DISS. ETH NO. 27430

TOWARDS MINIMALLY-SUPERVISED ROBOT-ASSISTED THERAPY OF HAND FUNCTION TO INCREASE THERAPY DOSE AFTER STROKE

A thesis submitted to attain the degree of

DOCTOR OF SCIENCES of ETH ZURICH

(Dr. sc. ETH Zurich)

presented by

RAFFAELE RANZANI

MSc in Robotics, Systems and Control, ETH Zurich

born on 21.11.1988

citizen of Occhiobello (RO), Italy

accepted on the recommendation of

Prof. Dr. Roger Gassert (examiner)
Dr. Olivier Lambercy (co-examiner)
Dr. med. Fabio Mario Conti (co-examiner)
Prof. Dr. David Reinkensmeyer (co-examiner)

2021

You are as heavy as the ground pulls you,
As light as your wings flutter...
You are as alive as your heart beats,
As young as your eyes see distance...
You are as good as the people you love,
As bad as the people you hate..
Whatever the color of your eyebrows and your eyes are,
Your color is what the one facing you sees..
Don't think that what you lived is what you gained:
You are as close to the end as you lived;
However long you live,
Your life is as long as you love...
You are as happy as you can smile.
Don't be sad, know that you will smile as much as you cry
Don't think that everything is over,
You will be loved as much as you love.
— Can Yücel

To my strong women: Stella, my mum, my grandmothers...

Acknowledgements

This thesis is the result of six years of work at the Rehabilitation Engineering Laboratory (RELab) at the ETH Zurich, one randomized controlled trial and several pilot studies, which were conducted at the Clinica Hildebrand centro di riabilitazione Brissago and at the Balgrist Campus in Zurich. Several people and friends significantly contributed to this thesis, even before the beginning of my PhD.

My biggest thanks go to Roger Gassert and Olivier Lambercy. Roger was an inspiring supervisor. He is thoughtful and maintains a flat organization of the lab, he is always available to help with any kind of problem with a one-to-one approach. His lessons in neurorehabilitation, robotics and daily-life surviving skills were precious. Olivier was an extremely knowledgeable mentor, I am deeply grateful for his continuous support and his availability at any time. I learned a lot from his supervision in any part of my PhD, all the way from goal setting, to implementation, to the presentation of research outcomes in scientific works. I would like to express to both of them my deepest gratitude for trusting me and supporting my dreams with an extreme flexibility in these years.

Thanks to my co-supervisors Dr. Fabio Mario Conti and Prof. David Reinkensmeyer, for their valuable suggestions on the project. In particular, I would like to thank Dr. Conti, who gave me important scientific sparks over the years. His example gave me the courage to take the decision to start my path in medicine.

Thanks to all the great PhD colleagues that I had the opportunity to meet and that made the RELab a young and stimulating environment. It was nice sharing with them moments at work and outside, or during conferences, retreats and ski weekends. Thanks for the fruitful scientific discussions that gave me inspiring ideas and for the friendship. Particular acknowledgments go to Julio and to the "RELab generation '15": Dominik, Stefan and Tobi, who shared this journey with me and became true friends. Thanks to Giada Devittori for all the help and valuable contributions that she brought to the project since she started her PhD. Thanks to Maya Kamber, for helping out whenever she could and for giving me suggestions and encouragement when needed. Thanks to Stefan Schneller and Bruno Kaufmann for their always-available support during the design and development of HandyBot and ReHandyBot.

Moreover, I would like to express my gratitude to all the students, civil servants or assistants that I had the honor to supervise during the last six years. They contributed to the success of

this thesis. Thanks to Lucas Eicher, Martin Albrecht, David Fisch, Federica Viggiano, Kevin Sin, Patrick Weber, Jiri Danihelka, Emily Koh Shuen Li, Jason Hu Shengjie, Krithika Swaminathan, Bernadette Engelbrecht, Lukas Matthys, Cherelle Connor and Aldiyar Semedyarov.

I would like to thank the medical doctors, therapists and the administrative staff from the Clinica Hildebrand centro di riabilitazione Brissago who supported me in conducting studies, defining requirements for our devices and in organizing the TRCR summer school in 2016. Special acknowledgements are dedicated to Paolo Rossi, Claudio Petrillo, Daria Dinacci, Antonella Califfi, Stefania Regazzi, Elena Binda and Antonella Mascetti for their commitment and friendship throughout the years.

Thanks to Jeremia Held, who was always available to help with patient recruitment and experiments in Zurich. We spent good times together!

Thanks to Claudia Haarman and Freek from Hankamp Rehab, for their significant contribution during the design and mechanical manufacturing of HandyBot.

Now it is the time to thanks family and friends, the most important people that shaped my life and turned me into the person I am today.

Thanks to my big big family, who surrounded me with love and happiness all my life. They thought me the importance of determination, optimism and serenity. Thanks for the memories and echos of loud shouts and laughter of children from yesterday and today, talks between relatives, sounds of family celebrations and conviviality that I bring with me. In particular, thanks to mamma Miky and papà Diego. They have always been my stability and are for me one of the most beautiful examples of hard work, honesty, love and altruism. Thanks to nonna Dina, for her inspiring cheerfulness, ambition and passion for culture. Thanks to nonna Angelina, for her simplicity, humbleness and dedication to family.

Thanks to my "famiglia pisana", who accompanied me starting from the bachelor through victories and pitfalls, dinners, parties and sleepless nights spent talking and growing together, becoming like a family.

Thanks to my "bella vita di Zurigo" and, in particular, to Serena, Elisa and Kavitha. We shared trips, parties, dreams, successes, lightheartedness, but also problems, confessions, discussions. What Zurich represents to me today is thanks to you.

Thanks to my best friend, Lorenzo, who is my brother by mind. I would have too many moments to thank since we met in middle school. I can only express my biggest gratitude for our bright friendship that always inspires me and fills me up, even from far away.

Thanks to my wife Stella. Thank you for your love and friendship. Thanks for your honesty, beautiful mind, and for your essentiality. Thanks for your humor that always makes me laugh and colors my days. Thanks for your adaptability, for supporting my dreams and my crazy life-style. Thanks for being my solid ground, my everything. I love you.

Finally, I would like to thank my inner self, for not giving up.

Zürich, 11 September 2021 Raffaele Ranzani

Abstract

Stroke is one of the leading causes of long-term upper limb impairment, which greatly reduces the quality of life of stroke survivors and their ability to perform activities of daily living. There is evidence that an increase in therapy dose (i.e., number of exercise repetitions per time unit and therapy time) could promote recovery. Unfortunately, due to economical and organizational limitations, it is currently a challenge to offer such intensive therapy schedules both in the clinics and after discharge. Robotic devices could be a viable solution to offer motivating and high-dose task-oriented therapies that are relevant for activities of daily living. However, the potential of robotic systems in complementing conventional therapy has only been exploited to a small extent. These devices are mostly used in clinical settings and require constant supervision of trained personnel, which contributes to a cost increase and limits the maximum doses achievable using this technology. Furthermore, they typically train pure motor tasks without focusing also on sensory and cognitive abilities that are important for hand function in daily life.

This PhD thesis firstly aims to evaluate whether robot-assisted therapy of hand function following a sensorimotor therapy approach is feasible and produces equivalent therapy outcomes compared to dose-matched conventional care. This will serve as necessary basis to investigate and develop the elements necessary to create a portable robot-assisted therapy platform (i.e., a haptic device to train hand and forearm function, a patient-centered user interface and a battery of therapy exercises and assessments), which could offer the same therapy approach with minimal supervision and potentially enable a therapy dose increase in different environments (e.g., clinic, home). To achieve this goal, the following steps were undertaken.

First, a robotic platform and therapy concept were developed and the equivalence of robot-assisted and dose-matched conventional therapy was established in supervised conditions in a randomized controlled trial with 27 inpatients in the subacute stage after stroke. This necessary result opened the way to use such platform to complement conventional care with non-inferior therapy outcomes.

Second, to increase therapy dose, physical and graphical user interface and therapy exercises have been redesigned to be usable with minimal supervision, and their usability was verified in a pilot study with ten chronic stroke patients.

Third, to increase safety and monitor unforeseen adverse events (e.g., abnormal increase in hand muscle tone) without supervision, novel concepts for online monitoring of patient's

ability and physical conditions were proposed. These monitoring methods are based on robotic metrics collected online during therapy exercises. An online muscle tone monitoring method was tested in five unimpaired subjects and five subjects after chronic stroke.

Finally, to allow the use of the therapy platform in different environments (e.g., at home), a novel compact, scalable and portable haptic device training grasping, forearm pronosupination and wrist flexion-extension was developed and preliminarily tested with minimal supervision on four subjects after chronic stroke using the developed user interface and therapy exercises. The usability insights from the pilot study allowed to identify usability challenges that led to the development of a second improved portable device.

The promising results of this PhD thesis open the possibility to use active robotic devices with minimal supervision to complement conventional therapies, reduce the costs of robot-assisted therapy (e.g., by reducing the need of therapist's supervision over time) and create a continuum of care that provides the same therapy concept from the clinic to home, increases therapy dose and progressively promotes subject involvement and autonomy.

This thesis brought three main contributions. First, through a resource demanding clinical trial, it was demonstrated that a robotic device can be used to offer sensorimotor and cognitive therapy of hand function after neurological injury, achieving non-inferior therapy outcomes compared to conventional care. This established the necessary ground to support the second contribution of the thesis, which is the development of a user-friendly robot-assisted platform for minimally-supervised therapy, which can be used with multiple devices to start the therapy in the clinic and continue it at home. The platform also allows basic autonomous monitoring of the patient ability, physical conditions and safety. The third contribution of the thesis is the development of two portable therapy devices that are compatible with the therapy platform. The platform and both devices have been developed in direct collaboration with clinical and industrial partners. No other portable active therapy device currently in research or on the market offers the possibility to haptically train the same hand functions with minimal supervision and with a structured sensorimotor therapy plan that could start in the clinic and continue at home after patient discharge.

Sommario

L'ictus è una delle principali cause di compromissione a lungo termine degli arti superiori, che riduce notevolmente la qualità della vita dei sopravvissuti all'ictus e la loro capacità di svolgere attività di vita quotidiana. Ci sono evidenze che mostrano che un aumento della dose della terapia (cioè il numero di ripetizioni di esercizi per unità di tempo e il tempo della terapia) favorisce il recupero funzionale dell'arto superiore. Sfortunatamente, a causa di limitazioni economiche e organizzative, è attualmente estremamente difficoltoso offrire ai pazienti programmi di terapia così intensiva sia nelle cliniche che dopo la dimissione. I dispositivi robotici potrebbero rappresentare una buona soluzione per offrire terapie funzionali stimolanti, ad alta intensità e rilevanti per le attività di vita quotidiana. Purtroppo, il potenziale dei dispositivi robotici nel complementare terapie convenzionali è stato fin'ora sfruttato solo in parte. I dispositivi robotici vengono utilizzati principalmente in ambiente ospedaliero e richiedono supervisione continua da parte di personale esperto. Ciò aumenta il costo del loro utilizzo e limita la dose terapeutica massima raggiungibile. Inoltre, questi dispositivi propongono esercizi puramente motori, tralasciando aspetti sensoriali e cognitivi che sono importanti per la funzione della mano nella vita quotidiana.

