17	39	Parietal Lobe; Precuneus	S2 - 7 L	1875	-4,518447	0,000	Processing somatosensory information
		3	-59,67	-24,72	7,95	Temporal Lobe	22 L	-61	-14	6	Temporal Lobe	22 L	1485	-5,38	0,000	Language comprehension
	Left	1	59,51	-16,47	4,16	Temporal Lobe; Superior Temporal Gyrus	42 R	69	-23	0	Temporal Lobe; Superior Temporal Gyrus	42 R	2132	-4,76	0,000	Processing auditory information
Manual + verbal vs Baseline	Right	1	-0,67	-6,14	7,7	Sub-cortical; Thalamus L	NA	-25	-8	9	Sub-cortical; Putamen L	NA	160427	-6,25	0,000	Processing motor information (planning)
		2	37,06	-61,71	-35,41	Cerebellum Anterior Lobe Crus I R	NA	41	-47	-36	Cerebellum Anterior Lobe Crus I R	NA	2654	-4,76	0,000	Processing emotions
		3	-39,41	-51,59	-34,95	Cerebellum Anterior Lobe Crus I L	NA	-46	-44	-43	Cerebellum Anterior Lobe Crus I L	NA	2849	-4,45	0,000	Processing emotions

Table 3. Cluster Analysis of Deactivations (continued)

			Center of Mass*					Peak Voxel*								
Contrast	**Run**	**Cluster**	**x**	**y**	**z**	**Region Area**	**BA**	**x**	**y**	**z**	**Region Area**	**BA**	**Nº Voxels**	**t-test**	**p-value**	**Function**
Manual + verbal vs Baseline (cont.)	Left	1	-3,87	-54,99	-10,82	Cerebellum Anterior; Lobe V L	NA	-40	-47	36	Parietal Lobe; Supramarginal Gyrus; White Matter L	NA	125170	-6,94	0,000	Processing somatosensory information
		2	18,02	-42,09	30,2	Parietal Lobe; Sub-parietal Gyrus; White matter R	NA	20	-26	24	Parietal Lobe; Sub-parietal Gyrus; White matter R	NA	3346	-5,02	0,000	Processing somatosensory information
		3	-20,56	35,47	17,79	Frontal Lobe; Sub,Middle Frontal Gyrus L	NA	-16	31	6	Frontal Lobe; Sub,Middle Frontal Gyrus L	NA	14126	-6,83	0,000	Processing motor information (planning)

* Talairach Coordinates; BA - Brodmann Area; R - Right hemisphere; L - Left hemisphere; S2 - Secondary somatosensorial area

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Appendix 1

Right Stimulation - Control Group			
Contrasts	**B.A**	**Peak Voxel**	**t***
Verbal vs Baseline	**BA1, BA2, BA3 -** *Somatosensorial Homunculus* (right, left)	2, -35, 57 -4, -41, 57	4,576 5,018
	BA4 - *Primary motor cortex* (right, left)	1, -35, 60 -1, -35, 60	4,400 4,506
	BA6 - *Premotor cortex* (left)	-4, -5, 51	4,761
	BA7 and **BA5** - *Secondary Somatosensorial Cortex* (right, left)	2, -47, 48 -28, -65, 55	5,077 5,604
	BA18 - *Extraestriate cortex V2* (right, left)	2, -61, 3 -4, -59, 4	4,995 4,580
	BA21 - *Lateral temporal lobe* (right, left)	59, -19, 0 -61, -32, 3	3,494 4,737
	BA22- *Posterior parte contains Wernicke´s area* (right, left)	59, -5, 3 -61, -14, 6	5,347 4,801
	BA24 - *Cingulate cortex (ventral)* (right, left)	1, -38, 51 -2, -38, 51	3,597 4,238
	BA30- *Retroesplenial Agranular córtex/ Cingulate gyrus* (right, left)	5, -47, 3 -4, -53, 6	4,600 4,169
	BA31 - *Isthmus of Cingulate gyrus* (right, left)	2, -59, 36 -1, -47, 48	3,729 4,552
	BA38 - *Temporal Pole* (left)	-61, 4, 0	4,868
	BA42 - *A1* (right, left)	59, -15, 12 -58, -32, 12	4,605 4,748
	Lingual Gyrus **(right, left)**	2, -61, 3 -4, -59, 3	4,995 5,231
Manual vs Baseline	**BA1, BA2, BA3 -** *Somatosensorial Homunculus* (left)	-4, -41, 57	4,990
	BA4 - *Primary motor cortex* (left)	-15, -29, 63	3,783
	BA5 and BA7- *Secondary somatosensorial cortex* (left)	-10, -71, 48	4,477
Verbal+Manual vs Baseline	**BA1+3 -** *Somatosensorial Homunculus* (left)	-4, -41, 57	5,003
	BA4 - *Primary motor cortex* (left)	-1, -23, 63	3,497
	BA5 - *Secondary Somatosensorial Cortex* (left)	-4, -41, 57	5,003
	BA21 - *Lateral temporal lobe* (right, left)	59, -19,0 -61, -29, 3	4,425 4,271
	BA22- *Posterior parte contains Wernicke´s area* (right, left)	59, -17, 0 -63, -32, 6	5,502 5,407
	BA24 - *Cingulate cortex (Ventral)* (left)	-4, -41, 55	3,388

	BA41 and BA42 - *A1* (right, left)	62, -17, 6 -58, -32, 12	4,831 5,015
Verbal vs Manual	**BA1 -** *Somatosensorial Homunculus* (left)	-38, -23, 45	3,364
	BA7 and **BA5** - *Secondary Somatosensorial Cortex* (left)	-1, -51, 45	4,701
	BA18 and BA 19 - *Extraestriate cortex V2* (left)	-4, -58, 3	4,229
	BA21 - *Lateral temporal lobe* (right, left)	64, -23, 6 -61, -32, 3	5,261 4,749
	BA22- *Posterior parte contains Wernicke´s area* (right, left)	47, -14, 6 -61, -14, 6	6,297 6,116
	BA24 - *Cingulate cortex (ventral)* (left)	-1, -36, 50	3,454
	BA30- *Retroesplenial Agranular cortex* (right, left)	5, -47, 3 -4, -50, 9	4,385 3,908
	BA31 - *Isthmus of Cingulate gyrus* (right, left)	14, -62, 15 -4, -50, 39	4,178 4,814
	BA38 - *Temporal Pole* (left)	-61, 4, 0	5,824
	BA41 and BA42 - *A1* (right), **BA 42 -** A1 (left)	59, -15, 12 -58, -32, 12	4,524 4,218
	Lingual Gyrus (right, left)	5, -62, -3 -4, -59, 3	4,600 4,997
Manual vs Verbal	**BA18 + BA19 -** *Extraestriate cortex V2* (right, left)	44, -56, -3 -46, -59, 6	4,230 5,044
	Orbital surface (right, left)	17, 31, -3 -1, 28, -3	4,274 3,203
Verbal vs Manual + Verbal	**BA3 -** *Somatosensorial Homunculus* (right), **BA1, 2** and **3** (left)	1, -36, 60 -4,-44, 57	5,640 3,767
	BA7 and BA5 - *Secondary Somatosensorial Cortex* (right, left)	20,-65, 53 -34, -59, 48	4,666 5,267
	BA18 and BA 19 - *Extraestriate cortex V2* (right, left)	14, -56, 18 -25, -80, 30	4,180 3,538
	BA24 - *Cingulate cortex (ventral)* (right, left)	1, -35, 51 -1, -37, 50	2,517 2,905
	BA30- *Retroesplenial Agranular cortex* (right, left)	14, -53, 9 -4, -53, 6	4,441 4,441
	BA31 - *Isthmus of Cingulate gyrus* (right, left)	2, -44, 39 -4, -53, 35	4,045 3,990
Manual + Verbal vs Verbal			

Manual vs Manual + Verbal			
Manual + Verbal vs Manual	**BA7 and BA5** - *Secondary Somatosensorial Cortex* (right, left)	2, -59, 36 -1, -50, 45	4,139 3, 529
	BA22 - *Wernicke* - (right, left)	59, -17, 0 -61, -23, 9	5,291 4,385
	BA41 and BA42 - *A1* (right), **BA42** (right)	62, -17, 6 -58, -32, 12	4,599 4,436

Left Stimulation - Control Group			
Contrasts	**B.A**	**Peak Voxel**	**t***
Verbal vs Baseline	**BA1, BA2, BA3 -** *Somatosensorial Homunculus* (right, left)	2, -44, 57 -1, -50, 57	4,135 4,196
	BA4 - *Primary motor cortex* (right, left)	1, -33, 60 -1, -32, 60	4,480 5,026
	BA5 - *Secondary somatosensorial cortex* (right, left)	20, -35, 60 -3, -53, 57	4,052 3,630
	BA6 - *Premotor cortex* (left)	-4, 4, 42	5,513
	BA21 - *Lateral temporal lobe* (right, left)	50, -23, 6 -49, -23, 9	5,310 5,252
	BA22- *Posterior parte contains Wernicke´s area* (right, left)	50, -3, 3 -59, -8, 6	3.,722 3,691
	BA24 - *Cingulate cortex (Ventral part)* (right, left)	5, -38, 48 -4, -33, 48	3,663 4,498
	BA38 - *Temporal Pole* (left)	-58, 7, 0	4,600
	BA41 and BA42 - *A1* (right, left)	47, -18, 7 -55, -18, 9	3,879 4,525
Manual vs Baseline	**BA1, BA2, BA3 -** *Somatosensorial Homunculus* (right, left)	11, -41, 60 -7, -38, 51	4,408 3,837
	BA4 - *Primary motor cortex* (right, left)	8, -37, 66 -1, -32, 57	4,759 3,781
	BA5 and BA7- *Secondary somatosensorial cortex* (right)/ **BA5** (left)	38, -41, 51 -16, -51, 57	5,300 3,910
	BA24 - *Cingulate Cortex* (ventral) (right, left)	5, -38, 48 -4, -33, 48	4,119 3,508
	BA32 - *Anterior Cingulate* (right, left)	5, -17, 45 -1, -17, 51	3,781 3,070
Verbal+Manual vs Baseline	**BA1, BA2 and BA3 -** *Somatosensorial Homunculus* (right) / **BA3** (left)	11, -41, 60 -4, -35, 50	4,274 4,115
	BA4 - *Primary motor cortex* (right, left)	8, -37, 66 -1, -32, 60	3,633 4,139
	BA5 - *Secondary Somatosensorial Cortex* (right, left)	20, -35, 57 -2, -50, 54	4,608 2,694
	BA21 - *Lateral temporal lobe* (right, left)	62, -23, 0 -47, -26, 6	4,321 3,043
	BA22- *Posterior parte contains Wernicke´s area* (right, left)	50, -5, 4 -58, -7, 6	5,171 4,324