Questa tesi di dottorato ha lo scopo in primo luogo di valutare se la terapia robot-assistita per la funzionalità della mano, seguendo un approccio di terapia sensorimotoria, è fattibile e produce risultati terapeutici equivalenti alla stessa dose di terapie convenzionali. Questo servirà come base necessaria per investigare e sviluppare gli elementi a supporto di una piattaforma portatile per la terapia robotica, che potrebbe offrire lo stesso approccio terapeutico con una supervisione minima e potenzialmente aumentare la dose di terapia in ambienti diversi (es., clinica, casa). La piattaforma robotica consiste in un dispositivo aptico utile alla riabilitazione della funzione della mano e dell'avambraccio, un'interfaccia utente specifica per questi pazienti, e una serie di esercizi e assessments terapeutici. Per raggiungere questo obiettivo sono stati intrapresi i seguenti passaggi.

In primo luogo, sono stati sviluppati una piattaforma robotica e un concetto di terapia. Attraverso uno studio controllato randomizzato con 27 patienti ricoverati in fase subacuta dopo l'ictus, è stata dimostrata l'equivalenza tra la terapia robot-assistita e la stessa dose di terapia convenzionale. Questo risultato è necessario per aprire nuove frontiere per integrare l'utilizzo di tale piattaforma e le cure convenzionali, ottenendo risultati terapeutici non inferiori.

In secondo luogo, per aumentare la dose della terapia, le interfacce fisiche e grafiche con l'utente e gli esercizi terapeutici sono stati riprogettati per essere usati con una supervisione

minima e la loro usabilità è stata verificata in uno studio pilota con dieci pazienti con ictus cronico.

In terzo luogo, per aumentare la sicurezza e monitorare eventi avversi imprevisti (es., l'aumento anomalo del tono muscolare della mano) senza supervisione, sono stati proposti e testati nuovi concetti per il monitoraggio real-time del livello di abilità del paziente e delle sue condizioni fisiche. Questi metodi di monitoraggio si basano su metriche robotiche raccolte online durante gli esercizi di terapia. Il monitoraggio del tono muscolare è stato testato in cinque soggetti sani e cinque soggetti dopo ictus cronico.

Infine, per consentire l'uso della piattaforma terapeutica in diversi ambienti (es., a casa), è stato sviluppato un nuovo dispositivo aptico, compatto e portatile per allenare la presa a livello della mano, la pronosupinazione dell'avambraccio e la flesso-estensione del polso. Il dispositivo è stato testato preliminarmente con una supervisione minima su quattro soggetti post ictus cronico, utilizzando la nuova interfaccia utente e gli esercizi terapeutici sviluppati. I risultati sull'usabilità ottenuti dallo studio pilota hanno permesso di identificare i punti critici del dispositivo, che hanno portato allo sviluppo di un secondo dispositivo portatile migliorato.

I risultati promettenti di questa tesi di dottorato aprono la possibilità di usare dispositivi robotici attivi con una supervisione minima per complementare le terapie convenzionali, riducendo i costi della terapia robot-assistita (es., riducendo nel tempo la supervisione costante da parte di un terapista). Ciò permette di creare un continuum di cura che fornisce lo stesso metodo di terapia prima in clinica e poi a domicilio, aumenta la dose della terapia e migliora progressivamente il coinvolgimento e l'autonomia del soggetto.

Questa tesi ha portato tre contributi principali. In primo luogo, attraverso una sperimentazione clinica con più soggetti, è stato dimostrato che un dispositivo robotico può essere utilizzato per offrire una terapia sensomotoria per la mano dopo un danno neurologico, ottenendo risultati terapeutici non inferiori a quelli ottenuti con cure convenzionali. Ciò ha gettato le basi necessarie per supportare il secondo contributo della tesi, ovvero lo sviluppo di una piattaforma robotica user-friendly per la terapia minimamente supervisionata, che può essere utilizzata con più dispositivi per svolgere la terapia in clinica e continuarla a domicilio. La piattaforma permettere un monitoraggio autonomo di base del livello di abilità del paziente, della sua sicurezza e condizioni fisiche. Il terzo contributo della tesi è lo sviluppo di due dispositivi terapeutici portatili compatibili con la piattaforma terapeutica. La piattaforma ed entrambi i dispositivi sono stati sviluppati in collaborazione diretta con partner industriali e clinici. Nessun altro dispositivo terapeutico portatile attivo attualmente in ricerca o sul mercato offre la possibilità di esercitare apticamente le stesse funzioni della mano con una supervisione minima e con un piano strutturato di terapia sensomotoria che può iniziare in clinica e continuare a domicilio dopo la dimissione del paziente.

Contents

List of Figures

List of Tables

1 Introduction

1.1 Stroke and hand impairment

Globally, there are over 80 million people currently living who have experienced a stroke and approximately 13.7 million new cases each year [Lindsay et al., 2019]. Stroke is among the major health conditions causing serious long-lasting disability [Morris et al., 2013]. This common and complex condition considerably impacts individuals' life with physical, psychological, and social consequences [Northcott et al., 2016, Northcott and Hilari, 2011, Franceschini et al., 2010]. Stroke survivors suffer from upper limb impairment early after the event in up to 80% of the cases [Nakayama et al., 1994, C et al., 2012, Lawrence et al., 2001]. Additionally, more than 40% subjects have limited functional recovery after four years [Broeks et al., 1999] due to a spectrum of joint alterations and pain, limited range of motion (ROM), muscle tone abnormalities, reduced sensory functions (e.g., proprioception, tactile perception), motor learning and motor control [Raghavan, 2007, Broeks et al., 1999]. This can greatly impair human-environment interactions and explorations, particularly at the level of the hand, which is characterized by one of the most complex and fine types of sensorimotor control in the human body. In fact, the hand can perform a wide range of tasks going from power tasks (e.g., power grip) to the manipulation of small objects with great precision. As a result, upper limb and hand impairments directly impact the ability of stroke survivors to execute activities of daily living (ADL), such as grasping objects, scissoring or writing [Broeks et al., 1999, Kelly-Hayes et al., 2003, Pandyan et al., 2003, Duncan et al., 1992], and greatly affect their quality of life [Franceschini et al., 2010, Lieshout et al., 2020]. Moreover, the probability of regaining functional use of the impaired hand is considered to be low [Kwakkel et al., 2003] and hand function is one of the domains with highest perceived impact at the Stroke Impact Scale six years after stroke [Ytterberg et al., 2017].

The nature of impaired hand function can be broken down into three interlinked impairment types, namely sensory, motor and cognitive impairment, which assume different weight depending on the lesion location.

More than half of stroke survivors [Connell et al., 2008] suffer from impaired integration of

sensory information from the upper limb (e.g., during interaction with the environment). In particular, impaired somesthesis (i.e., the faculty of bodily perception through the sense of touch, proprioception, pain, temperature) directly impacts hand motor and functional performance [Carlsson et al., 2018], as confirmed by the anatomofunctional interconnections in primates between motor cortices, somatosensory cortices and the sensory thalamus associated with hand control [Nudo et al., 1996, Romo et al., 1993]. Tactile and proprioceptive loss are among the key contributors to functional outcome reduction in patients with hemiplegia [Kato and Izumiyama, 2015, Twitchell, 1954], especially in tasks requiring fine motor skills, even more when associated with visual field loss that could otherwise help compensating for the deficit [Han et al., 2002]. The restoration of effective sensorimotor pathways is therefore crucial for the recovery of hand motor and functional performance [Zeman and Yiannikas, 1989], which directly correlates with the changes in activation within the ipsilesional primary somatosensory area [Laible et al., 2012]. Patients with poorer recovery tend instead to compensate with higher recruitment of parallel bilateral sensorimotor networks (e.g., premotor, supplementary, cingulate motor areas) [Ward and Cohen, 2004].

Hand motor impairment can derive either from deficits in motor execution (e.g., due to weakness, abnormal muscle synergies/co-activations, spasticity) or from deficits in higher order processes (e.g., motor learning and planning through internal involuntary models and sensorimotor associations). These deficits are directly interfaced and difficult to disentangle from sensory and cognitive processes and impairments [Raghavan, 2007, Miller and Dewald, 2012].

Stroke is indeed also the second most frequent cause of acquired cognitive impairment [Tang et al., 2018], which affects 44% of the subjects 2 to 6 months after stroke [Lo et al., 2019a] and up to 80% after 3 to 6 years [Zhang et al., 2020]. Detriments to four cognitive domains (each with a prevalence between 30 and 35%) can affect hand function [Lo et al., 2019a, Lezak et al., 2004, Zinn et al., 2007, Dancause et al., 2002] and motor recovery [Mullick et al., 2015]. First, impaired attention and processing speed can slow down reactions or error corrections during an action. Second, memory impairments reduce the ability to learn and retrieve previous sensorimotor skills/experiences to interpret or correct a motor plan. Third, high-level perceptual and motor dysfunctions can respectively reduce the awareness of the visual field or of the body (i.e., neglect), and the ability to perform skilled gestures (i.e., apraxia). Finally, frontal executive dysfunctions can, for instance, compromise the ability to react in an adaptive manner to novel situations. Frontal dysfunctions can rise from changes in gesture volition (e.g., awareness of the context, motivation), planning (e.g., organization of steps/skills needed for the gesture), production (e.g., initiation/termination of sequences of behaviors), and effective performance (e.g., regulation of gesture intensity or tempo).

In this complex puzzle of highly interconnected functions and impairment modalities, identifying the exact etiology of hand impairment after stroke is a challenge. For this reason, it is very difficult to define what should be prioritized within therapies focused on the hand [Gündüz and Toprak, 2019, Raghavan, 2007].

1.2 Hand therapy - a state of the art

Rehabilitation therapies are the principal intervention to regain hand function in both acute and chronic stages after stroke [Gündüz and Toprak, 2019]. A variety of approaches can be used to support functional recovery through neuroplastic changes in sensorimotor control pathways. Following the classification of Gündüz and Toprak [2019], the most frequently used approaches are:

- *Exercise/physical therapy and motor learning programs*: upper extremity and hand dexterity are enhanced through repetitive motor executions or strength training [Bütefisch et al., 1995, Chan et al., 2006, Donaldson et al., 2009, Woldag et al., 2010]. This is thought to facilitate the re-acquisition and retention of simple motor skills, which can be transferred to the execution of more complex tasks.

- *Neurophysiological approaches*: therapy focused on normalizing tone and utilizing sensory inputs to inhibit synergistic movements and relearn selective movement patterns, sometimes not directly linked to daily life functions [Kabat and Knott, 1953, Bobath, 1978, Brunnström, 1970, Vojta, 1976, Affolter, 1987, Perfetti and Grimaldi, 1979].

- *Task-specific training*: exercises focused on relearning activities relevant for daily life to promote functional recovery [Yoo and Park, 2015b, Bayona et al., 2005, Hubbard et al., 2009].

- *Constraint-induced movement therapy (CIMT)*: specialized task-specific training that restrain the less impaired side and intensively train the affected side during functional tasks [Kwakkel et al., 2015, Taub et al., 1999, Liu et al., 2017], assuming that this will enhance neuroplastic changes in the impaired brain hemisphere.

- *Bilateral arm training*: both affected and less affected hands are trained simultaneously, but independently of one another, to complete a task. This training assumes that bilateral movements will promote the activation of similar neural networks in both hemispheres. Movements may be symmetrical or asymmetrical [Waller and Whitall, 2008, Stewart et al., 2006].

- *Motor imagery*: according to the motor simulation theory, patients train the activation of the same brain areas of a real motor task by imagining the task without executing any real movement [Jackson et al., 2001, Munzert et al., 2009].

- *Mirror therapy*: the non paretic side is moved in front of a mirror and creates the visual feedback illusion of a movement on the paretic side [Zeng et al., 2018]. The assumption is that mirror training can stimulate the affected hemisphere through mirror neurons, which are activated both when an individual executes a specific motor act and when they observe the same or similar act performed by another limb or individual.

- *Robot-assisted therapy*: a robot is used to provide (sensori)motor training or support with the aim to offer a patient-tailored high-intensity training to promote recovery [Lambercy et al., 2018, Veerbeek et al., 2017].

- *Virtual reality training*: body movements are detected through various sensors and allow the user to interact with a virtual reality environment [Wattchow et al., 2018, Hatem et al., 2016, Sheehy et al., 2019, Laver et al., 2015]. The use of virtual reality can elicit attention and motivation, promoting patient compliance and an increase in therapy dose.

- *Electrical stimulation*: sensory or motor stimuli are triggered via transcutaneous or neuromuscular stimulation, respectively, either in passive conditions or during specific tasks [Hatem et al., 2016, Schuhfried et al., 2012, Quandt and Hummel, 2014, Capone et al., 2017]. Sensory stimulation is thought to reduce muscle hyperexcitability (e.g. in spastic syndrome), while motor stimulation allows to strengthen voluntary muscle control for patients with minimal ability for volitional muscle activation.

- *Noninvasive brain stimulation*: typically used in combination with other rehabilitation treatments to normalize the interhemispheric imbalance and promote brain plasticity via transcranial magnetic or direct current stimulation [Klomjai et al., 2015, Hatem et al., 2016]. Due to their complexity, invasive stimulation approaches (e.g., deep-brain, epidural) have been more rarely investigated [Levy et al., 2016, Hummel et al., 2008, Teixeira et al., 2015, Coscia et al., 2019].

- *Static or dynamic orthosis*: an orthosis maintains or supports tonic stretch positions to increase ROM, and to reduce muscle tone (e.g., biomechanical contracture), pain and edema [Lannin and Herbert, 2003, Greg Pitts and Peganoff O'Brien, 2008].

Frequently, these therapy methods have been established based on empirical and/or physiological assumptions rather than scientific evidence. There is typically no consensus on best practices to treat hand impairment to promote true recovery (i.e., restoring the ability to perform a movement in the same manner as it was performed before injury through the recovery of function in brain areas affected by the stroke) [Levin et al., 2009, Gündüz and Toprak, 2019, Raghavan, 2007]. Furthermore, there is no high-quality evidence to enable comparisons of the relative effectiveness of interventions [Pollock et al., 2014].

In this context of lack of evidence, some of the therapy approaches became very similar to philosophical and religious doctrines, which are applied depending on personal experience/beliefs. This limits their potential for further scientific exploration and maximization of patient's recovery. Instead, in clinical routine, it would be good practice to consider and apply therapy as a modular approach, which is designed for the patient (and considering the resources of the rehabilitation unit) by combining appropriate therapeutic elements [Basaglia et al., 2002]. In this sense, a better classification of therapy approaches should be rather focused on the possible therapy elements that could be combined within the intervention:

- Task: passive or active mobilization focused on either pure high-intensity movements, strengthening of weak muscles, reduction in spasticity, restoring the balance between agonist and antagonist muscle groups, intensive task-specific and/or sensorimotor practice with the affected hand [Raghavan, 2007, Gündüz and Toprak, 2019]

- Limb observation: without or with action observation, and motor imagery for the latter when there is no active movement in the affected limb [Zhu et al., 2020, Zeng et al., 2018, Perfetti and Grimaldi, 1979]

- Electromagnetic stimulation: magnetic or electrical central (e.g., transcranial direct current, magnetic stimulation, invasive stimulation) or distal (e.g., functional electrical stimulation, transcutaneous electrical nerve stimulation) stimulation to induce reflexes, sensory feedback or motor activation [Hatem et al., 2016, Schuhfried et al., 2012, Quandt and Hummel, 2014, Klomjai et al., 2015, Hatem et al., 2016, Capone et al., 2017, Levy et al., 2016, Coscia et al., 2019].

- Biofeedback: biomechanical (e.g., movement/posture, force/pressure) and physiological measurements (e.g., electromiography, real-time ultrasound imaging) used to provide biological information (via visual displays, acoustic or haptic signals) to the patient in real-time to facilitate normal movement patterns [Giggins et al., 2013].

- Physical interaction: mechanical or electromechanical support, resistance, constraint of either the impaired or less impaired limb. Possibility to focus on haptic and functional interaction through (instrumented) objects (e.g., sets of tools or handles) or tactile stimuli (e.g., textures) [Taub et al., 1999, Liu et al., 2017, Lannin and Herbert, 2003, Greg Pitts and Peganoff O'Brien, 2008, Lambercy et al., 2018, Wattchow et al., 2018, Hatem et al., 2016].

- Training side: mono- or bilateral training [Stoykov et al., 2009, Morris et al., 2008]

- Virtual reality: with or without virtual reality to increase the motivation and immersion/identification in the exercise [Wattchow et al., 2018, Hatem et al., 2016]

- Pharmacology and biotechnology: with or without pharmacological agents [Cramer, 2015, Mazzoleni et al., 2017, Tran et al., 2016] and, very recently, stem cells [Muir et al., 2020, Kamelska-Sadowska et al., 2019] under the name of neuroregenerative rehabilitation therapy (NRRT).

Unfortunately, the hand typically receives little treatment during in-hospital rehabilitation after stroke, which focuses mostly on large and proximal joints [Qiuyang et al., 2019]. After discharge, this often results in the learned non-use of the hand and in compensatory movements from the proximal joints of the upper-extremity, which are carried over to the chronic period due to insufficient distal practice in daily life [Gillen, 2015]. Furthermore, it is extremely challenging to develop targeted therapies that are impairment- and subject-specific at the level of the hand given its complexity in terms of movements (27 degrees of freedom controlled

by 34 muscles) [Feix et al., 2015, Wang et al., 2019], extremely fine and versatile sensorimotor control (involving more than 17000 tactile mechanoreceptors) [Johansson and Vallbo, 1979, Carlsson et al., 2018], and the entanglement of its impairment symptoms.

1.3 Task-oriented sensorimotor training

In the complex framework of therapy modalities, the selection of appropriate therapy tasks seems to be of utmost importance. Somatosensation plays an important role in motor skills learning [Mirdamadi and Block, 2020, Vidoni et al., 2010, Vahdat et al., 2014]. In particular, proprioception and haptic perception are crucial for the accurate generation [Butler et al., 2004] or correction [Pruszynski et al., 2016, Prokopenko et al., 2008] of upper limb movements, such as reaching [Sarlegna and Sainburg, 2009, Sober and Sabes, 2003] or grasping [Camponogara and Volcic, 2019], and are highly interlinked with motor and cognitive abilities needed during active object exploration/recognition [Reed and Ziat, 2018]. Somatosensory stimulation and training have been shown to improve and directly correlate with motor (re-)learning after stroke [Jayasinghe, 2019, Chen et al., 2018, Doyle et al., 2010]. Moreover, combining sensory and cognitive training could be beneficial to achieve better information processing needed for sensorimotor relearning [McEwen et al., 2015, Wolf et al., 2016, Zhang et al., 2020]. Despite increasing evidence of the importance of somatosensory function, assessment and treatment, current rehabilitation strategies are still mostly focused on motor training and somatosensory rehabilitation is still largely neglected [Carlsson et al., 2018, Pumpa et al., 2015, Yekutiel, 2000] and the number of randomized controlled trials that focus on somatosensation is still relatively low [Kessner et al., 2016].

Furthermore, there is moderate-quality evidence that task-oriented therapy, intended as the active execution of challenging tasks relevant for daily life with the intention of (re-)acquiring a skill [McDermott et al., 2014], may be beneficial to promote neuroplasticity [Bowden et al., 2013], improve hand function and ADL [French et al., 2016, Yoo and Park, 2015a], and prevent the development of learned non use [Winstein et al., 2016]. Unfortunately, the definition of task-oriented therapy is still highly heterogeneous [McDermott et al., 2014], and only few studies tested its efficacy in the subacute stage [Thant et al., 2019, Bosch et al., 2014]. Furthermore, with the goal to increase functional capacity, several task-oriented therapies neglect the quality of execution of the rehabilitative task or focus on the teaching of compensatory strategies [Almhdawi et al., 2016], which are difficult to remove in the long term. These could have mixed effects on functional outcome depending on the stroke severity [Jones, 2017] (e.g., dominant reliance on the non-paretic limb or reliance on the trunk to move the paretic arm counter the recovery of more-normal arm movement [Michaelsen et al., 2006], but may be the only option for severe impairments). The therapeutic association of fine-controlled tasks that are meaningful for daily life with sensorimotor training modalities seems to have positive outcomes on motor recovery in terms of Fugl-Meyer of the upper extremity, and may conceal an unexploited potential that would deserve further focus both in research and in clinical routine [da Silva et al., 2020].

1.4 Therapy dose: a key factor for rehabilitation outcomes

In the last thirty years, animal and human research showed that behavioural experience is one of the most important modulators of cortical function and structure after brain damage, particularly when reinforced by the simultaneous activation of a given sensorimotor circuits for a high number of repetitions [Nudo, 2013].

Animal models suggested that therapy dose (i.e., number of task repetitions per time unit and total therapy time) is important to promote recovery. Training doses up to 600 reps per session (for 5 to 7 days per week [Nemchek et al., 2021]) allow to alter brain representations and synapses during motor skills learning either in healthy rats or monkeys [Nudo et al., 1996, Kleim et al., 1998, 2002] or post-stroke [Jeffers et al., 2018, Bell et al., 2015, Nudo, 2013, Kleim and Jones, 2008, Nudo and Milliken, 1996]. Conversely, lower training doses in the order of tens of repetitions [O'Bryant et al., 2007, Starkey et al., 2011], or administered intermittently every second day [Nemchek et al., 2021], are associated with lower neuroplasticity. Forced physical training (i.e., treadmill running, [Lee et al., 2009, Ploughman et al., 2007]) and CIMT (i.e., restraint of the unaffected upper limb to enhance the use of the affected limb [Maldonado et al., 2008]) can reduce the infarct volume by 30% and 18%, respectively, and skilled reaching training (e.g., repeated reaching for food pellets [Schabitz et al., 2004]) improved the limb function by 26.7% [Schmidt et al., 2014]. Moreover, a training combining environment enrichment and intensive task-specific training (e.g., reaching) resulted to be more effective than either of the two trainings alone [Clarke et al., 2014], and has been proposed as the best-practice for pre-clinical recovery of upper limb function [Corbett et al., 2015, Livingston-Thomas et al., 2016]. A recent study showed that, in severely impaired rats, a higher number of repetitions per session is required to recover, and could be predefined at baseline as a function of infarct volume and initial impairment [Jeffers et al., 2018]. These results support the hypothesis of a direct dose-recovery relation and of a dose threshold below which it is unlikely that surviving motor networks supporting recovery can undergo a neuroplastic reorganisation [MacLellan et al., 2011, Jeffers et al., 2018]. Unfortunately, it is debated to which extent animal models could be translated to evidence-based therapies for humans, who have different neurophysiology and conventionally receive therapy doses that are lower by one or multiple orders of magnitude [Dalton et al., 2019, Bernhardt et al., 2016, Walker et al., 2014].