	BA24 - *Cingulate Cortex* (ventral) (right, left)	5, -38, 48 -4, -35, 49	4,394 4,328
	BA38 - *Temporal Pole* (left)	-58, 7, 0	4,327
	BA41 and BA42 - *A1* (right, left)	47, -18, 7 -55, -18, 9	4,975 4,388
Verbal vs Manual	**BA21** - *Lateral temporal lobe* (left)	-64, -20, -6	5,354
	BA22- *Posterior parte contains Wernicke´s area* (right, left)	50, -5, 6 -63, -11, 6	3,863 3,832
	BA38 - *Temporal Pole* (left)	-58, 7, 0	3,716
	BA42 - *A1* (right, left)	50, -15, 9 -55, -17, 9	3,582 5,067
Manual vs Verbal	**BA1**, **BA2, BA3** - *S1* (right, left)	9, -35, 72 -16, -35, 51	4,655 3,875
	BA4 - *M1* (right, left)	26, -13, 63 -40, -11, 33	3,927 3,083
	BA6 – Premotor (right, left)	38, -2, 42 -40, -2, 42	5,112 3,192
	BA5 and **BA7 -** *S2* (right, left)	48, -35, 51 16, -35, 51	5,441 3,878
	BA10 - *Prefrontal Cortex* (right)	11, 38, 15	3,918
	BA17 - *V1* (right)	17, -47, 6	3,221
	BA18 and BA19 - *V2* (right)	29, -89, -6	4,144
	BA21 - *Lateral Temporal Lobe* (left)	-52, -17, -12	3,732
	BA23 - *Cingulate Cortex - Posterior* (right, left)	2, -38, 24 -7, -44, 30	3, 457 3,716
	BA24 - *Cingulate Cortex - Ventral* (right, left)	11, -22, 36 -13, -32, 42	4,031 2,873
	BA30 - *Retroesplenial Agranular Cortex* (right, left)	2, -38, 20 -4, -41, 15	2,755 3,947
	BA31- *Isthmus - Cingulate córtex* (right, left)	5, -53, 15 -4, -35, 36	3,227 3,755
	BA32 - *Anterior Cingulate* (right)	8, -17, 44	3,141
	BA37- *Fusiform gyrus - caudal* (right)	38, -47, -6	4,398
	BA39 - *Angular gyrus* (right)	53, -41, 18	4,106
	BA40 - *Secondary Somatosensorial representation* (right)	53, -35, 33	4,187
	BA44 - *Broca* (right, left)	38, 13, 30 -37, 13, 21	3,840 4,177
	BA46 - *Dorsolateral Prefrontal Cortex* - (right)	35, 31, 15	4,291

	Anterior Lobe Cerebellum (right, left)	17, -41, -30 -19, -38, -27	3,414 5,131
	Posterior Lobe Cerebellum (right)	14, -53, -33 -14, -53, -33 (esq.)	5,260
	Amygdala (right)	26, -2, -15	4,069
	Thalamus (right, left)	23, -29, 6 -7, -14, 9	4,864 4,905
	Brainstem-Pons (left)	-1, -29, -24	4,776
Verbal vs Manual + Verbal			
Manual + Verbal vs Verbal	**BA4 -** *M1* (right)	26, -11, 48	3,386
	BA6 - *Premotor cortex* (right)	38, -2, 36	4,410
	BA7 - *S2* (right)	44, -41, 36	3,330
	BA10 - *Prefrontal cortex* (right)	5, 49, 27	3,651
	BA18 and **BA19 -** *V2* (right)	35, -62, 0	3,882
	BA21 - *Lateral Temporal Lobe* (right)	41, -20, -3	3,597
	BA22 - *Wernicke* (right)	47, -11, -9	3,718
	BA32 - *Anterior Cingulate* (right)	11, 37, 15	2,996
	BA37 - *Fusiform Gyrus* (right)	45, -40, 12	2,585
	BA39 - *Angular Gyrus* (right)	44, -38, 12	3,217
	BA40 - *Secondary somatosensorial representation* (right)	53, -37, 33	3,215
	BA41 and **BA42** - *A1* (right)	32, -23, 15	4,106
Manual vs Manual + Verbal	**BA5** and **BA7 -** *S2* (right)	26, -47, 42	3,396
	BA31- *Isthmus - Cingulate córtex* (right)	14, -35, 39	3,393
Manual + Verbal vs Manual	**BA21 -** *Lateral Temporal lobe* (right, left)	62, -23, 0 -64, -20, -6	4,587 3,304
	BA22 - *Wernicke* (right, left)	63, -20, 6 -59, -8, 6	4,325 3,794
	BA38 - *Temporal Pole* (left)	-58, 7,0	3,142
	BA42 - *A1* (right, left)	62, -18, 9 -55, -17, 9	4,073 5,064

ICF Linking Process for Categorization of Interventions and Outcomes Measures on Stroke Physiotherapy

Authors: Patrícia Maria Duarte de Almeida[1,2], Carla Sandra Pereira[3,4], Hugo Filipe Coelho Miragaia dos Santos[1], Anabela Correia Martins[5], Emanuel Vital[6], Teresinha Noronha[7], Rui Jorge Dias Costa[8], Lia Jacobsohn[9] and Alexandre Castro Caldas[2]

[1]Alcoitão School of Health Sciences, Rua Conde Barão, Alcoitão 2649-506 Alcabideche, Portugal

[2]Institute of Health Sciences - Catholic University of Portugal, Palma de Cima 1649-023 Lisboa, Portugal

[3]Polytechnic Institute of Castelo Branco and [4] D.Estefania Hospital, Portugal

[5]College of Health Technology of Coimbra (ESTeSC) , Portugal

[6]Health Center of Marinha Grande - Pinhal Litoral II, Portugal

[7]Health Center of Caldas da Rainha - Oeste Norte, Portugal

[8]University of Aveiro, Portugal

[9]Atlantic University, Portugal

Contacts: 00351214607459; patriciamdalmeida@gmail.com

Number of words in the Abstract – 201

Number of Text words - 2837

The authors declared no potential conflicts of interest with respect to the authorship and/or publication of this article.

This study had no funding resources.

This study and manuscript haven't been presented or published anywhere before.

Abstract

Appropriate relation of dimensions and categories among interventions, outcomes and outcomes measures are needed on physiotherapy context, in order to improve rehabilitation programs and research conclusions.

International Classification of Functioning (ICF) core sets can facilitate this organization, by the use of ICF linking rules developed to link ICF categories to the common intervention and outcomes used in practice and research.

The goal of this study is to propose a categorization of PT interventions and outcome measures on stroke patients under the ICF model.

A list of 43 interventions and a list of 65 outcome measures on stroke was selected and initially categorized according to the ICF 10 linking rules, within 43 previous selected 2nd level categories related with movement. This categorization proposal was then validated on a 2-round electronic-mail survey of 7 Portuguese physical therapists using the Delphi technique.

The 43 interventions are categorized in a total of 223 ICF codes: “body functions” - 97; “body structures” - 18; “activity” - 106 and “participation” .

The 65 outcome measures are categorized in a total of 243 ICF codes: “body functions” - 86; “body structures” - 11; “activity” - 125 and “participation” - 20.

This categorization should be validated at international level.

Keywords: physiotherapy, interventions, outcome measures, ICF categorization, coherence

Introduction

The International Classification of Functioning, Disability and Health (ICF), is mainly used to facilitate interdisciplinary team communication, to structure the rehabilitation process, for goal setting and assessment and for documentation and reporting. In (electronic) clinical health care records the ICF can be used to register the findings of the patient, the findings of the therapists, the functional diagnosis, and the goals and the results of treatment. The ICF can also be used in the selection of outcomes[1] and development of the outcome measures instruments[2]. To distinguish that outcomes and outcomes measures are different issues. The first one is related with the variables that we want to measure and the second one with the instruments or tests that we can use to assess the variable.

Besides the clinical importance, ICF can also be used to formulate (in)dependent variables in research, to find literature in databases, to describe the health status or problems of patients in guidelines and in communication instruments or to select relevant assistive products for patients with problems in their functioning.

However, the ICF as a whole is not feasible and to facilitate its implementation, “ICF Core Sets” were developed[3,4]. These sets are directed to a specific health condition and/or intervention phase, comprising specific categories or outcomes.

Regarding the neurological conditions, ICF Core Sets for Acute and Post-acute phases were developed using a specific methodology of development and validation among health professionals and patients[5,6,7]. From these, specific Sets were created for specific conditions.

Regarding stroke patients, the “Comprehensive ICF Core Set for Stroke” (ICF-CSS) with 166 second level ICF categories covers the typical spectrum of problems on acute, post-acute and chronic phases[5,8]. A practice-friendly tool with 18 categories was defined – “Brief ICF Core Set for stroke” (BICF-CSS)[8] that represent 14% of the categories from the Comprehensive Core Set and should account for the most striking aspects of stroke-related functioning according to experts[9]. As ICF is a tool for several health professionals, Starrost and colleagues studied the core competence categories for physical therapists (PT), having identified 56 categories from the 166 of the ICF-CSS10[10].

For both clinical practice and research, one major barrier to analyze the intervention effects is the description of the intervention itself in a standardized way and the adequate relation with outcomes and outcomes measures[11]. Different research studies and systematic reviews show the innumerous interventions and outcome measures available for the same variables, however its coherence remains unclear. A coherence analysis in our study refers to the ICF categories and dimensions logical correspondence between interventions and outcome measures or expected impact of one dimension into other dimension. Two examples can be used to illustrate this coherence:

1) We can infer from the results of research about neuromuscular electric stimulation (NES)[12,13], that the positive effects are mainly at the dimension “body function” on categories like: b730 - muscle power functions and b735 - muscle tone functions with no impact on activity and participation on stroke patients. On our perspective this relation is coherent as the electric stimulation is directed to the fiber muscle activation or relaxation, considered as body (muscle) functions. Thus, outcomes measures directed to “body functions”

dimensions are coherent with the intervention NES but no coherence exists with the dimension “activity”. From this perspective, NES is a valid intervention on stroke rehabilitation when aiming for the muscle function but not for activity.

2) On the other hand, interventions like constraint induced therapy[14] have positive effects at the dimensions “activity” on categories like: d430 - lifting and carrying objects and d445 - hand and arm use and “body functions” on categories like: b147 - psychomotor functions and b199 - mental functions, unspecified. On our perspective this relation is also coherent, despite that constraint induced therapy has focus on activity of upper limb, the neuroplasticity phenomenon and the relation with task experience generates influence on the brain function. Thus, specific outcomes measures directed to “body functions” and “activity” dimensions are coherent with the intervention CIMT. From this perspective, CIMT is focused on “activity” but a valid intervention on stroke rehabilitation when aiming for the brain function - “body functions” and for “activity”.

This is the analysis that should be developed to every intervention, outcomes and outcomes measures in order to improve rehabilitation programs and research conclusions.

ICF core sets can facilitate this organization, by the use of ICF linking rules developed to link ICF categories to the common intervention and outcomes used in practice and research[15].

The goal of this study is to propose a categorization of PT interventions and outcome measures on stroke patients under the ICF model. The final categorization will be tested in the analysis of coherence of interventions and outcomes measures found in the systematic review "Physiotherapy Hands-on Interventions and Stroke" [16].

Methods

Definition of variables to study

Regarding two systematic reviews[16,17] and an extensive literature review[18] related with physiotherapy interventions and outcome measures for stroke rehabilitation, a list of 43 interventions (table 2) and a list of 65 outcome measures (table 3) were created and consisted on the variables to study.

ICF Linkage Process

Categorization of variables and validation process

Considering the focus of PT on stroke rehabilitation and specifically on movement related interventions, our ICF list of variables used for the linkage was retrieved from the ICF-CSS. If in one hand the ICF-CSS 166 categories are to extended as framework for our research the 18 categories of the BICF-CSS are not enough. Thus, a selection of 43 categories/outcomes of 2nd level related with movement is proposed (table 1) and used for the linkage process of the 43 interventions and 65 outcome measures selected. This selection was based on the recommendations of PT experts for stroke patient's management of movement disorders[10,19]. It almost corresponds to the goals of PT interventions for neurological conditions, found in the research of Mittrach R. et al.[11]. However, this research was directed to acute phase so didn't include categories/outcomes related with Domestic Life and Community, social and civic life, which will be included in our research.

Two researchers proposed an initial ICF categorization of the defined variables, according to the 10 linking rules[15], which was then validated with a Delphi technique on a 2-round electronic-mail survey of 7 Portuguese physical therapists with anonymity among panelists.

Delphi process

1. Development of two forms with variables = interventions and outcomes measures on stroke, previously categorized by two researchers as described above and with a brief description of each variable (as recommended by the linkage rules[15]);
2. A letter of introduction and explanation of the goals and process of this study was sent by email to the experts;
3. The 1st round was sent by email, containing the instructions and the following documents:
    a. Excel file with 3 sheets: 1) form of interventions, 2) form of outcomes measures, 3) table with the 43 selected ICF categories codes and description, 4) some outcomes specificities, 5) some interventions specificities and 6) expert characterization - to be filled in by each expert.
    b. Comprehensive ICF Core Set for Stroke
    c. ICF Linking Rules
4. To respond to the 1st round a period of 10 consecutive days was given and a reminder was sent five days before the deadline;
5. A 1st round consensus analysis was performed based on the method explained above and a 2nd round forms were created;

6. The 2nd round was sent by email, containing the instructions the excel file with two forms for final analysis and the table with the 43 selected ICF categories codes and description;
7. To respond to the 2nd round a period of 10 consecutive days was given and a reminder was sent five days before the deadline;
8. A 2nd round consensus analysis was performed based on the method explained above and a final consensus categorization achieved and presented on the results.

The goal of a Delphi technique is to gain consensus of a specific topic, by the analysis of a group of experts on that topic[20]. The stages and number of rounds may differ according to the goal of the process and the starting point of analysis[21]. As we started already with a proposal of categorization and not an open questionnaire, a 2-round method seemed to be sufficient for final consensus.

For the 1st round, experts were asked to indicate their level of agreement with a likert scale: “1 - Agree”; “2 - No opinion”; “3 - Don't agree”, to the categorization proposed and when applicable to present their proposal of categorization. For the 2nd round, experts were asked to give a dichotomous answer: yes or no. When necessary, after each round, the researchers contacted individually the experts by phone interview for further explanations of decision-making.

After the 1st round, the analysis of the level of agreement was performed on the base of the acceptance of the classification when at least 85% of the experts agreed. Categorizations were accepted when 85% of the experts agreed and the specific variable would not be included on the 2nd round.

Variables and categorizations were included for a 2nd round of analysis with a dichotomous answer when: more then two experts classified with “2- No opinion”; an expert proposed a new categorization which was coherent with the other categorizations or the literature; classifications were not coherent with classifications with similar variables.

Categorizations were proposed to be rejected when: proposals were not included on the 43 categories selected, except for the brain activity was we pretend to propose it’s inclusion to the ICF Core Set for Stroke regarding the relevance for movement; proposals were from of 3rd and 4th level; < 85% of the experts to accept the categorization.

After the 2nd round, the analysis of the level of agreement was performed on the base of the acceptance of the classification when at least 85% of the experts agreed with “yes”.

Experts’ selection and characterization

The panel of experts was selected from a group of Portuguese physiotherapists experienced on clinical use and research of ICF and neurological patients. The individual characteristics are presented on table 4.

Results

ICF Linkage for Interventions

Initial proposal of categorization

Forty-three interventions were analyzed (table 2) and clustered as: massage n=1; trunk stability training n=3; lower limb movement and gait activities n=6; upper limb movement and activities n=6; neurodevelopmental training n=1; functional activities n=4; electrical muscle stimulation n=4; conventional physiotherapy n=2; movement and activities in water n=1; joints and muscle movement n=13 and balance training n=2.

These interventions were analyzed by the panel, under a proposal of 295 categorizations in total: “body functions” - 101; “body structures” - 82; “activity” - 107; “participation - 5 (appendix 1).

Consensus of the 1st round

From the 295 categorizations proposed, 201 (68,81%) (body functions” - 80; “body structures” - 15; “activity” - 104; “participation - 2) were accepted with more than 85% of concordance; 75 were rejected (25,42%) (body functions” - 8; “body structures” - 64; “activity” - 2; “participation - 1) and 20 (6,78%) (body functions” - 12; “body structures” - 6; “activity” - 0; “participation - 2) needed a 2nd round of analysis.

Experts proposed 83 new categorizations (“body functions” - 51; “body structures” - 14; “activity” - 17; “participation” - 1), which were added to the previous 20 for the 2nd round. From these, 41 were proposed by the researchers to be rejected as they: were not included on the list of 43 categories (n=14); belonged to a 3rd level of categorization (n=2); were not coherent with similar variables categorizations or literature background (n=25).

Consensus of the 2nd round

From the 103 categorizations proposed for analysis on the 2nd round, 22 were accepted with more than 85% of concordance, the others were rejected.

Final proposal of categorization

The 43 interventions are categorized in a total of 223 ICF codes: “body functions” - 97; “body structures” - 18; “activity” - 106 and “participation” - 2 (table 2).

ICF Linkage for Outcome measures

Initial proposal of categorization

Sixty-five outcome measures were analyzed (table 3), clustered as: brain activity n=3; aerobic capacity n=1; tonus n=2; sensibility and pain n=3; articular integrity n=3; muscular strength n=6; kinetic and kinematics n=2; general motricity and sensibility functions n=3; upper limb dexterity and control n=10; balance and postural control n=14; standing and walking activities n=7; mobility and daily activities n=9 and health self perception n=2.

These outcome measures were analyzed by the panel, under a proposal of 320 categorizations in total: “body functions” - 74; “body structures” - 101; “activity” - 125; “participation - 20 (appendix 2).

Consensus of the 1st round

From the 320 categorizations proposed, 221 (69,06%) (body functions” - 78; “body structures” - 8; “activity” - 114; “participation - 20) were accepted with more than 85% of concordance; 96 were rejected (30,00%) (body functions” - 2; “body structures” - 84; “activity” - 10; “participation - 0) and 3 (0,94%) (body functions” - 3; “body structures” - 0; “activity” - 0; “participation - 0) needed a 2nd round of analysis.

Experts proposed 60 new categorizations ("body functions" - 36; "body structures" - 6; "activity" - 8; "participation" - 10), which were added to the previous 3 for the 2nd round. From these, 25 were proposed by the researchers to be rejected as they: were not included on the list of 43 categories (n=22); were not coherent with similar variables categorizations or literature background (n=3).

Consensus of the 2nd round

From the 63 categorizations proposed for analysis on the 2nd round, 22 were accepted with more than 85% of concordance, the others were rejected.

Final proposal of categorization

The 65 outcome measures are categorized in a total of 243 ICF codes: "body functions" - 86; "body structures" - 11; "activity" - 125 and "participation" - 20 (table 3).

Test application of coherence analysis of interventions and outcome measures

The final list was used to analyze the coherence of nine interventions and 13 outcomes measures.

In a general analysis of linkage with ICF domains (table 5): five interventions are related to *Body Functions* and *Activity & Participation* and three are related to *Body Structures* and *Functions*. SBM was not linked to any category related with movement. Four outcome measures are related to *Body Functions* and *Activity & Participation;* one is related to *Body Structures* and *Functions*; three are solely related to *Body Structures* and two are solely related to *Activity & Participation.*

In a specific analysis of category coherence between interventions and outcome measures, we found in general a good relation on ICF dimensions. It seems also, that by the use of outcome measures on the activity dimension, researchers are looking for the impact of some interventions applied to body structures and functions on activity. A more detailed analysis is found on table 5.

Discussion

The interventions analyzed are coherent with the interventions found on the latest systematic review about evidence of physiotherapy for stroke[22]. Similarly with this systematic review our results indicate that physiotherapy interventions are mainly directed to “body functions” and “activity” dimensions. Curiously, only CIMT was categorized in the dimension “participation”. This result can be questionable regarding the opinion of the panelists, nevertheless can also be a point of reflection regarding the other interventions that theoretically claim that they are promoting social participation of patients.

Coherently outcome measures used by physiotherapists are also mainly directed to “body functions” and “activity” dimensions. However, more outcome measures aim to assess “participation” dimension, which confirms the idea that physiotherapy pretends to contribute for improvement of social participation.

From this we can open the discussion: do the interventions directed to “activity” dimension contribute for “participation”? If yes, which ones have this impact? Do physiotherapy have more interventions directed to participation? Again studies of coherence are needed to respond these questions or others related.

The clusters of interventions and outcome measures are consistent with the categorization proposed, highlighting the expertise and opinion of the panelists and the result of the Delphi process.

According to the proposal of the some panelists, the codes b750 (Functions of involuntary contraction of muscles automatically induced by specific stimuli.) and b176 (Mental function of sequencing complex movements.), could have been applied to some of the interventions, however, the agreement of the panel in total didn't achieve more than 85% for acceptance. Despite that these categorizations are part of the ICF-CSS and are relevant to be added to the 43 categories previously selected, the result of this Delphi process will not include them in this phase..

Another aspect of discussion was the categorization of falls on the ICF. Falls are categorized on the activity level regarding the disturbances of walking[23]. Falls in people with stroke are extremely common and present a significant health risk to this population. Development of fall screening tools is an essential component of a comprehensive fall reduction plan[24]. However, considering that falls on stroke patients are mostly related with lack of postural and movement control and environment awareness, this variable needs further attention on ICF categorization analysis.

One of our critics to the ICF-CSS and to the BICF-CSS, is the limited inclusion of outcomes related with *Structure* and *Function* of the brain, regarding the importance of those in neurological conditions and stroke. Motor and movement performance on healthy and neurological injured subjects, is directly related with brain performance and reorganization[25], thus these variables are of extreme importance when dealing with stroke patients. Consequently, as a framework for our research, the categories/outcomes *b147* (specific mental functions of control over both motor and psychological events at the body level) and *b199* (mental functions, unspecified), which relate brain functions to movement, were added to the 43 categories/outcomes of table 1. with 100% of consensus of the panelists. May this information reach the working groups of ICF later for analysis.

From the test of using the final categorization, we could make more clear the relation between interventions and outcomes measures, being of easy application. Good levels of coherence were verified for most of the studies. Curiously massage has no linkage with the selected ICF categories related to movement. However, the efficacy is important with regard to how frequent the shoulder pain occurs in stroke patients.

Conclusion

This categorization can become a framework for better understanding and relation among interventions and outcomes.

The use of a Delphi method to obtain consensus of an expert's panel, for the proposed categorization of 43 interventions and 65 outcome measures, was successful and permitted a consensus after 2 rounds.

As the starting point was a already structured document requiring expert validation, the use of a 3 items Likert scale on the first round and dichotomous answer on second round showed to be efficient. However the number of experts showed to be small, when deciding for controversial classifications like Berg scale or Massage intervention. Also the use of a panel constituted by Portuguese experts constraints the external validity of results in the international context.

Thus, continuity for international analysis should be performed for this framework.

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Tables

Table 1. Authors's selection of 43 ICF Core Set for Stroke Categories related with Movement

BODY FUNCTIONS	ACTIVITY & PARTICIPATION
Chapter 2: Sensory functions and pain	**Chapter 4: Mobility**
b260 Proprioceptive functions	d410 Changing basic body position
b265 Touch function	d415 Maintaining a body position
b280 Sensation of pain	d420 Transferring oneself
Chapter 4: Functions of the cardiovascular, hematological, immunological and respiratory systems	d430 Lifting and carrying objects d435 Moving objects with lower extremities
b455 Exercise tolerance function	d440 Fine hand use
	d445 Hand and arm use
Chapter 7: Neuromusculoskeletal and movement-related functions	d450 Walking
b710 Mobility of joint functions	d455 Moving around
b715 Stability of joint functions	d460 Moving around in different locations (d455)
b730 Muscle power functions	d465 Moving around using equipment
b735 Muscle tone functions	d470 Using transportation
b740 Muscle endurance functions	d475 Driving
b755 Involuntary movement reactions	**Chapter 5: Self-care**
b760 Control of voluntary movement functions	d510 Washing oneself
b770 Gait pattern functions	d520 Caring for body parts
b780 Sensations related to muscles and movement functions	d530 Toileting
	d540 Dressing
BODY STRUCTURES	d550 Eating
Chapter 1: Structures of the nervous system	d560 Drinking
s110 Structure of brain	**Chapter 6: Domestic life**
Chapter 7: Structures related to movement	d620 Acquisition of goods and services
s710 Structure of head and neck region	d630 Preparing meals
s720 Structure of shoulder region	d640 Doing housework
s730 Structure of upper extremity	**Chapter 9: Community, social and civic life**
s750 Structure of lower extremity	d910 Community life
s760 Structure of trunk	d920 Recreation and leisure