The dose-recovery hypothesis could be supported in humans after large increases in sensorimotor and functional recovery were shown in subjects after stroke training at high doses via conventional [Han et al., 2013, Vloothuis et al., 2016], robot-assisted care [Duret et al., 2019, 2015, Pila et al., 2017, Hsieh et al., 2012, Burgar et al., 2011], or either of the two [Ward et al., 2019, Schneider et al., 2016, McCabe et al., 2015, Lang et al., 2015, Lohse et al., 2014, Veerbeek et al., 2014]. Unfortunately, comparing dose results between and within human and animal studies is problematic due to different definition, controlling and reporting of therapy dose. Indeed, most of the scientific literature does not report all the subportions of dose, namely total scheduled exercise time, its frequency over sessions/days/weeks, number of repetitions per effective exercise time and, very importantly, a clear definition of the exercise

repetition (e.g., movement, task) [Lang et al., 2015]. The majority of the high-dose human studies achieved scheduled (exclusive) upper-limb therapy time above 2 hours per working day (maximum 5-6 hours per working day [Gomez et al., 2014, McCabe et al., 2015, Ward et al., 2019]), typically distributed over four to six weeks (maximum eight to twelve training weeks [Page et al., 2012, Tariah et al., 2010, McCabe et al., 2015, Lohse et al., 2014]). In few cases, the combination of the two reached a total prescribed therapy time, which is the most frequently reported measure of therapy dose in humans [Lohse et al., 2014, Lang et al., 2015], above 80 hours [Ward et al., 2019, Han et al., 2013, Tariah et al., 2010, McCabe et al., 2015, Page et al., 2012]. Regarding the number of repetitions, although rarely reported in humans, plastic changes were demonstrated above 300 movement repetitions in chronic patients during a 1 hour session [Birkenmeier et al., 2010, Volpe et al., 2008, Waddell et al., 2014] and not below 100 [Carey et al., 2007]. Unfortunately, in clinical practice, dose is not consistent with this evidence. Upper limb therapy programs in the subacute stage after stroke frequently consist of less than 40 repetitions for three sessions per week [Lang et al., 2009] and, even when they are claimed to be high dose [Winstein et al., 2016, Lo et al., 2010, Klamroth-Marganska et al., 2014], they offer a relatively low therapy time (e.g., 18-36 hours) independently of the patient's time/stage after stroke [Ward et al., 2019]. On the one hand, this is due to skepticism on what is the maximum dose that stroke survivors and therapists could tolerate [Lang et al., 2016], while maintaining sufficient motivation and energy to work hard in the subsequent hours of a comprehensive multidisciplinary program or for a typical 8-hours workload, respectively [Duret et al., 2019]. On the other hand, despite showing lower long-term healthcare costs compared to conventional care [Wagner et al., 2011], intensive therapy regimes pose immediate economical and logistical concerns, such as the costs and difficulties in organizing infrastructure, equipment and therapist time needed for a therapy session often requiring a 1:1 therapist to patient ratio, as well as hospitalization for inpatients (in long therapy programs) or travel for outpatients [Islam and Brunner, 2019, Allen et al., 2019, Lloréns et al., 2015]. To achieve high dose therapy programs in clinical practice, it is therefore important to find ways to boost the patient motivation during therapy, and tools to relieve the therapists and reduce economical and organizational burden on the healthcare facility.

1.5 Robot-assisted therapy: an effective solution for hand therapy

Robot assisted therapy could represent a solution to complement conventional therapy while respecting all the necessary elements for effective therapy of hand function [Lambercy et al., 2018, Grosmaire et al., 2019]. Since the publication of the first controlled study with stroke inpatients [Aisen et al., 1997], several studies have demonstrated the potential of robot-assisted therapy for the upper limb in stroke rehabilitation. Firstly, it has been shown that robotic devices offer motivating task-oriented training with comparable therapy outcomes compared to conventional dose-matched therapy [Rodgers et al., 2019, Mehrholz et al., 2018, Burgar et al., 2011, Conroy et al., 2011, Klamroth-Marganska et al., 2014, Lo et al., 2010, Masiero and Armani, 2011]. Secondly, robotic devices could be used to achieve higher therapy dose compared to

conventional therapy [Daly et al., 2019, Veerbeek et al., 2017, McCabe et al., 2015, Han et al., 2013]. For instance, therapy sessions could become longer by letting multiple patients train simultaneously with the same therapist [Büsching et al., 2018, McCabe et al., 2015], instead of training one after the other. Additionally, exercise repetitions could increase up to 871 [Duret et al., 2015] and 1295 [Pila et al., 2017] per 45 minute session. Thirdly, robots are able to accurately control the patient-robot interaction, i.e. they are capable of supporting/resisting the patient if needed and/or they can accurately render different sensorimotor tasks/environments visually and mechanically (through visual and haptic displays). Finally, robotic devices can be used to precisely assess the patient's ability and performance [Germanotta et al., 2020, Duret et al., 2019, Lambercy et al., 2011, Loureiro et al., 2009, Prange et al., 2006] and to continuously adapt therapy difficulty to the current state of the patient [Metzger et al., 2014b, Giang et al., 2020].

In the last decade, several robotic hand therapy devices were developed. These devices are based on end-effector and/or exoskeletal designs [Aggogeri et al., 2019, Lambercy et al., 2018] that are either standalone [Yeong et al., 2009], tabletop (e.g., Hand of Hope [Tong et al., 2010]) or wearable [Ou et al., 2020, Nycz et al., 2016], with or without the possibility to support the limb against gravity. They offer object-based [Choi et al., 2011] or virtual therapy tasks [Huang et al., 2017, Khor et al., 2014] and therapy modalities ranging from passive mobilization [Sale et al., 2012] to active manipulation [Lambercy et al., 2011]. Less frequently, they have been tested with additional types of feedback (e.g., biofeedback [Zadravec et al., 2020], auditory [Rosati et al., 2013], vibrations [Decker and Kim, 2017]), stimulation (e.g., neuromuscular stimulation [Lee et al., 2015b]), control interfaces (e.g., invasive or non-invasive brain-machine interfaces [Kapsalyamov et al., 2019, Soekadar et al., 2015, Buch et al., 2008]), or to train bimanually [Yang et al., 2012].

Unfortunately, most rehabilitation robots are currently not used at their maximum potential. They are most frequently used in short therapy sessions in clinical or research environments [Klamroth-Marganska et al., 2014, Page et al., 2013, Lum et al., 2012] under constant supervision of trained personnel, which contributes to a cost increase and limits the maximum doses achievable using this technology. Most devices typically focus on pure motor training and do not explore the ability of the robot to offer haptic training of sensorimotor tasks relevant for daily life [Veerbeek et al., 2017, Bertani et al., 2017]. Additionally, robot-assisted therapies do not usually consider the importance of cognitive training [Aprile et al., 2020, Fasoli and Adans-Dester, 2019], which can facilitate skill acquisition [McEwen et al., 2015] and significantly improve its transfer to ADL [Wolf et al., 2016]. To better exploit their potential, robotic technologies should be adapted to provide higher therapy dose, which could be achieved by allowing to perform therapy with minimal supervision. This approach could also increase therapy dose after discharge from the clinic through the minimally-supervised use of portable (i.e., that can be carried in a suitcase), scalable and affordable active devices. These devices should offer sensorimotor therapy exercises that require active cognitive involvement and train tasks relevant for skill transfer to ADL. Moreover, when considering to use such technology in a minimally-supervised way, safety should be ensured through autonomous monitoring

of the patient and device conditions. Finally, device usability should be guaranteed to ensure technology acceptance and patient compliance.

1.6 Goals of the thesis

This thesis firstly aims to evaluate whether robot-assisted therapy of hand function following a sensorimotor therapy approach is feasible and produces equivalent therapy outcomes compared to conventional care. This will serve as necessary basis to investigate and develop the elements necessary to create a robot-assisted therapy platform (i.e., robot with user interface and exercises), which could offer the same therapy approach with minimal supervision to potentially enable a therapy dose increase.

A previous work from Metzger and Lambercy et al. led to the development of the ReHapticKnob, an end-effector based, two degrees-of-freedom hand rehabilitation robot, which trains grasping (i.e., hand opening and closing) and forearm pronosupination after stroke [Metzger et al., 2011]. The robot can accurately render therapy tasks/objects visually through a virtual reality interface and haptically trough powered instrumented finger pads, which measure 6-DOF forces applied at the level of the thumb and fingers. The ReHapticKnob allows a variety of interactions, ranging from passively guided movements, which are important for plegic patients, to the training of fine motor skills in mildly impaired stroke victims. The neurocognitive therapy approach proposed by Carlo Perfetti in the seventies was selected as therapy approach since it focuses on the training of sensorimotor functions as well as cognition, which are fundamental during functional interactions between body and environment, particularly at the level of the hand [Perfetti and Grimaldi, 1979]. For instance, subjects are asked to manually explore objects (e.g. sponges, sticks, springs), discriminate and memorize their haptic properties, and identify them based on their relative differences often without vision. The level of difficulty of the exercises was customized to the patient's impairment level using robotic assessments conducted at baseline, as well as to the patient performance during the therapy progression to appropriately balance exercise challenge and patient motivation.

This work builds on the neurocognitive robot-assisted therapy concept developed on the ReHapticKnob, which showed encouraging preliminary results in terms of user acceptance and impairment reduction [Metzger, 2014]. Furthermore, some promising work suggested that conventional neurocognitive therapy can significantly improve upper-limb function, ability to perform activities of daily living and quality of life [Lee et al., 2015a], and recently found increasing interest in the scientific community [Carey et al., 2011, Albiol-Pérez et al., 2014, Yu et al., 2014, Morreale et al., 2016], but its efficacy was so far only preliminarily investigated, particularly if administered via robot-assisted therapy.

This thesis aims to develop new solutions for neurorehabilitation of hand function after stroke through four research goals, which are detailed below with their expected significance for the neurorehabilitation field.

1. Establish the equivalence of robot-assisted and dose-matched conventional neurocognitive therapy. Showing equivalent efficacy (per dose-unit) is an important first step, which opens the road to the potential use of this technology with minimal supervision as a complement to conventional care. Furthermore, our approach will demonstrate the feasibility of executing with a robotic device therapy tasks that are relevant for hand function (e.g., functional, sensorimotor and cognitive therapy tasks).