Table 2. Physiotherapy Interventions for Stroke submitted to ICF linkage

	Clinical Intervention	Description	Body functions	Body Structures	Activity	Participation	Additional Information
Massage	Slow-stroke back massage	Effleurage and pettrissage on the muscles of the neck, dorsal and low back	b735				Muscle tonus
Trunk stability training	Trunk exercises for stability	Muscle strength during lying and sitting activities and active trunk control on sitting activities	b730		d415		Muscle power and maintaining body position
	Training UL reach activities for trunk stabilization	Use of bilateral and unilateral reaching tasks to improve trunk control	b730		d415		Muscle power and maintaining body position
	PNF on trunk	Rhythmic stabilizations on trunk	b260 b715 b730 b735 b740		d415		Proprioceptive, stability, muscle power, tone and endurance
lower limb movement and gait activities	PNF on Lower limb	Diagonal for flexion, adduction and external rotation with resistance, on lower limb on standing position, simulating gait	b260 b730 b735 b740				Proprioceptive, muscle power, tone and endurance
	Treadmill with BWS	Walking on a treadmill with discharge of weight (suspension)	b760 b770		d450		Control of voluntary movements and gait
	Facilitation technique during treadmill training	Hands on the pelvic girdle and thigh to facilitate the flexion of the hip and knee during swing phase	b260 b265		d450		Proprioceptive, touch, control of voluntary

			b760 b770		movements and gait
	Facilitation technique during walking backwards training	hands on the pelvic girdle to facilitate movement dissociation	b260 b265 b760 b770 b780	d450	Proprioceptive, touch, control of voluntary movements and gait
	Cycling ergometer	Cycling ergometer	b455 b740		Exercise tolerance and endurance
	Sit-to-stand practice	Repetitive training of activities that demand sit-to-stand		d420 d410	Changing basic position and transference
upper limb movement and activities	Mirror therapy	Application of a Mirror on the affected hand to move the non affected hand and view the movement on the affected side	b260 b760	d445	Proprioceptive, control of voluntary movement and hand use
	Sensorimotor Active Rehabilitation Training (SMART)	Arrangement of a pulley, weights and near-friction less linear track, provides a goal for movement, feedback on performance via an interactive computer program and incremental increases in load and reaching range	b260 b730 b760	d440	Proprioceptive, control of voluntary movement, hand use and muscle power
	General Responsibility Assignment Software Patterns (GRASP)	Functional activities for upper limb: reach, folding cloth, put the buttons, carrying objects	b730 b740	d430 d440 d445	Muscle power and endurance, gross motor and hand fine use
	Coupled bilateral movements for upper limb	Training of activities with bilateral performance of upper limbs		d430 d440 d445	Gross motor and hand fine use
	Unilateral training	Training of activities for UL unilaterally	b730	d430	Muscle power

				d440 d445		and gross motor and hand fine use
	Constraint induced movement therapy (CIMT) and Short CIMT	Directed to upper extremity function by increasing the use of their affected upper limb in all functions and activities by restraint of the less affected arm or hand. Restraint to be used during at least 3 hours a day	b260 b760 b780	d430 d440 d445 d510 d520 d530 d540 d550 d560	d630 d640	Proprioceptive, control of voluntary movement, upper limb mobility, self-care and domestic life
neurodevelopmental training	Bobath	Typical bobath facilitation or neurodevelopmental approach for movements and activities	b260 b265 b710 b715 b730 b760 b770	d410 d415 d420 d430 d435 d440 d445 d450 d455 d510 d520 d530 d540 d550 d560		Proprioceptive, touch, mobility and stability, muscle power, control of voluntary movement, gait functions, mobility and self-care

functional activities	Imagetics	Mental visualization of limb movements or activities	b260 b760 b780	d410 d415 d420 d430 d435 d440 d445 d450 d455 d510 d520 d530 d540 d550 d560	Proprioceptive, control of voluntary movement, sensations related with movement, mobility and self-care
	Task-oriented approach	Intensive practice a specific task (upper limb or lower limb)		d410 d415 d420 d430 d435 d440 d445 d450	Mobility and stability, muscle power, control of voluntary movement, gait functions, mobility and self-care
	Standing activities	Activities with trunk and upper limb for trunk control and lower limb	b260 b760	d415	Proprioceptive, control of voluntary movement, sensations

			b780		related with movement, maintaining body position
	Circuit exercises	Variety of functional exercises sitting and standing in a circuit	b730 b740	d420 d430 d435 d445 d450 d455	Muscle power and endurance and mobility
electrical muscle stimulation	TENS	Application for spasticity reduction	b735 b280		Sensation and tonus
	Functional electric stimulation	Surface Electric stimulation on the muscles during functional activities for synchronized contraction	b730		Muscle power
	Neuromuscular electric stimulation	Surface Electric stimulation on the muscles for contraction	b730		Muscle power
	Intramuscular electric stimulation	Deep electric stimulation on the muscles for contraction	b730		Muscle power
conventional physiotherapy	CPT Conventional Physical Therapy 1	Physiotherapist hands on therapy with joints and muscles preparation for activity and activity training	b260 b265 b710 b715 b730 b760 b770 b780 b735	d410 d415 d420 d430 d435 d440 d445 d450 d455 d510	Proprioceptive, touch, mobility and stability, muscle power, control of voluntary movement, gait functions, mobility and self-care

				d520 d530 d540 d550 d560	
	CPT Conventional Physical Therapy 2	Functional exercises with verbal feedback or supervision	b710 b715 b730 b760 b770 b780	d415 d420 d430 d435 d440 d445 d450 d455 d510 d520 d530 d540 d550 d560	Proprioceptive, mobility and stability, muscle power, control of voluntary movement, gait functions, mobility and self-care
activities in water	Physical activity in water	Upper limb, trunk and lower limb exercises in water	b730 b735 b740 b760	d445 d450	Muscle power, tonus and endurance, control of voluntary movements, hand and arm use and walking
and muscle moveme	Local vibration	Application of a electrical vibrator on a specific muscle or tendon to recruit muscle activity	b730		Muscle power

Whole-body vibration	Application of a electrical vibrator platform to recruit general muscle activity and stabilization	b730		Muscle power
Proprioceptive training (passive)	External feedback of expected movement (screen, biofeedback)	b260 b760		Proprioceptive and control of voluntary movement
ROM exercises	Additional passive facilitation to physiological movements of upper and lower limb	b710	s730 s750	Mobility of joints
Self mobilization	Patient auto-mobilizing joints passively with the help of the other limb or external aid (sling)	b710	s730 s750	Mobility of joints
Mobilization and Touch stimulation	Upper limb joint and soft tissue mobilization techniques and passive or active-movement with the aim of priming and/or augmenting activity in the motor execution system to enhance the ability to voluntarily contract paretic muscle	b265 b710 b735	s730 s750	Touch, mobility of joints and muscle tonus
Stretching	Passive stretching	b710 b735	s730 s750 s760	Mobility of joints and muscle tonus
Positioning for static stretching	Use of static maintained stretched positions for upper or lower limbs muscles	b710 b735	s730 s750	Mobility of joints and muscle tonus
Splint for stretching	Use of hand or ankle ortothesis on stretch positions	b710 b735	s730 s750	Mobility of joints and muscle tonus
Joint tapping	Tapping for joint stabilization with movement	b715	s730 s750	Stability of joints and muscle tonus
Muscle tapping	Tapping for muscular stimulation	b730		Muscle power
Resistance training	Application of resistance to upper limb or lower limb movements, for strength	b265 b730	s730 s750	Muscle power
Inspiratory muscles training	Use of a Threshold device	b455		Exercise

			b730			tolerance and endurance
balance training	Balance control training platform	Maintain or shift weight, in the sagittal and frontal plane as appropriate, to control the center of gravity presented visually on a screen	b260		d415	Proprioceptive and maintaining body position
	Balance training	Use of activities with upper limb for trunk and lower limb stabilization in sitting and standing activities	b260	s760	d415	Proprioceptive and maintaining body position

Table 3. Physiotherapy Outcome Measures for Stroke submitted to ICF linkage

	Outcome Measure	Description	Body functions	Body Structures	Activity	Participation	Additional Information
Brain activity	fMRI	Brain activity	b147* b199*	s110			Psychomotor and mental functions
	TMS	Brain activity	b147* b199*	s110			Psychomotor and mental functions
	PET	Brain activity	b147* b199*	s110			Psychomotor and mental functions
AC	Aerobic capacity	VO2 max	b455				Exercise tolerance
Tonus	(Modified) Ashworth Scale	Tone - spasticity	b735				Muscle tonus
	Composite Spasticity Scale	Tone - spasticity	b735				Muscle tonus
Sens.	2 point Discrimination Test	Discriminative sensibility	b260				Proprioceptive
Pain	Visual Analogue Scale (VAS)	Pain	b280				Sensation of pain
	Pain Scale	Pain	b280				Sensation of pain
Articular integrity	Radiographic image	Shoulder sub-luxation image	b715	s730 s720			Stability of joints
	Ritchie Articular Index	Range of motion	b710	s730 s750			Mobility of joints
	Goniometer	Range of motion	b710	s730 s750			Mobility of joints
cula r stre	JAMAR - dynamometer	Muscular strength	b730	s730			Muscle power

	Dynamometer	Muscular strength	b730		Muscle power
	EMG	Muscular strength	b730		Muscle power
	Biodex	Muscular strength	b730		Muscle power
	Muscular Testing	Muscular strength	b730		Muscle power
	Motricity Index	Measure strength in upper and lower extremities after stroke	b730		Muscle power
Kinetic and kinematics	Force Platform	Movement forces and angles for standing or gait activities	b770 b730	d410 d415 d450	Muscle power, gait pattern and walking and maintaining position
	GAITrite System	Carpet with sensors to acquire temporal and spatial gait parameters	b770	d450	Gait pattern and walking
General motricity and sensibilityfunctions	Fugl-Meyer Assessment (motor and sensoric)	Joint motion, joint stability, pain, sensibility, balance and muscle strength	b710 b715 b280 b260 b265 b780 b730	d415	Joint mobility and stability, pain, proprioceptive, muscle power and tonus and maintaining position
	Brunnstrom Scale	Joint motion, sensibility, balance and muscle strength	b710 b260 b265 b780 b730	d415	Joint mobility, pain, proprioceptive, muscle power and tonus and maintaining position
	Stroke Rehabilitation Assessment of Movement Measure (STREAM)	Joint motion, joint stability, balance, coordination and muscle strength	b710	d410	Joint mobility and stability,

			b715 b760 b730	d415 d420	muscle power, control of voluntary movement, changing and maintaining position and transferring
upper limb dexterity and control	16 Hole Peg-test	Finger dexterity (fine) with time measure (control, strength and ROM)	b710 b730 b760	d440	Joint mobility, muscle power, control of voluntary movement and hand fine use
	9 Hole Peg-test	Finger dexterity (fine) with time measure (control, strength and ROM)	b710 b730 b760	d440	Joint mobility, muscle power, control of voluntary movement and hand fine use
	Box and Block Test	Finger dexterity (fine) with time measure (control, strength and ROM)	b710 b730 b760	d440	Joint mobility, muscle power, control of voluntary movement and hand fine use
	Ebsen Taylor Test	Fine motor skills activities (control, strength and ROM)	b710 b730 b760	d440 d445	Joint mobility, muscle power, control of voluntary movement and hand and arm use
	Wolf Motor Function Test (WMFT)	Dexterity, strength and upper limb use (control, strength and ROM)	b710 b730	d440 d455	Joint mobility, muscle power, control of voluntary movement and

		b760		hand and arm use
Sollerman Hand Function Test	Hand use for several activities: coins, writing, opening a door, screwdriver, zipper, paper, envelopes (control, strength and ROM)	b710 b730 b760	d440 d445	Joint mobility, muscle power, control of voluntary movement and hand and arm use
Arm Research Attainable Test (ARAT)	Grasp, Grip, Pinch, Gross Movement (control, strength and ROM)	b710 b730 b760	d440 d445	Joint mobility, muscle power, control of voluntary movement and hand and arm use
Test d'Évaluation des Membres Supérieurs des Personnes Âgées (TEMPA)	Strength, ROM and precision on hand and upper limb use on specific activities (coins, cards, writing, opening)	b710 b730 b760	d440 d445	Joint mobility, muscle power, control of voluntary movement and hand and arm use
Frenchay Arm Test	Proximal and distal control of upper limb during activities (strength and ROM)	b710 b730 b760	d440 d445	Joint mobility, muscle power, control of voluntary movement and hand and arm use
Arm Motor Ability Test	Tests fine and gross motor skills, handling a mug, coin, buttons, a spoon	b710 b730 b760	d440 d445	Joint mobility, muscle power, control of voluntary movement and hand and arm use
Biofeedback	Awareness of many physiological functions	b710	d415	Maintaining

	(postural sway, strength, ROM)	b730 b760		position, muscle power and joint mobility
Number of Falls	Postural and movement control during gait		d450	Walking
Romberg Test	Balance		d415	Maintaining position
Assessment Trunk Control Test	Rolling to weak side, rolling to strong side, balance in sitting position, sit up from lying down		d415	Maintaining position
Berg Scale	Sitting and Standing balance and transfers		d415 d420 d410	Maintaining position, changing and transferring
Activities-specific Balance Confidence Scale	Level of confidence on balance during sitting and standing activities		d415	Maintaining position
Trunk Impairment Scale	Static and dynamic sitting balance		d415	Maintaining position
Four Test Balance Scale	Static standing balance		d415	Maintaining position
Postural Assessment Scale for Stroke (PASS)	Ability to maintain or change a given lying, sitting, or standing posture		d410 d415	Maintaining position and changing
Standing Balance Test	One leg standing balance		d415	Maintaining position
Upright Motor Control Test	One leg standing balance and ability to flex and extend	b730	d415	Maintaining position and muscle power
Activities-based Confidence Scale	16-item self-report measure in which patients rate their balance confidence for performing activities: reach, walk around, standing		d415 d420 d450 d455	Maintaining position, changing and transferring, walking and moving around

	Tinetti Balance & Gait Scale	Sitting and standing balance, gait temporal and spatial parameters	b770		d410 d415 d450	Maintaining position, changing, walking and gait pattern
	Dynamic Gait Index Maximum Reach Distance	Balance during walking	b770		d415 d450	Maintaining position, walking and gait pattern
standing and walking activities	Functional Ambulance Category (FAC)	Level of assistance for walking	b770		d450	Gait pattern and walking
	Fast Gait Speed	Speed	b770		d450	Gait pattern and walking
	6 min Walking Test	Distance gait parameter and exercise tolerance	b770 b455	s750	d450	Gait pattern, walking and exercise tolerance
	10 m Walking Test	Velocity gait parameter	b770		d450	Gait pattern and walking
	Timed-up and Go Test (TUG)	Time spent to stand, walk, and seat back again	b770		d420 d450	Gait pattern, walking and transferring
	Sit To Stand Repetitions	Amount of times able to sit-to-stand in a certain timing			d420	Transferring
	Gait parameters	Speed, distance, step, cadence	b770		d450	Gait pattern and walking
mobility and daily activities	Chedoke McMaster Stroke Assessment	Limbs strength and tone, pain, balance, mobility on the bed, walking indoor and outdoor, stairs	b730 b735 b280		d415 d420 d450 d455 d460	Muscle power and tonus, pain, walking, maintaining position and transferring
	Rivermed Index	Ability to perform activities: turning on the bed, sit, stand up, walk, shower			d410 d420 d450	Mobility activities

		d455 d460 d510		
Functional Independence Measure (FIM)	Eating, Grooming, Bathing, Upper body dressing, Lower body dressing, Toileting, Bed to chair transfer, Toilet transfer, Shower transfer, Locomotion (ambulatory or wheelchair level) ,Stairs, Social interaction, Problem solving	d550 d510 d520 d540 d530 d420 d450 d460	d630 d640 d910 d920	Mobility activities, domestic life, community and social life
Barthel Index	Feeding, Bathing, Grooming, Dressing, Toileting, Chair transfer, Ambulation, Stair climbing	d550 d510 d520 d530 d420 d450 d455 d465 d540		Mobility activities and self-care
Motor Activity Scale (MAS) Modified MAS	Rolling, Lie to sit, Balanced sitting, Sit to stand, Walking, Upper arm function, Hand movements, Advanced hand activities	d410 d420 d415 d450 d455 d440		Mobility activities

		d445		
Motor Activity Log (MAL)	Functional activities for arm, hand and fingers use, wash hands, wash teeth, dressing, carrying objects, drink, write, using fork, comb hair, put make-up, buttons, open a door	d430 d440 d445 d510 d520 d530 d540 d550 d560		Mobility activities and self-care
Physical Activity and Disability Scale	Measuring amount of exercise, leisure time physical activity, and household activity		d640 d920	Domestic life and community and social life
Rehab Activities Profile Index (RAP)	Balance, changing position, walking, stairs, using transport, eating, drinking, washing, dressing, providing meals, householding, leisure activities	d410 d415 d450 d470 d510 d520 d530 d540 d550 d560	d630 d640 d920	Mobility activities, self-care, domestic life, community and social life
Frenchay Activities Index	Preparing meals, housework, driving, social, doing shopping, walking	d450 d460 d474	d620 d630 d640 d910	Walking, moving around, driving, domestic life and community and social life

				d920	
health self perception	Stroke Impact Scale (SIS)	Self perception of most affected limb, fine and gross motor skills, transferring, walking, self-care, domestic life community life and recreation	d420 d450 d460 d510 d530 d540 d550	d620 d630 d640 d910 d920	Mobility activities, self-care, domestic life, community and social life
	SF-36	Physical Functioning, Role Limitations due to Physical Problems, General Health Perceptions, Vitality, Social Functioning, Role Limitations due to Emotional Problems, General Mental Health, Health Transition	d410** d445** d450** d455** d510**	d920**	Mobility activities, self-care, community and social life

* Not present on the ICF core Set for Stroke- proposal to be included regarding the need of neuroplasticity for stroke recovery, thus the need of outcome measures on the brain synapses function.

** Categorization already proposed by Faria CDCM, Silva SM, Corrêa JCF, Laurentino GEC, Teixeira-Salmela LF. Identificação das categorias de participação da CIF em instrumentos de qualidade de vida utilizados em indivíduos acometidos pelo acidente vascular encefálico. Rev Panam Salud Publica. 2012:31(4):338–44.

Table 4. Characteristics of Experts

	EXPERTS						
CHARACTERISTICS	1	2	3	4	5	6	7
Years of experience ICF	13	13	12	10	12	12	12
Context	E,P	E,P	E,P	E	P	E,P	E,P
Clinical experience in neurology	□	□	□	□	□	□	□
How long (years)	19	13	8	0	30	29	30
ICF working groups	□	□	□	□	□	□	□
National	□	□	□	□	□	□	□
International	-	□	-	-	-	-	-
Research group	□	□	□	□	□	□	□
National	□	-	-	□	□	□	□
International	-	□	-	-	-	-	-
Research projects	3	58	0	0	2	1	1
Research projects ICF	3	30	0	0	0	0	1
ICF publications	4	45	0	1	2	1	0
Other publications	2	78	0	15	12	7	1
ICF communications	15	30	0	14	6	5	1

Legend: E-education; P-practice

Table 5. Hands on interventions identified and respective outcome measures and link with ICF categories

Intervention	ICF link to the intervention			ICF link to the outcome measure			Outcome measures	Coherence
	Structure	Function	Activity & Participation	Structure	Function	Activity & Participation		
Proprioceptive Neuromuscular Facilitation (PNF-T) trunk exercises (35)	-	b260 b715 b730 b735 b740	d415	-	b710 b730 b760	d440 d445	Functional Reach Test	Good relation on the domains of body function and activity. However, intervention is centered on trunk function and control and the outcome measures focus on the function and activity of upper limb mobility.
					b730		EMG (soleus, hamstrings, quadriceps, tibialis anterior)	
Range Of Motion (ROM) exercises (36)	s730 s750	b710	-	-	-	d420 d450 d460 d510 d520 d530 d540 d550 d630 d640 d910 d920	FIM (ADL sub-scale)	Intervention centered on the domain of body structures and functions, related with mobility of the limbs. The outcomes measures comprise these domains and specific categories but also look on the sensation of pain and on impact on activities: mobility, self-care, domestic life and community, social and civic life.
				s730 s750	b710	-	Goniometer	
					b280	-	Pain scale of 3 ratings	
Bobath therapy for upper limb function (BT) (26)	-	b260 b265 b710 b715 b730 b760 b770	d410 d415 d420 d430 d435 d440 d445 d450 d455 d510 d520 d530 d540 d550	-	b260 b265 b280 b710 b715 b730 b780	d415	Fugl-Meyer test	Good relation on the domains and categories on the body functions, centered on proprioceptive and touch, mobility, stability and control of voluntary movements. The domain of Activity is wider for the intervention when compared with the outcome measure, aiming for integration of upper limb on specific activities of mobility and self-care.
				-	b710 b730 b760	d440 d445	ARAT	

			d560					
Mobilization and Tactile Stimulation (PMTS) on upper limb function (42)	s730 s750	b265 b710 b735	-	-	b730	-	Motricity index	Intervention centered on the domain of Body structures of upper limb and functions of touch, mobility and muscle tone. The outcome measures differ on the categories of the body functions, focused on muscle power and control of voluntary movements; have no structures and look for the impact on the domain of activity of upper limb mobility.
				-	b710 b730 b760	d440 d445	ARAT	
Slow-stroke back massage (SSBM) (39)	-	-	-	-	b280	-	VAS	Intervention has no codification on the selected categories related with movement. Outcome measures related with movement are only on the domain of body functions and the category of pain.
Facilitation technique coupled with treadmill (FT-BWSTT) (38)	-	b260 b265 b760 b770	d450	-	-	d420 d450 d460 d510 d520 d530 d540 d550 d630 d640 d910 d920	FIM	Intervention is centered on body functions related with proprioception and control of movement and activity of walking. The outcome measures, assess these categories and also activities where walking is integrated related with mobility, self-care, domestic life and community, social and civic life.
				-	b260 b265 b280 b710 b715 b730 b780	d415	Fugl-Meyer	
				-	b770	d450	Gait velocity	
				-	b770	d450	Gait cadence	
PNF-based exercise for gait (PNF-G) (37)	-	b260 b730 b735 b740	-	-	b770	d450	Gait temporal parameters (velocity, phase time)	No direct relation between the intervention and the outcome measures. Intervention is centered on the domain of functions of muscles and outcomes measures are focused on gait pattern functions and activity of walking.
				-	b770	d450	Gait spatial parameters (step length)	
				-	-	d450	FAP	
Conventional Physical	-	b260	d410	-	-	d410	Rivermed index	Intervention is centered on body functions related

Therapy (CPT) (40)		b265 b710 b715 b730 b735 b760	d415 d420 d430 d435 d440 d445 d450 d455 d510 d520 d530 d540 d550 d560			d420 d450 d455 d460 d510		with proprioception, muscle and control of movement and on activities related with mobility, self-care and domestic life. Outcome measures are centered on gait pattern functions and activities related with mobility only.
				-	b770	d450	Gait velocity	
				-	b770	d450	Gait cadence	
				-	b770	d450	Step length	
				-	b770	-	Knee peak torque	
Backward walking with facilitation technique (BWTFT) (41)	-	b260 b265 b760 b770 b780	d450	-	b770	d450	Gait velocity	Good relation between intervention and outcome measures. Intervention is centered on body functions related with proprioception, muscle, control of movement and gait pattern functions, and with walking activity. Outcome measures focus on gait pattern functions and walking activity.
				-	b770	d450	Step length	
				-	b770	-	Symmetry index	

Appendices

Appendix 1. Interventions' proposal of categorization submitted to the Delphi process

ICF language linking process to Physiotherapy Clinical Interventions in Stroke (identified on Systematic Reviews)

Delphi Panel Validation - 1st Round

Dear expert, below I am proposing a categorization for specific **Clinical interventions** for Stroke. This categorization was based on: **1) Description** of how that intervention was applied, **2) ICF linking rules** (see article attached on the email) and **3) 43 ICF categories** related with movement selected from ICF Core Set for Stroke (see respective sheet below).