2. Develop a robot-assisted minimally-supervised therapy platform for task-oriented sensorimotor training of hand function, and show that the platform is safe, usable with appropriate changes by stroke patients with limited supervision and requires appropriate workload during preliminary learning phases and during therapy. The usability of our platform will preliminarily show that it is possible to offer robot-assisted therapy in a sustainable way with minimal external supervision. This opens the road to increase therapy doses and create a continuum of care that starts in the clinic and continues at home.

3. Develop a method for autonomous monitoring of patient ability and physical conditions during therapy, which could detect the onset of patient abnormal health conditions early, and through a set of smart algorithms (i.e., "clinical artificial intelligence"), automatically adapt the therapy plan. This approach will allow to implement minimally-supervised therapy while guaranteeing safety and appropriate tailoring of the therapy plan and exercises to the patient needs.

4. Develop a complementary portable/scalable device that would allow to adopt the minimally-supervised therapy platform to train hand function in any environment, and show that the device is perceived as usable by subjects after stroke. This new device is the last necessary element to implement sensorimotor robot-assisted therapy with minimal supervision in the home environment. This could allow to further promote a dose increase and functional gains, establish a longer relation with the clinic (which starts as inpatient and continues after discharge), avoid learned non-use of the affected arm and increase subject's independence.

1.7 Thesis outline

In this thesis, the chapters represents the necessary elements and steps needed for the development a novel portable minimally-supervised robot-assisted therapy platform:

- **Chapter 2** describes the equivalence between dose-matched robot-assisted and conventional neurocognitive therapy of hand function
- **Chapter 3** describes the development of a robot-assisted platform designed for minimally-supervised therapy of hand function and its preliminary usability evaluation with a non-portable haptic device for use in the clinic

- **Chapter 4** describes the autonomous monitoring of hand muscle tone during the execution of active sensorimotor therapy exercises as a proof of concept for the online monitoring of possible adverse events during minimally-supervised therapy
- **Chapter 5** describes the development of HandyBot, a portable device for minimally-supervised therapy of hand function, which builds on the previous device/platform tested in clinical settings
- **Chapter 6** provides a general discussion of the outcomes of this thesis and further ongoing developments. The end of the chapter provides suggestions for future work.

2 Equivalence of supervised neurocognitive robot-assisted therapy of hand function after stroke

This chapter is adapted from

Neurocognitive robot-assisted rehabilitation of hand function: a randomized control trial on motor recovery in subacute stroke

Raffaele Ranzani*, Olivier Lambercy*, Jean-Claude Metzger, Antonella Califfi, Stefania Regazzi, Daria Dinacci, Claudio Petrillo, Paolo Rossi, Fabio M. Conti, and Roger Gassert

Journal of NeuroEngineering and Rehabilitation, 2020.

*Raffaele Ranzani and Olivier Lambercy contributed equally to this work.

The authors would like to thank Jürg Hartmann for handling part of the data collection, Dr. Gianni Rossi for his support throughout the study, Maya Kamber for her support with ethics and data monitoring, all the physiotherapists, speech therapists and neuro-psychologists from the Clinica Hildebrand that were involved in the trial execution, Mike D. Rinderknecht for his MATLAB toolboxes, as well as Janine Burren for her help with statistical analyses.

This work was supported by the National Center of Competence in Research on Neural Plasticity and Repair of the Swiss National Science Foundation (NCCR Neuro), the ETH CHIRP1 Research Grant on Cortically-Driven Assistance Adaptation during Sensorimotor Training, the Olga Mayenfisch Stiftung, the ETH Zurich Foundation in collaboration with Hocoma AG, and the Clinica Hildebrand Centro di Riabilitazione Brissago, Switzerland.

Raffaele Ranzani coordinated half of the data collection of the randomized controlled trial and, since the middle of the study, conducted the robot-assisted therapy sessions with the patients. Furthermore, he performed the data analysis and wrote the manuscript with Olivier Lambercy.

Final publication is available from https://doi.org/10.1186/s12984-020-00746-7.

2.1 Robot-assisted rehabilitation of hand function

Upper-limb robot-assisted therapy has been established as a safe and feasible treatment to complement rehabilitation after neurological injury, such as stroke [Veerbeek et al., 2017]. Robots can precisely control the interaction with a patient (e.g., supporting or resisting in an assist-as-needed manner) and render virtual environments both visually and mechanically, making them ideal tools for sensorimotor training, providing engaging and challenging therapy [Klamroth-Marganska et al., 2014, Lo et al., 2010]. Over the past two decades, several robotic devices to train the proximal upper extremity [Maciejasz et al., 2014] were developed and clinically evaluated, achieving outcomes comparable to dose-matched conventional therapy [Veerbeek et al., 2017, Klamroth-Marganska et al., 2014, Lo et al., 2010, Lum et al., 2006, Burgar et al., 2011, Masiero and Armani, 2011, Mehrholz et al., 2018, Lambercy et al., 2018, Rodgers et al., 2019].

However, distal arm function is essential for the execution of activities of daily living (e.g., eating, dressing) and is often severely impaired after stroke [Raghavan, 2007], with low probability of regaining its full functional use [Fischer et al., 2007]. Several studies have shown that functional motor training at the level of the hand with robotic devices can be beneficial and positively translate into recovery of proximal arm function [Lambercy et al., 2011, Hsieh et al., 2018]. Despite recent investigations to develop novel robots to train hand function [Lambercy et al., 2018, 2007, Lum et al., 2012], only few systems took advantage of the haptic rendering capabilities of robots to support somatosensory training, nor evaluated this in clinical trials. As such, most systems for robot-assisted therapy developed to date focus on movement practice without incorporating an established therapy concept adapted to the capabilities of the respective technology.

In this work, the clinical equivalence of sensorimotor, robot-assisted rehabilitation of hand function is investigated within a preliminary four-week randomized controlled trial (RCT) on subacute stroke patients. The neurocognitive rehabilitation method proposed by Perfetti [Perfetti and Grimaldi, 1979] was selected as reference therapy approach. It focuses on the training of motor function, somatosensation and cognition, which all contribute to functional interactions between body and environment (e.g., information perception, as well as elaboration, selection and execution of motor plans) [Sallés et al., 2017, McEwen et al., 2009, Turville et al., 2017]. Because of the relevance of the cognitive processing of sensory inputs, this approach is particularly interesting for hand rehabilitation. Moreover, the integration of multisensory inputs promotes the involvement of associative cortices that play a key role in learning and consequently in neuronal plasticity and recovery [Van de Winckel et al., 2012]. While only a few studies compared neurocognitive therapy to other rehabilitative approaches [Sallés et al., 2017, Lee et al., 2005], some promising work suggested that it can significantly improve upper-limb function, ability to perform activities of daily living and quality of life compared to conventional task-oriented training [Lee et al., 2005]. Consequently, this approach has recently found increasing interest in the scientific community, applied both in conventional [Carey et al., 2011, Chanubol et al., 2012, Morreale et al., 2016] and in technology-assisted therapy

[Albiol-Pérez et al., 2014, Yu et al., 2014], but has so far not been evaluated when administered through a robotic device. The therapy concept inspired by the neurocognitive approach was implemented on a high-fidelity 2 degrees of freedom end-effector haptic device to train hand function (i.e., the ReHapticKnob [Metzger et al., 2014a]). The therapy exercises focused on grasping and pronosupination (e.g., tactile discrimination tasks, teach and reproduce tasks, haptic exploration tasks, [Metzger et al., 2014b]) and were performed using virtual objects rendered both visually and haptically by the robot, mimicking the physical objects used in conventional therapy. The primary objective of this RCT was to investigate if the implemented robot-assisted hand therapy concept could be integrated into the rehabilitation program of participants with subacute stroke during their inpatient stay (i.e., replace one conventional neurocognitive therapy session on each intervention day) and if, at precisely matched dose, an equivalent reduction in upper limb motor impairment could be achieved. This study design was motivated by the need to establish noninferiority in terms of rehabilitation outcomes per dose unit when comparing the proposed intervention to conventional neurocognitive therapy. This is an important first step towards the investigation of more specific robot-assisted protocols that could further take advantage of the abilities of the robotic device (e.g., increasing therapy dose through minimally-supervised therapy, automatically monitor the patient conditions and propose personalized therapies). As secondary objectives, we hypothesized that neurocognitive robot-assisted therapy of the hand would lead to improvements in motor, sensory and cognitive functions in participants with subacute stroke.

2.2 Design of a randomized controlled trial

2.2.1 Trial design

A single center, parallel group, randomized control trial was conducted at the Clinica Hildebrand Centro di Riabilitazione Brissago, Switzerland. Study participants were recruited among inpatients undergoing an intensive interdisciplinary rehabilitation therapy program post-stroke. After screening for eligibility by a medical doctor, participants were randomly assigned (by balanced prerandomization [1:1]) to a robot-assisted group (RG), receiving robot-assisted neurocognitive therapy with the ReHapticKnob (see Fig. 2.1) haptic device, or to a control group (CG), receiving dose-matched conventional neurocognitive therapy without the robot.

On 15 days distributed over 4 weeks, all subjects received three neurocognitive therapy sessions (i.e., 2×45 min and 1×30 min) per day focusing on hand function (see Fig. 2.2). In the RG, one of the 45 min therapy sessions per day was substituted with robot-assisted therapy. Based on ethical grounds, only one session of upper limb therapy per day was replaced to guarantee that all patients could still get access to the standard treatment for subacute inpatients. These sessions were embedded in the weekly therapy plan of each individual participant. The study protocol was reviewed and approved by the local Ethics Committee (EC 2646) and Swissmedic (2013-MD-0002) prior to participant recruitment. Simultaneously, the study was registered on the (non-public) European register EUDAMED and subsequently in Clinialtrials.gov.

Figure 2.1: A subject with stroke using the ReHapticKnob. The ReHapticKnob is a haptic device used to train hand opening-closing and forearm pronosupination. The device integrates a set of 7 therapy exercises reproducing typical neurocognitive exercises [Metzger et al., 2014b]. In the present exercise, the compliance of different virtual sponges rendered by the device has to be memorized and identified by relying on hand somatosensory inputs during active interaction with the device.

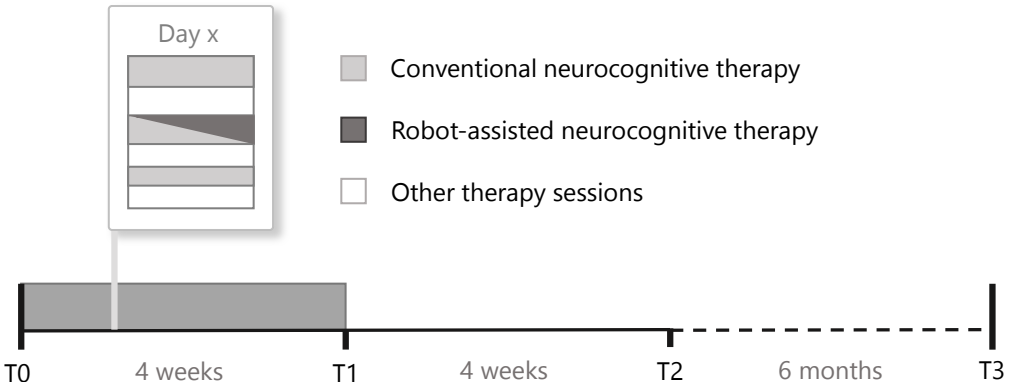


Figure 2.2: Study protocol. Integration of RCT therapy sessions into the weekly therapy schedule of participants and assessment scheduling. Assessment sessions were performed at therapy start (T0), after the 4-week intervention (T1), as well as at 4-week (T2) and 6-month (T3) follow-ups.

2.2.2 Participants

Subjects were enrolled in the study if they met the following inclusion criteria: age between 18 and 90 years old, first and only cerebrovascular event, subacute lesion (i.e., occurred not earlier than 6 weeks before recruitment), hemiparesis with arm motor deficit as assessed with a National Institutes of Health Stroke Scale (NIHSS, [Brott et al., 1989])≥ 1. Subjects were excluded if they presented an altered state of consciousness, severe aphasia (Goodglass and Kaplan test <1, [Huber et al., 1993]), severe cognitive deficits (Levels of Cognitive Functioning-Revised, LCF-R<6, [Hagen, 2000]), severe pathologies of the upper limb of traumatic or rheumatic nature, severe pain in the affected arm (≥ 5 on a visual analogue scale for pain (VASp)), or if they had active pacemakers and other active implants.

2.2.3 Interventions

The neurocognitive therapy approach proposed by Perfetti [Perfetti and Grimaldi, 1979] includes sensorimotor and cognitive aspects, all fundamental during the execution of complex tasks and activities of daily life. Focusing on haptic and postural perception, often without vision, subjects are asked to explore objects (e.g. sponges, sticks, springs), discriminate their properties and perceive relative differences. A robotic device is an ideal tool to perform such exercises, as a wide range of haptic stimuli can easily and accurately be rendered in a repeatable and well-controlled manner [Metzger et al., 2014b]. Seven exercises were available both in conventional and robot-assisted therapy: passive grip aperture discrimination, passive pronosupination angle identification, stiffness identification during grasping, stiffness identification during index finger pinching, teach and reproduce of grip apertures, teach and reproduce of pronosupination angles. The seventh exercise in the conventional therapy was a texture identification exercise, while in the robot-assisted therapy, the exercise consisted in the identification of specific pronosupination angles, indicated by a vibratory cue on the grasping DOF (within a 4° window around the targeted pronosupination angle). Within these exercises, the motor aspects of the intervention consisted of symmetric thumb and fingers flexion/extension, as well as forearm pronation/supination, which were executed either independently or combined. The sensory aspects of the intervention entailed encoding (i.e., perception and processing) the following types of somatosensory signals without visual information: sponge/spring stiffnesses, size and shape of objects (e.g. stick lengths, sponge size), arm positioning (e.g., pronosupination orientations), and vibratory cues. The cognitive aspects of the training demanded elaboration/recognition of perceptual information (e.g., understand and memorize object length/stiffness), encoding/decoding of this information in the working memory for comparison purposes of more than one object (e.g., identify length/stiffness of an unknown object), planning/execution/correction of fine motor plans. The tasks were executed either passively (i.e., guided by the therapist/robot) when they only required sensory perception (e.g. of object length or forearm orientation), or actively by the subject (against the resistance of the object/robot) when they required active object manipulation (e.g., stiffness identification). The robotic device used in this study can haptically reproduce the same

objects and, thereby, motor, sensory and cognitive tasks used in conventional therapy. The objects are rendered via the robotic handles by generating appropriate forces during hand opening/closing and forearm pronosupination, while they are displayed on a screen (see Figure 2.1) [Metzger et al., 2014a].

In both groups, all the conventional neurocognitive therapy sessions included two or three exercises depending on the session duration (i.e., 30 or 45 minutes), as typically done in the standard clinical setting. The exercises were performed with the help of the therapist, who progressively adapted the assistance and difficulty level of the exercise (e.g., number of objects, object length or stiffness) depending on his/her evaluation of the subject's ability.

Similarly, each 45-minute session of robot-assisted therapy included three exercises (selected each day following a predefined plan common to all participants) consisting of up to 30 task repetitions with the robot (each involving multiple movements and interpretation of sensory information), in a maximum of 15 minutes per exercise. The exercise type, number of task repetitions per exercise and the maximum exercise duration were selected based on pilot tests on subjects with stroke [Metzger et al., 2014b] to precisely match therapy type and dose typically performed in conventional therapy. In each exercise, the difficulty level was initially adapted to the subject according to a baseline robotic assessment and continuously updated at the end of each session depending on the subject's performance. An experienced physio- or occupational therapist supervised all the sessions. For a more detailed description of the robotic assessments, exercises and difficulty adaptation, refer to our earlier work [Metzger et al., 2014b].

2.2.4 Outcome measures and masking

Participants were evaluated on separate days with respect to the therapy sessions, at four time points: before (T0) and after (T1) the intervention, and in two follow-ups at 8 weeks (T2) and 32 weeks (T3) (see Figure 2.2). Assessors were masked to treatment allocation, while participants, therapists and data analysts were unmasked.

Primary outcome. The primary outcome of the study, which was tested for equivalence, was the change from baseline in upper extremity motor impairment at the end of treatment (i.e., T1-T0), assessed with the Fugl-Meyer Assessment of the Upper Extremity (FMA-UE) [Fugl-Meyer et al., 1975]. The FMA-UE scale was chosen as primary outcome due to its relevance in sensorimotor rehabilitation and related literature, especially with respect to robot-assisted therapy.

Secondary outcomes. The secondary outcomes of the study are divided into three categories to compare the two intervention groups at each time point:

1. Motor, sensory and cognitive scales: changes in upper limb impairment at each time point were measured using the FMA-UE and its subcomponents related to hand and

wrist (FMA-WH) as well as shoulder and elbow (FMA-SE), gross manual dexterity using the Box and Block Test (BBT) [Mathiowetz et al., 1985], spasticity level of the upper limb (i.e., shoulder adductors, elbow flexors and extensors, wrist flexors and finger flexors) with the Modified Ashworth Scale (MAS) [Charalambous, 2014], tactile sensation and proprioceptive ability of the upper limb with the Erasmus MC Nottingham Sensory Assessment (EmNSA) [Stolk-Hornsveld et al., 2006], cognitive impairment with the Mini Mental State Examination (MMSE) [Folstein et al., 1975], unilateral spatial neglect with the Albert Test (AT) [Albert, 1973], and behavioral ability and dementia with the Frontal Assessment Battery (FAB) [Dubois et al., 2000].

2. Therapy intensity: to verify dose matching, the two groups were compared in terms of average number of task repetitions performed in one session and therapy intensity (i.e., number of task repetitions per minute of effective therapy). During conventional therapy, the number of task repetitions and the effective therapy time were recorded by the supervising therapist, while they were directly logged by the robot during the robot-assisted therapy.

3. Acceptance of neurocognitive robot-assisted therapy: in the subjects from the RG, acceptance was evaluated by a subjective 4-item questionnaire: (Q1) "Are the exercises with the robot motivating?" (0 no, 1 yes), (Q2) "Would you recommend the additional robot therapy to other subjects with stroke?" (0 no, 1 yes), (Q3) "Did the robot-therapy lead to concrete improvements?" (0 no, 1 yes), (Q4) "How comfortable were the exercises with the robot for you?" (0 uncomfortable, 10 very comfortable).

2.2.5 Statistical methods and sample calculation

The Wilcoxon Rank Sum Test was used to assess homogeneity between groups at baseline for time post lesion, FMA-UE, FMA-WH, NIHSS, LCF-R and Goodglass-Kaplan, and a two-sample t-test for age and VASp, which resulted to be normally distributed. Fisher's exact test was applied to investigate group differences in gender, side of stroke, and stroke type. Measurements of the average dose and therapy intensity in RG and CG were also compared using the two-sample t-test or the Wilcoxon Rank Sum Test.

Equivalence testing [Walker and Nowacki, 2011] was used to investigate whether the groups showed an equivalent change in terms of the primary outcome measure. Equivalence was established if the difference in change in FMA-UE between the two groups lies within an equivalence boundary of ±5.2 points, which was reported to be the minimal detectable change for the FMA-UE [Wagner et al., 2008]. The confidence intervals were calculated as described by D'Agostino et al. for small sample sizes (<30) [D'Agostino et al., 2006]. The equivalence test was repeated at T1 (primary outcome), T2 and T3 to evaluate if equivalence is retained over time. A pre-study power calculation for equivalence testing estimated that 28 subjects would provide 80% power to prove equivalence between the two groups in terms of FMA-UE, given the selected equivalence boundary and an estimated standard deviation of 4.66 FMA-UE

points in the FMA-UE score change after therapy (based on preliminary data [Metzger et al., 2014b]). To compensate for an expected dropout rate of 15%, a sample size of 32 participants was selected.

For all outcome measures, the groups were compared after the intervention (T1-T0) and at the follow-ups (T2-T0 and T3-T0) in a 2x3 (i.e., group x time) repeated measures analysis of variance (ANOVA) analyzing between and within-group differences. In presence of significant differences, post-hoc comparisons were performed between T1-T0, T2-T0 and T3-T0. The statistical significance level of $\alpha = 0.05$ was corrected using Bonferroni correction in the analyses of the primary and secondary outcome measures (i.e., ANOVA), leading to a value of 0.0046 and 0.0025, respectively.

To obtain a meaningful estimate of the treatment effect, all analyses were performed by modified intention to treat (MITT): all assigned participants for whom outcome data at the end of the intervention (T1) are available were analyzed. For missing data, we inferred the missing value by last observation carried forward or, if no former value was available, by next observation carried backward.

2.3 Results of the Randomized Controlled Trial

Between April 2013 and March 2017, 33 subjects with subacute stroke were eligible and agreed to participate in the study (Figure 2.3). We did not keep a complete log of subjects who were screened for eligibility, but this number was estimated to be between 80-90 by the principal investigator. The target sample size was reached with 17 subjects allocated to the RG and 16 subjects allocated to the CG. Only 27 subjects received the allocated intervention and completed the T1 assessment (MITT population: 14 RG, 13 CG), six subjects did not complete the intervention protocol or withdrew before the T1 assessment due to lack of motivation, concomitant unrelated medical pathologies or cognitive deficits that were not detected at recruitment. Twenty-three subjects (12 RG, 11 CG) completed the full protocol up to T3 as 1 subjects had a recurrent stroke and 3 additional subjects withdrew due to a lack of motivation after the completion of the intervention. During the duration of the study, no adverse event related to the intervention was observed.