Please indicate your Level of Agreement to the categorization proposed and when applicable present your Proposal of categorization. When you agree with all the categorizations but you consider more to be included, present it on cell for proposals.

LIKERT SCALE - Level of Agreement: **1** - Agree **2** - No opinion **3** - Don't agree

		ICF Categorization											
Clinical Intervention	Description	Body functions	Level of Agreement	Proposal	Body Structures	Level of Agreement	Proposal	Activity	Level of Agreement	Proposal	Participation	Level of Agreement	Proposal
Slow-stroke back massage	Effleurage and pettrisage on the muscles of the neck, dorsal and low back	b735			s760								
Trunk exercises for stability	Muscle strenght during lying and sitting activities and	b730			s760			d415					

	active trunk control on sitting activities				
Training UL reach activities for trunk stabilization	Use of bilateral and unilateral reaching tasks to improve trunk control	b730	s760	d415	
PNF on trunk	Rhytmic stabilizations on trunk	b260 b715 b730 b735 b740	s760	d415	
PNF on Lower limb	Diagonal for flexion, adduction and external rotation with resistance, on lower limb on standing position, simulating gait	b260 b730 b735 b740	s750 s760	d450	
Treadmill with BWS	Walking on a treadmill with discharge of weight (suspension)	b760 b770	s750	d450	
Facilitation technique during treadmill training	Hands on the pelvic girdle and thigh to facilitate the flexion of the hip and knee during swing phase	b260 b265 b760 b770	s750	d450	

		b780			
Facilitation technique during walking backwards training	hands on the pelvic girdle to facilitate movement dissociation	b260 b265 b760 b770 b780	s750	d450	
Cycling ergometer	Cycling ergometer	b455 b730 b740	s750		
Sit-to-stand practice	Repetitive tranning of activites that demand sit-to-stand	b730 b740	s750 s760	d420	
Mirror therapy	Application of a Mirror on the affected hand to move the non affected hand and view the movement on the affected side	b260 b760 b780	s730	d445	
Sensorimotor Active Rehabilitation Training (SMART)	Arrangement of a pulley, weights and near-friction less linear track, provides a goal for movement, feedback on performance via an interactive computer	b260 b730 b760 b780	s730	d440	

	program and incremental increases in load and reaching range				
General Responsibility Assignment Software Patterns (GRASP)	Functional activities for upper limb: reach, folding cloth, put the buttons, carrying objects		s730	d430 d440 d445	
Coupled bilateral movements for upper limb	Training of activities with bilateral performance of upper limbs		s730	d430 d440 d445	
Unilateral tranning	Tranning of activities for UL unilaterally		s730	d430 d440 d445	
Constraint induced movement therapy (CIMT) and Short CIMT	Directed to upper extremity function by increasing the use of their affected upper limb in all functions and activities by restraint of the less affected arm or hand. Restraint to be used during at least 3 hours a day	b260 b760 b780	s730	d430 d440 d445 d510 d520 d530 d540 d550 d560	d620 d630 d640
Bobath	Typical bobath	b260	s710	d410	d640

	facilitation or neurodevelopmental approachfor movements and ativities	b265 b710 b715 b730 b760 b770 b780	s720 s730 s750 s760	d415 d420 d430 d435 d440 d445 d450 d455 d510 d520 d530 d540 d550 d560	
Imagetics	Mental visualization of limb movements or activities	b260 b760 b780	s710 s720 s730 s750 s760	d410 d415 d420 d430 d435 d440 d445 d450 d455 d510 d520 d530 d540 d550 d560	

Task-oriented approach	Intensive practice a specific task (upper limb or lower limb)		s730 s750 s760	d410 d415 d420 d430 d435 d440 d445 d450	
TENS	Application for spasticity reduction	b735	s730, s750*		
Functional electric stimulation	Surface Electric stimulation on the muscles during funcrional activities for sincronized contraction	b730	s730, s750*		
Neuromuscular electric stimulation	Surface Electric stimulation on the muscles for contraction	b730	s730, s750*		
Intramuscular electric stimulation	Deep electric stimulation on the muscles for contraction	b730	s730, s750*		
CPT Conventional Physical Therapy 1	Physiotherapist hands on therapy with joints and muscles preparation for activity and	b260 b265 b710 b715 b730	s710 s720 s730 s750 s760	d410 d415 d420 d430 d435	d640

	activity trainning	b760 b770 b780		d440 d445 d450 d455 d510 d520 d530 d540 d550 d560	
CPT Conventional Physical Therapy 2	Functional exercises with verbal feedback or supervision	b710 b715 b730 b760 b770 b780	s720 s730 s750 s760	d415 d420 d430 d435 d440 d445 d450 d455 d510 d520 d530 d540 d550 d560	
Standing activities	Activities with trunk and upper limb for trunk control and lower limb	b260 b760 b780	s750 s760	d415	
Circuit exercises	Variety of funtional exercises sitting	b730	s730	d420	

	and standing in a circuit	b740	s750 s760	d430 d435 d445 d450 d455	
Physical activity in water	Upper limb, trunk and lower limb exercises in water	b730 b735 b740 b760	s730 s750 s760	d445 d450	
Local vibration	Apllication of a electrical vibrator on a specific muscle or tendon to recruit muscle activity	b730	s730, s750*	d415	
Whole-body vibration	Apllication of a electrical vibrator platformn to recruit general muscle activity and stabilization	b730	s730 s750 s760		
Proprioceptive training (passive)	External feedback of expected movement (screen, biofeedback)	b260 b760	s730, s750*		
ROM exercises	Additional passive facilitation to	b710	s730, s750*		

	physiological movements of upper and lower limb				
Self mobilisation	Patient auto-mobilizing joints passively with the help of the other limb or external aid (sling)	b710	s730, s750*		
Mobilisation and Touch stimulation	Upper limb joint and soft tissue mobilization techniques and passive or active-movement with the aim of priming and/or augmenting activity in the motor execution system to enhance the ability to voluntarily contract paretic muscle	b265 b710 b735	s730, s750*		
Balance control training platform	Maintain or shift weight, in the sagittal and frontal plane as appropriate, to controlf the center of gravity presented visually on a screen	b260	s750 s760	d415	

Balance tranning	Use of activities with upper limb for trunk amd lower limb stabilization in sitting and standing activities	b260	s750 s760	d415	
Resistance training	Application of resistance to upper limb or lower limb movements, for strenght	b265 b730	s730, s750*		
Streching	Passive streching	b710 b735	s730, s750*		
Positioning for static streching	Use of static mantained streched positions for upper or lower limbs muscles	b710 b735	s730, s750*		
Splint for streching	Use of hand or ankle ortothesis on strech positions	b710 b735	s730, s750*		
Joint tapping	Tapping for joint stabilization with movement	b715	s730, s750*		
Muscle tapping	Tapping for muscular stimulation	b730	s730, s750*		
Inspiratory muscles traning	Use of a Threshold device	b455 b730	s760		

Appendix 2. Outcome Measures' proposal of categorization submitted to the Delphi process

ICF language linking process to Physiotherapy Clinical Interventions in Stroke (identified on Systematic Reviews)

Delphi Panel Validation - 1st Round

Dear expert, below I am proposing a categorization for specific **Outcome Measures** for Stroke. This categorization was based on: **1) Description** of what that instrument measures, **2) ICF linking rules** (see article attached on the email) and **3) 43 ICF categories** related with movement selected from ICF Core Set for Stroke (see respective sheet below).

Please indicate your Level of Agreement (Likert scale) to the categorization proposed and when applicable present your Proposal of categorization. When you agree with all the categorizations but you consider more to be included, present it on cell for proposals.

LIKERT SCALE - Level of Agreement: **1** - Agree **2** - No opinion **3** - Don't agree

		ICF Categorization											
Clinical Intervention	Description	Body functions	Level of Agreement	Proposal	Body Structures	Level of Agreement	Proposal	Activity	Level of Agreement	Proposal	Participation	Level of Agreement	Proposal
fMRI	Brain activity	b199*			s110								
TMS	Brain activity	b199*			s110								
PET	Brain activity	b199*			s110								
Aerobic capacity	VO2 max	b455											
(Modified) Ashworth Scale	Tone - spasticity	b735			s730, s750**								
Composite Spasticity Scale	Tone - spasticity	b735			s730, s750**								
2 point Discrimination	Discrimininative sensibility	b260			s730, s750**								

Test					
Visual Analogue Scale (VAS)	Pain	b280	s730, s750**		
Pain Scale	Pain	b280	s730, s750**		
Radiographic image	Shoulder sub-luxation image		s730		
Ritchie Articular Index	Range of motion	b710	s730, s750**		
Goniometer	Range of motion	b710	s730, s750**		
JAMAR - dynamometer	Muscular strenght	b730	s730		
Dynamometer	Muscular strenght	b730	s730		
EMG	Muscular strenght	b730	s730, s750**		
Biodex	Muscular strenght	b730	s750		
Muscular Testing	Muscular strenght	b730	s730, s750**		
Force Platform	Movement forces and angles for standing or gait activities	b770	s750	d410	
Motricity Index	Measure strength in upper and lower extremities after stroke	b730	s730, s750**		
Fugl-Meyer Assessment (motor and sensoric)	Joint motion, joint stability, pain, sensibility,	b710	s730, s750**	d415	

	balance and muscle strenght	b715 b280 b260 b265 b780 b730			
Brunnstrom Scale	Joint motion,sensibility, balance and muscle strenght	b710 b260 b265 b780 b730	s730, s750**	d415	
Stroke Rehabilitation Assessment of Movement Measure (STREAM)	Joint motion, joint stability, balance, coordination and muscle strenght	b710 b715 b760	s730, s750**	d410 d415 d420	
16 Hole Peg-test	Finger dextrity (fine) with time measure (control, strenght and ROM)	b710 b730 b760	s730	d440	
9 Hole Peg-test	Finger dextrity (fine) with time measure (control, strenght and ROM)	b710 b730 b760	s730	d440	
Box and Block Test	Finger dextrity (fine) with time measure (control, strenght and ROM)	b710 b730 b760	s730	d440	

Ebsen Taylor Test	Fine motor skills activities (control, strenght and ROM)	b710 b730 b760	s730	d440 d445	
Wolf Motor Function Test (WMFT)	Dextrity, strenght and upper limb use (control, strenght and ROM)	b710 b730 b760	s730	d440 d455	
Solleman Hand Function Test	Hand use for several activities: coins, writing, opening a door, screwdriver, zipper, paper, envelopes (control, strenght and ROM)	b710 b730 b760	s730	d440 d445	
Arm Research Attainable Test (ARAT)	Grasp, Grip, Pinch, Gross Movement (control, strenght and ROM)	b710 b730 b760	s730	d440 d445	
Test d'Évaluation des Membres Supérieurs des Personnes Âgées (TEMPA)	strenght, ROM and precision on hand and upper limb use on specific activities (coins, cards, writing, opening)	b710 b730 b760	s730	d440 d445	
Frenchay Arm	Proximal and	b710	s730	d440	

Test	distal control of upper limb during activities (strenght and ROM)	b730 b760		d445	
Arm Motor Ability Test	Tests fine and gross motor skills, handling a mug, coin, buttons, a spoon	b710 b730 b760	s730	d440 d445	
Biofeedback	Awareness of many physiological functions (postural sway, strenght, ROM)	b710 b730	s730, s750**	d415	
GAITrite System	Carpet with sensors to acquire temporal and spatial gait parameters	b770	s750	d450	
Number of Falls	Postural and movement control during gait	b760	s750 s760	d410 d415 d450 d455	
Romberg Test	Balance		s750 s760	d415	
Assessment Trunk Control Test	Rolling to weak side, rolling to strong side, balance in		s760	d415	

	sitting position, sit up from lying down				
Berg Scale	Sitting and Standing balance and transfers		s750 s760	d415 d420	
Activities-specific Balance Confidence Scale	Level of confidence on balance during sitting and standing activities		s750 s760	d410	
Trunk Impairment Scale	Static and dynamic sitting balance		s760	d410 d415	
Four Test Balance Scale	Static standing balance		s750	d415	
Postural Assessment Scale for Stroke (PASS)	Ability to maintain or change a given lying, sitting, or standing posture		s750 s760	d410 d415	
Standing Balance Test	One leg standing balance		s750	d415	
Upright Motor Control Test	One leg standing balance and ability to flex and extend	b730	s750	d415	
Activities-based Confidence Scale	16-item self-report measure in which patients rate their balance		s730 s750	d415 d420	

	confidence for performing activities: reach, walk around, standing		s760	d450 d455	
Tinetti Balance & Gait Scale	Sitting and standing balance, gait temporal and spatial parameters	b770	s750 s760	d410 d415 d450	
Dynamic Gait Index Maximum Reach Distance	Balance during walking		s750	d415 d450	
Functional Ambulance Category (FAC)	Level of assistance for walking		s750	d450	
Fast Gait Speed	Speed		s750	d450	
6 min Walking Test	Distance gait parameter and exercise tolerance	b770	s750	d450	
10 m Walking Test	Velocity gait parameter		s750	d450	
Timed-up and Go Test (TUG)	Time spent to stand, walk, and seat back again			d420 d450	
Sit To Stand Repetitions	Amount of times able to sit-to-stand in a certain timing			d420	
Gait parametrs	Speed, distance, step, cadence	b770	s750	d450	
Chedoke McMaster	limbs strenght and tone, pain,	b730	s730	d415	

Stroke Assessment	balance, mobility on the bed, walking indoor and outdoor, stairs	b735 b280	s750 s760	d420 d450 d455 d460	
Rivermed Index	Ability to perform activities: turning on the bed, sit, stand up, walk, shower		s730 s750 s760	d410 d420 d450 d455 d460 d510	
Functional Independence Measure (FIM)	Eating, Grooming, Bathing, Upper body dressing, Lower body dressing, Toileting, Bed to chair transfer, Toilet transfer, Shower transfer, Locomotion (ambulatory or wheelchair level) ,Stairs, Social interaction, Problem solving		s730 s750 s760	d550 d510 d520 d540 d530 d420 d450 d460	d630 d640 d910 d920
Barthel Index	Feeding,		s730	d550	

	Bathing, Grooming, Dressing, Toileting, Chair transfer, Ambulation, Stair climbing		s750 s760	d510 d520 d530 d420 d450 d455	
Motor Activity Scale (MAS) Modified MAS	Rolling, Lie to sit, Balanced sitting, Sit to stand, Walking, Upper arm function, Hand movements, Advanced hand activities		s730 s750 s760	d410 d420 d415 d450 d455 d440 d445	
Motor Activity Log (MAL)	Functional activities for arm, hand and fingers use, wash hands, wash teeth, dressing, carrying objects, drink, write, using fork, comb hair, put make-up, buttons, open a door		s730	d430 d440 d445 d510 d520 d530 d540 d550 d560	
Physical Activity and Disability Scale	Measuring amount of exercise, leisure time physical activity, and household		s730 s750		d640 d920

	activity				
Rehab Activities Profile Index (RAP)	Balance, changing position, walking, stairs, using transport, eating, drinking, washing, dressing, providing meals, householding, leisure activities		s730 s750	d410 d415 d450 d470 d510 d520 d530 d540 d550 d560	d630 d640 d920
Frenchay Activities Index	Preparing meals, housework, driving, social, doing shopping, walking		s730 s750	d450 d460 d474	d620 d630 d640 d910 d920
Stroke Impact Scale (SIS)	Self perception of most affected limb, fine and gross motor skills, transferring, walking, self-care, domestic life community life and recreation		s730 s750	d420 d450 d4560 d510 d530 d540 d550	d620 d630 d640 d910 d920
SF-36	Physical Functioning,		s730	d410* **	d920***

	Role Limitations due to Physical Problems, General Health Perceptions, Vitality, Social Functioning, Role Limitations due to Emotional Problems, General Mental Health, Health Transition		s750	d445* ** d450* ** d455* ** d510* **	

* not present on the ICF core Set for Stroke- proposal to be included regarding the need of neuroplasticity for stroke recovery, thus the need of outcome measures on the brain synapses function

** according to its application on Upper Limb our Lower Limb

*** categorization already proposed by Faria CDCM, Silva SM, Corrêa JCF, Laurentino GEC, Teixeira-Salmela LF. Identificação das categorias de participação da CIF em instrumentos de qualidade de vida utilizados em indivíduos acometidos pelo acidente vascular encefálico. Rev Panam Salud Publica. 2012:31(4):338–44.

Discussion

Achievement of Research Aims

The reflection of the literature review and the scientific information of the four studies developed, gave us an overview towards evidence and needs of PT and neuro-rehabilitation on stroke.

Instead of a “black box”[75] or a magic intervention, Physiotherapy shows efficacy scientifically proved on the domains of Structure & Functions and Activities & Participation of stroke patients and is an important profession at neuro-rehabilitation teams. This affirmation is supported by the recent systematic review and meta-analysis[49] on “What Is the Evidence for Physical Therapy Poststroke”, developed with high standards on methodological aspects.

The efficacy of intervention is mainly centered in outcomes related with movement, movement-related structures and functions and functional autonomy (activity and participation). In these domains, interventions show specificity of efficacy regarding specific outcomes. These results support the recommendations for a multi-approach model of intervention on stroke rehabilitation[3], centered on meaningful tasks and active involvement of the patient.

Some strategies show no benefits to any domain and outcomes. Included on this group are the conventional approaches and the passive and merely biomechanical interventions. These results are coherent with the theories of motor re-learning[83] and neuroplasticity[84], stressing the need of experience, goal orientated and active interventions.

On the other hand, the lack of efficacy can result of methodological issues of the research and research settings not similar with real rehabilitation settings[135]. Despite the increase of quality of the RCT’s, limitations like: time since stroke; description of interventions; systematic application of interventions; sample size; sample heterogeneity and ethical issues with real control groups, can be the reason for the non-efficacy of certain strategies[77].

These aspects, can also justify the changes overtime of efficacy of certain strategies like the Treadmill gait training, reported on the last systematic review[49]. The non-systematic use of the ICF framework for the development of intervention programs and interventions researches can lead to the mismatching of results regarding the domains and targeted outcomes of interventions and the assessed outcomes and outcome measures used. Contributing this way to no efficacy or non-conclusive results.

Being concerned with efficacy of strategies, issues related with economical benefits and efficiency is still limited[76]. However, considering the enormous impact of disability and the epidemiological perspectives for the future about stroke[19], this variable needs be exhaustively explored and researched.

This overall perspective shows how preferably hands off strategies are on stroke rehabilitation. However, a better translation into practice and real rehabilitation settings research are needed[135].

After a specific analysis of the extent of effects of PT hands on interventions on Structures & Functions and Activity & Participation outcomes related with movement, on patients with stroke, we can also find some benefits of these strategies. Recommendations with moderate evidence are in favor of the use of: slow-stroke back massage for shoulder pain; ROM exercises for upper limb and lower limb structures and functions of muscles and joints; PNF during gait step and walking backwards with hip facilitation for gait parameters and gait performance and conventional physiotherapy with facilitation techniques for gait parameters.

Recommendations with limited evidence in favor of the use PNF with trunk rhythmic stabilizations for function and mobility of upper limb. Recommendations with moderate evidence for the non-efficacy of the use of Bobath Therapy for upper limb function and activity and facilitation of the step during body weight support treadmill training for gait parameters and performance.

Regarding other interventions mentioned in the introduction as hands on interventions, we didn’t find eligible studies, consequently we can not make any recommendations of use or non use of them.

Results on the extent of effects of PT on brain activity for patients with stroke are not surprising and were expected given the impact showed on the other dimensions and outcomes. Considering what was already said about motor re-learning and neuroplasticity and recovery, the benefits obtained at the level of Structure & Function and Activity & Participation could only result from brain reorganization.

Hands off strategies, that demand involvement of the patient and goal-orientated interventions, like: Constraint Induced Movement Therapy with Transference for practice, Assistance with robotics for the realization of computer tasks, Mirror Therapy, Mental

Imagery for upper limb tasks and Treadmill training for gait improvement, have impact on brain activity.

The benefits are on the increase of areas of activation both on ipsilesional and contralesional hemisphere; decreases of limiars of excitability of synapses and increase of the metabolism of cerebral glucose. These findings are verified on motor, somatosensorial and sub-cortical areas.

Others then these approaches might also be effective on brain activity, however they were not included on our analysis due to specific criteria aiming for high quality studies.

Of course these results refer to effects of longitudinal intervention protocols, which are the valid methods for intervention efficacy research. However, the knowledge of immediate effects of strategies provides information for a better understanding of causal effects of specific strategies[76].

It's almost bizarre that this knowledge is not scientifically explained by the physiotherapist community and was also not found on our literature review and search, regarding to the brand image strategy of PT, the hands on or manual therapy techniques.

On the context of neurological rehabilitation and physiotherapy intervention the understanding of the neurobiological effects of manual facilitation is fundamental as most of the rehabilitation institutions and conventional/traditional physiotherapy programs are based on this approach.

The results of our research can give new insights on this topic providing scientific based information, that on healthy subjects manual facilitation promotes brain activity and that this activation is similar with the activation during autonomous movement for lower limb. The activity is observed both on grey and white matter of motor, somatosensorial and sub-cortical areas and cerebellum. Also deactivations were found, revealing how important this physiological event might be important for the understanding of neurophysiological processes of motor tasks.

As neuroplasticity depends on the maintenance of changes of brain activity, these results need to be validated on a longitudinal approach. Also, damaged brain can have different responses so it needs also confirmation of immediate effects on subjects with stroke or other brain damage.

If manual facilitation has effects on brain activity, how can we explain that the non-benefits on the domains of Structure & Function and Activity & Participation related with movement? The already presented eventual differences on response of damaged brain and the previous mentioned methodological limitations of the studies could be the major cause. Also the already referred non-real rehabilitation setting research contemplating diversity, complexity and patient-centered care, can constraint these results.

On our understanding, the phase of stroke when strategies are applied and the mismatching of targeted outcomes of the strategies and the outcome measures are relevant justifications for this phenomenon. To minimize this, it's pertinent to consider the recommendations of ICF working groups for the use of ICF frameworks and specific Core Sets, when designing researches[120].

Regarding our literature review and systematic reviews, 43 physiotherapy interventions and 65 outcome measures were found. To contribute for a better framework for future research and intervention programs we implemented a process of categorization of these PT interventions and outcome measures on stroke patients under the ICF model.

Using the ICF Core Set for Stroke and valuing the outcomes related with movement, these 43 interventions and 65 outcome measures were linked to 43 selected outcomes, already validated as the most selected by physiotherapists[136]. After 2 rounds of a Delphi panel process, a final consensus categorization permitted to verify that PT intervention research is centered on the domain of Activity, meeting the same reflections of the last systematic review on physiotherapy interventions and stroke[49].

During this process, we verified that the ICF-CSS is limited on outcomes on the domain of *Functions* of the brain related with movement. Regarding the importance of those in neurological conditions and stroke and as result of 100% consensus of the panel of experts, the categories/outcomes *b147* and (specific mental functions of control over both motor and psychological events at the body level) and *b199* (mental functions, unspecified), which relate brain functions to movement, were added to the 43 categories/outcomes and will be proposed to be included on the ICF-CSS, to the ICF Stroke working group.

On result of the attempted analysis of coherence of the studies included on the study: Physiotherapy Hands-on Interventions and Stroke: Systematic Review, we consider ICF coherence as a complex issue that needs to be taken in account when designing interventions programs and research. If in some cases the lack of coherence between interventions and outcome measures can influence the lack of efficacy on results, in other cases like it can elucidates how these interventions can have or not have impact on other categories. Again, in this study the focus of PT interventions are on the Activity domain.