2.3.1 Baseline characteristics

Table 2.1 reports the baseline demographics and clinical characteristics of the two groups at T0. No statistically significant differences were found in baseline characteristics (Wilcoxon Rank Sum Test, two-sample t-test, Fisher's exact test, see Table 2.1 for more details). The participant age range was 38 to 85 years and there were 12 right and 15 left hemisphere lesions. Most subjects showed mild/moderate [Woytowicz et al., 2017] initial upper-limb impairment (FMA-UE 50.48±13.50 (mean±std)) due to both ischemic and hemorrhagic stroke. In the two groups, a different distribution in stroke type was evident (although not significantly different

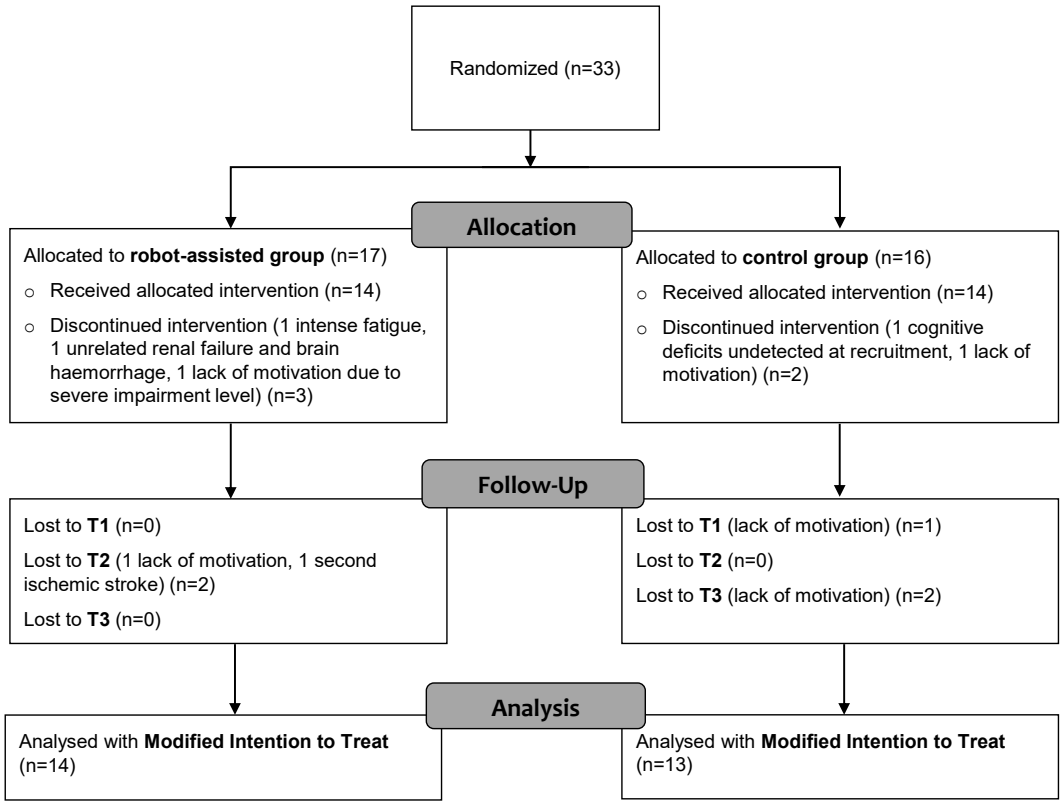


Figure 2.3: Trial profile describing the participants population of the RCT.

Table 2.1: Baseline characteristics of the randomized study participants (MITT, N = 27)

Characteristics[a]	Robot-assisted (n = 14)	Control (n = 13)	p[b]
Age (years)	70.00 (12.79)	67.46 (11.39)	0.5921 (t(25) = 0.543)
Time since stroke (weeks)	3.14 (1.51)	3.08 (1.32)	0.8794 (Z = -0.2)
Sex			0.6946
Male	10	8	
Female	4	5	
Side of stroke			1.000
Left	8	7	
Right	6	6	
Stroke type			0.0054
Ischemic	13	5	
Hemorrhagic	1	7	
Both	0	1	
FMA-UE	50.14 (12.50)	50.84 (15.01)	0.7891 (Z = −0.3)
FMA-WH	17.86 (5.61)	19.39 (6.20)	0.1478 (Z = -1.4)
NIHSS	1.36 (0.75)	1.69 (1.03)	0.3500 (Z = -0.9)
VASp	0.00 (0.00)	0.85 (1.63)	0.0623 (t(25) = −1.951)
LCF-R	8.86 (1.10)	8.31 (1.44)	0.3390 (Z = 1.0)
Goodglass-Kaplan	4.43 (0.76)	4.31 (1.18)	0.8438 (Z = -0.2)

Abbreviations: *FMA-UE* Fugl-Meyer Assessment of the Upper Extremity; *FMA-WH* Fugl-Meyer Assessment of Wrist and Hand functions; *NIHSS* National Institutes of Health Stroke Scale; *VASp* Visual Analogue Scale for Pain; *LCF-R* Revised Levels of Cognitive Function; Goodglass-Kaplan, Assessment of aphasia and related disorders

[a]Continuous data are expressed as mean (standard deviation), categorical data as number

[b]p values are associated with the Fisher's exact test for categorical variables (used for small samples), while Wilcoxon rank sum test and two-sample t-test are used for continuous variables (independent samples). According to the Bonferroni correction, the significance level $\alpha^* = \frac{0.05}{11} = \mathbf{0.00455}$)

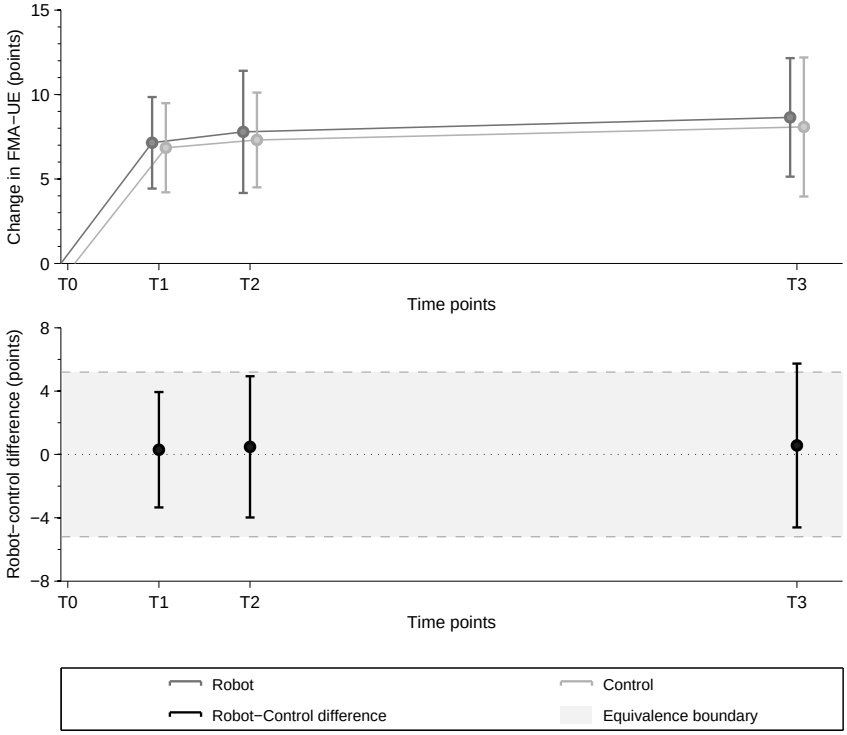


Figure 2.4: Equivalence test between robot-assisted and control group w.r.t. the FMA-UE change. The test was performed at 4 weeks (T1), 8 weeks (T2) and 8 months (T3) compared to baseline.

after Bonferroni correction), with a majority of ischemic strokes in the robot-assisted group. Before enrollment, all participants were informed about the study and gave written consent.

2.3.2 Equivalence in Fugl-Meyer of the upper extremity

According to the equivalence analysis (Figure 2.4), the change in FMA-UE in the robot-assisted group can be considered as non-inferior to the control group. The 90% confidence interval lies within the equivalence boundaries at T1 (i.e., primary outcome) but tends to move outside the equivalence boundary in favor of the robot-assisted therapy at the end of the study (T3). Between T0 and T1, subjects in the RG improved on average by 7.14 FMA points, while those in the CG showed an average increase of 6.85 FMA points. In both groups, these changes are above the minimal detectable/clinically important change (i.e., 5.2 and 5.25 FMA-UE points, respectively) [Wagner et al., 2008, Shelton et al., 2001].

The changes in FMA-UE were maintained at T2 and T3 (i.e., secondary outcome measures). Between T0 and T2, subjects in the RG improved on average by 7.79 FMA points, while those in the CG showed an average increase of 7.31 FMA points. Finally, from T0 to T3, RG subjects improved by 8.64 FMA points and CG subjects by 8.08 FMA points.

2.3.3 Changes in secondary outcome measures

Comparing the changes in clinical scales with respect to baseline over time (see Table 2.2), the two groups did not show any significant between-group difference, as shown by the group factor in ANOVA. Additionally, therapy-induced T1-T0 within-group changes of each scale were maintained at T2 and T3, as shown by the time factor in the ANOVA analysis, except for the BBT score that continued to increase. At T1, the FMA-WH improved by 2.93 and 2.39 FMA points in the RG and CG, respectively, while the FMA-SE improved by 4.21 FMA points in the RG and 4.46 FMA points in the CG. BBT increased by 11.43 blocks/min on average in the RG, and 12.85 blocks/min in the CG. As for the FMA-UE, the BBT change at T1-T0 was above its minimal detectable change of 5.5 blocks/min [Chen et al., 2009] in both groups. A significant time dependency after the end of therapy was observed, and post-hoc analysis suggested an increase of BBT between T1 and T3 ($t(52) = -2.396$, $p = 0.020$), although this change was not significant following Bonferroni correction. The EmNSA-T increased by 1.07 points in the RG and 2.85 points in the CG, while the EmNMA-P increased by 0.14 and 0.54 points, respectively. The MAS showed a negligible increase of 0.07 points in the RG and decreased by 1.54 points in the CG at T1, converging to the same score range (i.e., around 1 MAS point) at T3. A T1-T0 decrease above the MAS minimal detectable change of 1 point [Shaw et al., 2010] was only detected in the CG, which could be explained by the slightly higher MAS baseline score of this group. From T0 to T3, the MAS decreased by 0.29 and 0.85 points in the RG and CG, respectively. The MMSE increased by 0.57 and 1.05 points in the RG and CG, respectively, but both changes were below the MMSE minimal detectable change of 3 points [Feeney et al., 2016]. The FAB increased by 0.43 and 1.26 points in the RG and CG, respectively, while the Albert Test showed minor increases of 0.07 and 0.15 points.

2.3.4 Therapy intensity

During a therapy session, the RG performed on average 71.49±10.84 task repetitions while the CG received 73.47±45.19 task repetitions, as reported by the supervising therapist. The average number of task repetitions per session received in the RG and in the CG was not significantly different as revealed by the two-sample t-test ($t(23) = -0.159$, $p = 0.875$). In terms of therapy intensity, there was also no statistically significant difference between the two groups, either comparing robot-assisted and conventional therapy sessions (RG = 1.45±0.33 reps/min, CG = 1.40±0.81 reps/min, Wilcoxon Rank Sum Test $Z = -0.8$, $p = 0.427$) or comparing all conventional therapy sessions in both groups (RG = 1.63±0.85 reps/min, CG = 1.40±0.81 reps/min, Wilcoxon Rank Sum Test $Z = -0.6$, $p = 0.529$). In addition to the neurocognitive therapy sessions, the average daily amount of occupational therapy and/or lower limb physiotherapy did not statistically differ in the two groups (RG = 40.68±17.88 min, CG = 50.33±6.41 min), as revealed by the two-sample t-test ($t(23) = -1.699$, $p = 0.103$).