Another aspect learned during this research is the amount of studies and literature available for practical settings in a mixture of high and low quality, leading to misunderstandings, exhaustion and non applicability, which is contributing for the "crisis" of evidence-based medicine[137]. This factor phenomenon also demands a direct translation of research into practice, by the implementation of more realistic research.

Critical appraisal of the overall research and of the specific methods

The organization within the ICF framework for the outcomes related with movement, revealed to be efficient on the systematization of the information and in keeping our goals in mind.

Regarding the methodological aspects of the systematic reviews implemented, we followed the basic steps recommended by PRISMA[138] as a guarantee of quality.

However, the lack of human resources didn't permit a more extensive search, limiting the retrieved studies.

The inexperience with PEDro Scale, could have biased the quality assessment of the RCT's, as some items are of difficult understanding and some studies are not clear and specific enough.

The methodological option for the criteria of the control group is controversial as the results of the studies can be influenced by the phenomenon of extra time of therapy, considering the eventual benefits of intense therapy[139,140,141]. However, exists some evidence that extra time therapy doesn't lead immediately to better results, they are rather dependent on the content of the therapy[142]. The same criteria, not considering studies of comparisons can also be a factor for the reduced amount of studies found and included.

Regardless these aspects, this method showed to be relevant in the collection of scientific information and provided an updated overview. Specifically the study Physiotherapy Interventions and Brain Activity on Stroke: Systematic Review, contributes for new insights on scientific information on the field of PT and neuro-rehabilitation.

However we also agree that our information can suffer the limitations of translation into practice as we used the method of systematic review of RCT's, mainly developed in controlled conditions even in real settings.

The other innovative method used in our research, was the use of fMRI for the analysis of brain activity during multijoint lower limb movement and the immediate effects of manual facilitation.

This study showed more complexity on methodological aspects, as the domain of fMRI features and studies was none at the beginning. To be able to design a high quality paradigm and protocol for fMRI experiments, a full time dedication is needed and most of the times the experiment itself constitutes the development of the PhD and the thesis. This was not our case as we were focused on the overview of physiotherapy and the brain activity was one of the components. Due to this, some methodological options might compromise the final analysis of the results. An aspect like the use of two runs instead of one, limitates the comparisons between right and left leg as well activations or deativations intensities analysis. Another aspect was the inexperience of using the image analysis software and the adequacy of statistical methods.

However the minimal aspects of developing an fMRI study are guaranteed[143] and the novelty of the experiment, as is the first fMRI study with the multijoint movement of lower limb on a complex functional task highlights the relevance of this study. The analysis of the immediate effects of manual facilitation of movement using a specific approach of physiotherapy, the analysis of white matter activity and the attempt to analyze the deactivations also contributes for the scientific value of this study.

The experimental procedure raised some difficulties with head stabilization, leading to the need of more conservative thresholds and to include 6 motion confound predictors (x, y, z, rotation, translation) into the whole-brain Random Effects - General Linear Model Analysis (RFX-GLM). This option might have deleted some important activations, although we have the guarantee that the remaining signal has external validity.

This method showed to be efficient in gathering the aimed information about the effects of manual facilitation of movement, representing a valuable instrument to demonstrate the neurobiological effects of physiotherapy and monitor recovery and rehabilitation processes.

The use of a Delphi method to obtain consensus of an expert's panel, for the proposed categorization of 43 interventions and 65 outcome measures, was successful and permitted a consensus after 2 rounds.

As the starting point was a already structured document requiring expert validation, the use of a 3 items Likert scale on the first round and dichotomous answer on second round showed to be efficient.

Also the number of experts showed to be small, when deciding for controversial classifications like Berg scale or Massage intervention. The use of a panel constituted by

Portuguese experts constraints the external validity of results in the international context.

The final categorization was tested on the analysis of the coherence of interventions and outcomes of the studies analyzed on the study Physiotherapy Hands-on Interventions and Stroke: Systematic Review, showed to have scientific utility and to be friendly-user.

Translation from the results to the practice

Physiotherapy is a well evidence based profession on the field of stroke rehabilitation. Thus, national policies and health organizations need to accentuate the inclusion of physiotherapists on the rehabilitation teams and decision-making groups related with neuro-rehabilitation.

Hands off PT are the most scientifically supported strategies, which need to be integrated on rehabilitation services and physiotherapy programs. According to the results of different strategies and the outcomes attained, diversity of interventions, seem to be the best approach to stroke patients.

Regarding conventional approaches of physiotherapy there's recommendations with moderate evidence are in favor of the use of: slow-stroke back massage for shoulder pain; ROM exercises for upper limb and lower limb structures and functions of muscles and joints; PNF during gait step and walking backwards with hip facilitation for gait parameters and gait performance and conventional physiotherapy with facilitation techniques for gait parameters. Recommendations with limited evidence in favor of the use PNF with trunk rhythmic stabilizations for function and mobility of upper limb.

So far, the recommendations for the use of Bobath Therapy for upper limb function and activity and facilitation of the step during body weight support treadmill training for gait parameters and performance, are for the non use regarding the moderate evidence for the non-efficacy.

Regarding other interventions mentioned in the introduction as hands on interventions, we didn't find eligible studies, consequently we can not make any recommendations of use or non use of them.

The use of contextualized, goal orientated, active, meaninfull and patient centered strategies promotes brain reorganization and those like Constraint Induced Movement Therapy with Transference for practice, Assistance with robotics for the realization of computer tasks, Mirror Therapy, Mental Imagery for upper limb tasks and Treadmill training for gait improvement, should be privileged.

Considering the different behavior of the brain between upper limb and lower limb activities, the intervention also this to promote and respect this differentiation. The bilateral brain activation and bilateral dependence of the lower limbs, indicate the need of a bilateral approach for movements and tasks for lower limb. On the other hand, upper limb is independent and solicitates contra-lateral activation, giving the space for unilateral activities and also bilateral activities regarding inter-hemispheric connectivity and task features.

The type of stimulus is also an important feature when designing an intervention plan. *Manual stimulus* elicites cortical and sub-cortical brain activity on healthy subjects, while verbal stimulus only elicits cortical activation, inferring that when we need to stimulate the sub-cortical areas the manual stimulus without any verbal support can be appropriate. However when looking for more cognitive stimulus, verbal or mixed stimulus can be more adequate. The presence of cingulate areas shows the importance of meaningful tasks for motor control in order to stimulate motivation and willingness for movement.

All the results found, need to take in consideration a patient-centered model of decision-making, when deciding for the best intervention.

Translation from the results to the future of research

Questions about external validity and practice translation of results of RCT's are raised during the last 10 years[144,145,146]. Still this is the most preferred method when searching for interventions efficacy and evidence. High rigorous RCT's are requested for most of the systematic reviews[138,147]. This can lead to reduction of scientific information and limitation to application into practice[135]. Especially neurology settings are complex demanding research that should include that complexity and be patient-centered.

Research on the filed of physiotherapy intervention demands RCT's comparing interventions with placebo, or no treatment. The argument of deprivation of treatment benefits as an ethical issue is valid. But the recent findings of neuroplasticity post-lesion for a longer period even in chronic phases can minimize the adverse effects of deprivation.

Also research on different phases post-stroke is relevant to specify the benefits of each intervention. The use of ICF categories for consistency between interventions and outcomes measures will also contribute for the specification of each intervention.

The detailed description of intervention protocols and duration of sessions (even of conventional interventions) is also a demand on future research.

After clear findings about interventions efficacy individually, research on comparisons, mixed interventions and efficiency studies will be relevant for economical and societal impact of the interventions.

Considering that physiotherapy is centered on the domain of Activity but as implicit on the ICF framework, different domains and outcomes have an intrinsic interaction with the capacity of multidirectional influences, the knowledge of such interactions and behavior is needed.

To promote improvements at the Activity level, physiotherapist also need to intervene on functions and structures and thus the normal behavior is of extreme importance as a reference for recovery.

On the field of lower limb function and activity the understanding of brain activity is required. Specific regions of interest and connectivity studies are needed to understand the mechanisms of control of lower limb activity.

The other issue regarding brain activity maps is the question of what is represented in the motor cortex: muscles, postures, or movements. While this area remains controversial, the demonstration of population codes for movement in M1 has suggested that body centered movements are at least one feature represented. The fine structure of the motor map appears not to be map-like, meaning that recovery processes within small areas may not be best interpreted as remapping. In fact, the characterization of changes in activity and connectivity that appear to support recovery as "reorganization" or "remapping" often seem overblown in situations in which synaptic strength and excitability of preexisting circuits are adjusted[67]. Thus the brain analysis of patients with neurological disorders is also of great importance in different phases of recovery.

Regarding the methods used in this study, we recommend fMRI procedures for functional sequences in the same run to minimize instrumental bias and allow direct comparisons between right and left limbs and strengthen the validity of results.

Conclusion

Regarding the questions that motivated and conducted this thesis and regardless the limitations encountered, the non-conclusive findings and some non-identified evidence, it seems still valid to conclude that **Physiotherapy is no longer a "black box"**, instead is a **evidence-based profession**.

Exists clear and evidence based information for clinical settings and scientific community, that hands off physiotherapy is relevant and has efficacy proved on the rehabilitation of stroke patients on the domains of Structure & Functions and Activities & Participation.

This efficacy is extended to the brain activity, which validates the idea that PT can influence neuroplasticity process and consequently contribute for a better recovery in a neurobiological perspective with impact on human performance and autonomy.

Despite of the existence of only a few studies supporting the hands on interventions with a moderate scientific level, it's also clear that the "hands of the physiotherapists" are not only magic. Their effects can reach external structures and functions, like muscles, range of motion; activities like walking and use of the upper limb, but they also reach higher to the brain, both on cortical and sub-cortical areas. However more detailed and high quality research is needed on this field, especially on real rehabilitation settings, integrating complexity and diversity.

To remark that, instead of passive and not goal orientated interventions, Physiotherapist should promote active and dynamic involvement of the patients and tailor-made programs, requiring more time and attention to patients. This perspective goes against the conventional and public services provided to these patients, on the Portuguese reality. However, regarding the statistics of disability, health managers and politicians need to reconsider the policy, organization and quality of health services.

The analysis and organization of the process of rehabilitation under the ICF model, facilitates the coherence among interventions and outcomes and the better understanding of the focus of interventions and outcome measures.

During the processes of analysis of scientific information, it's also clear the urgency of research with better possibility for translation into practice.

On the academic perspective of the development of this thesis, we consider that the demands of the Dublin Descriptors were achieved both on the conception and implementation of research and on the contribution with original information for the scientific community. The exploration of physiotherapy evidence and needs by the use of different research methodologies gave a general perspective of the state of physiotherapy and its evidence and a specific understanding of neurobiological basis of specific strategies.

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Appendices - digital support

Thesis Appendices

Appendix 1 - Comprehensive ICF Core Set for Stroke

Articles Extra Appendices

Physiotherapy Hands-on Interventions and Stroke: Systematic Review

Appendix 1 - Terms Linkage

Appendix 2 - Article suggesting the relevant databases for PT studies

Appendix 3 - Article suggesting the levels of evidence for Best-evidence synthesis

Appendix 4 - Syntaxes of databases

Appendix 5 - Included articles

Appendix 6 - PEDro classifications

Physiotherapy and Brain Activity on Stroke: Systematic Review

Appendix 1 - Terms Linkage

Appendix 2 - Article suggesting the relevant databases for PT studies

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Appendix 6 - PEDro classifications

Brain activity during lower limb movement with physiotherapy manual facilitation – an fMRI study.

Appendix 1 - Experimental paradigm video

Appendix 2 - Experimental audio files

Appendix 3 - Brain Voyager outputs of clusters of activations

Appendix 4 - Brain Voyager outputs of clusters of deactivations

Appendix 5 - Article presenting cerebellum areas localization

ICF Linking Process for Categorization of Interventions and Outcomes Measures on Stroke Physiotherapy - Delphi panel

Appendix 1 - Comprehensive ICF Core Set for Stroke

Appendix 2 - ICF Linking Rules

Appendix 3 - Letters and instructions given to the Panel of Experts

Appendix 4 - Results of Round 1

Appendix 5 - Results of round