Table 2.2: Patients' scores in all the clinical and robotic outcome measures

Assessment (Max/Healthy Value)	Group	Baseline (T0) value, Mean (SD)	Change from baseline, Mean (SD)			Repeated Measures ANOVA on change from baseline			
			T1	T2	T3	Group		Time	
						F (1,25)	*P*	F (2,52)	*P*
FMA-UE (66)	RG	50.14 (12.50)	+ 7.14 (5.72)	+ 7.79 (7.65)	+ 8.64 (7.42)	0.035	0.8537	1.206	0.3076
	CG	50.85 (15.00)	+ 6.85 (5.34)	+ 7.31 (5.68)	+ 8.08 (8.32)				
FMA-WH (24)	RG	17.86 (5.61)	+ 2.93 (2.62)	+ 3.64 (3.25)	+ 3.64 (3.23)	0.371	0.5480	3.701	0.0314
	CG	19.39 (6.20)	+ 2.39 (1.81)	+ 2.54 (2.22)	+ 3.39 (3.62)				
FMA-SE (42)	RG	32.29 (8.08)	+ 4.21 (4.14)	+ 4.14 (5.92)	+ 5.00 (5.68)	0.012	0.9152	0.303	0.7403
	CG	31.46 (8.95)	+ 4.46 (3.91)	+ 4.77 (4.46)	+ 4.69 (5.62)				
BBT (–)	RG	17.79 (9.67)	+ 11.43 (6.60)	+ 13.50 (7.33)	+ 17.57 (10.91)	0.504	0.4842	11.330	8.241e-05*
	CG	15.15 (8.44)	+ 12.85 (8.22)	+ 17.54 (13.39)	+ 19.92 (13.96)				
EmNSA-T(24)	RG	20.93 (5.44)	+ 1.07 (2.20)	+ 1.43 (2.59)	+ 1.86 (3.33)	2.986	0.0964	2651	0.0801
	CG	15.15 (9.44)	+ 2.85 (4.45)	+ 5.54 (7.33)	+ 4.92 (7.53)				
EmNSA-P(8)	RG	7.79 (0.58)	+ 0.14 (0.36)	−0.21 (0.43)	0.00 (0.56)	5.258	0.0305	0.520	0.5976
	CG	6.77 (1.92)	+ 0.54 (0.97)	+ 0.69 (1.18)	+ 0.46 (0.78)				
MAS(0)	RG	1.29 (1.77)	+ 0.07 (2.37)	−0.21 (2.36)	− 0.29 (2.56)	1.012	0.3241	0.558	0.5756
	CG	2.15 (2.94)	−1.54 (2.91)	−1.31 (3.12)	−0.85 (3.69)				
MMSE(30)	RG	25.89 (3.60)	+ 0.57 (1.91)	+ 0.93 (1.64)	+ 1.71 (3.07)	0.072	0.7906	1.088	0.3446
	CG	23.62 (5.47)	+ 1.05 (1.87)	+ 0.59 (2.41)	+ 0.93 (3.33)				
FAB(18)	RG	14.60 (2.38)	+ 0.43 (1.74)	+ 1.14 (1.70)	+ 1.61 (1.67)	0.144	0.7079	1.625	0.2067
	CG	11.98 (5.29)	+ 1.26 (1.71)	+ 1.49 (1.76)	+ 1.05 (1.60)				
Albert Test (32)	RG	31.86 (0.36)	+ 0.07 (0.27)	+ 0.07 (0.48)	+ 0.14 (0.36)	0.034	0.8544	0.000	1.000
	CG	31.77 (0.83)	+ 0.15 (0.90)	+ 0.15 (0.56)	+ 0.08 (0.28)				

Abbreviations: *SD* Standard deviation; *FMA-UE* Fugl-Meyer Assessment of the Upper Extremity; *FMA-WH* Fugl-Meyer Assessment of Wrist and Hand functions; *FMA-SE* Fugl-Meyer Assessment of Shoulder and Elbow functions; *MAS* Modified Ashworth Scale; *EmNSA-T* Erasmus MC Nottingham Sensory Assessment of Tactile sensation; *EmNSA-P* Erasmus MC Nottingham Sensory Assessment of Tactile of Proprioceptive ability; *MMSE* Mini Mental State Examination; *FAB* Frontal Assessment Battery

Symbols: * Statistically significant according to Bonferroni correction (i.e., significance level $\boldsymbol{\alpha^* = \frac{0.05}{20} = 0.0025}$)

2.3.5 Acceptance of neurocognitive robot-assisted therapy

Out of 12 participants that answered the questionnaire in the RG, 91.7% found the robot-assisted therapy motivating (Q1), 84.6% would recommend the robot-assisted therapy program to other persons with stroke (Q2), and 84.6% found concrete improvements in their health status at the end of the therapy program (Q3). Participants found the robot-assisted therapy to be comfortable, rating it at 7.42±1.34 out of 10 (Q4). The questionnaire revealed mild sporadic discomfort in the finger fixation, and that, in three out of seven exercises, difficulty levels were sometimes perceived as too high.

2.4 Discussion

This paper presents the clinical feasibility and outcomes of a RCT conducted on subjects with subacute stroke evaluating the effect of robot-assisted neurocognitive therapy of hand function, and in particular, if therapy with the haptic device could lead to an equivalent and lasting sensorimotor recovery compared to dose-matched conventional neurocognitive therapy. In contrast to most robot-assisted rehabilitation trials, which placed a strong focus

on movement training, our approach takes full advantage of the haptic rendering abilities of the robot, and proposes a therapy program adapted to these capabilities. We could show that this approach is well accepted and recommended by the majority of the patients, and that it could be integrated in the daily schedule of inpatients in the subacute stage after stroke. Most participants found the program motivating, comfortable, and could perceive concrete improvements in their health status after the end of the treatment.

2.4.1 Equivalent reduction in upper limb motor impairment

Traditionally, most RCTs have aimed to prove that robot-assisted therapy per se could increase upper limb recovery with respect to conventional therapy (e.g., by increasing therapy intensity, subject engagement, or by providing exercises targeting specific motor impairments). However, large clinical studies on arm rehabilitation with subjects with chronic stroke, aiming to demonstrate the superiority of robot-assisted therapy, were rarely successful, or only observed small, non-clinically meaningful differences [Klamroth-Marganska et al., 2014, Lo et al., 2010]. Similarly, other studies focusing solely on robot-assisted rehabilitation of hand function in chronic [Rowe et al., 2017, Connelly et al., 2010, Thielbar et al., 2017, Susanto et al., 2015] or subacute stroke [Fischer et al., 2007, Kutner et al., 2010, Hwang et al., 2012] were not able to show statistically significant differences between robot and control therapy groups, or reported minor differences in secondary outcome measures [Rodgers et al., 2019, Vanoglio et al., 2017, Orihuela-Espina et al., 2016]. The present RCT directly investigated equivalence in motor impairment reduction between a robot-assisted and a conventional therapy group focusing on the training of the upper limb, and in particular the hand. For this purpose, the therapy dose (i.e., number of task repetitions and therapy time) as well as the therapy intensity (i.e., task repetitions per time unit) were precisely matched between groups.

The results of the equivalence test comparing the evolution in FMA-UE demonstrate that, for our specific intervention, the motor recovery in the robot-assisted group is non-inferior with respect to the control group. In general, it is not surprising to observe little to no difference between conventional and robot-assisted therapy in the context of studies where therapy dose and the therapy exercises/movements are designed to be similar, qualitatively and/or quantitatively, between groups. In this context, the haptic device primarily supports the therapist, providing additional motivation for the subjects to train, and delivering objective readouts (e.g., based on task performance, or kinematic and kinetic data) that can be used for monitoring, difficulty adaptation, or research purposes [Metzger et al., 2014b]. Nevertheless, the fact that a session of conventional therapy could be replaced without affecting the overall rehabilitation outcome opens promising avenues for further developing robot-assisted therapy programs.

2.4.2 Neurocognitive hand rehabilitation led to improvements on motor, sensory and cognitive scales

Secondary outcome measures further support the equivalence analysis. After four weeks of treatment (T1), in addition to motor deficits, also sensory and cognitive deficits were concurrently reduced in both groups, with improvements in all the secondary clinical scales (i.e., proximal and distal arm impairment, functional ability, somatosensation, executive functions and cognitive control). The decrease in upper limb impairment (FMA-UE, RG +7.14 pts, CG +6.85 pts) was clinically meaningful in both groups, and favorably compares to other work focusing on robot-assisted hand rehabilitation in subacute stroke, where changes between 3.0 to 5.3 FMA-UE points were typically reported [Lambercy et al., 2018]. Improvements were retained over time up to 7 months after the end of treatment. No significant differences were found between the groups in terms of changes with respect to baseline for all outcome measures. Only the BBT showed a significant effect of time, with additional increases in changes with respect to baseline after completion of the intervention (i.e, above 98% at T3). FMA-WH also showed steady improvements over time after the end of the intervention (i.e. after T1), but these were not significant after Bonferroni correction. These further increases in BBT and FMA-WH suggest improvements in unilateral gross manual dexterity, which represents an essential element in the interaction with objects. This supports the approach of, whenever possible, focusing therapy on hand function training rather than proximal arm segments only, as distal training may promote impairment reduction in the entire arm [Lambercy et al., 2011, Hsieh et al., 2018, Stein et al., 2011].

Only minor improvements were observed in both groups over time in cognitive functions (i.e., FAB, MMSE, Albert Test), somatosensory function (i.e., EmNSA), and muscle tone control (i.e., MAS). These changes were small mostly due to the saturation of these scales in a mildly/moderately impaired population, and did not show significant changes between the groups and over time following T1. A decrease in MAS was observed in the CG, but not in the RG where a small, clinically non-relevant increase was observed. This is partly in line with a recent review [Veerbeek et al., 2017], which analyzed changes in MAS of the paretic arm in 13 dose-matched RCTs and found negative effects on muscle tone reduction (i.e., increase in MAS) following robot-assisted therapy and a significant difference in favor of the respective control groups. This could possibly be caused by higher forces/muscle recruitment involved in robot-assisted exercises, but was not monitored in the present study. Also, it is debatable whether a minor, temporary, increase in muscle tone would negatively affect functional recovery in subjects with stroke [Perfetti and Grimaldi, 1979, Shumway-Cook and Woollacott, 2007]. In the present study, the increase in MAS disappeared in follow-up assessments, and the different behavior of the two groups could also be explained by slightly higher baseline MAS in the CG. Additional studies are necessary to investigate how muscle tone evolves depending on subject conditions (e.g., lesion type), therapy type and intensity.

Finally, given the majority of hemorrhagic stroke survivors, a better functional recovery could have been expected in the control group compared to the robot-assisted group [Paolucci et al.,

2003, Kelly et al., 2003]. Our results do not support this hypothesis, probably due to the rather mild impairment level of a majority of patients across both groups, indicating smaller lesions independent of the lesion type.

2.4.3 Study Limitations

The participants involved in both groups were mostly mildly or moderately impaired (initial FMA>29) [Woytowicz et al., 2017]. This led to ceiling/floor effects in some of the clinical sensory and motor assessments, which might have masked some of the intervention effects. This was, however, not imposed by our study design, subject screening or inclusion criteria, as the feasibility of the proposed robot-assisted therapy approach was also demonstrated in more severely impaired outpatients in the chronic stage after stroke [Metzger et al., 2014a]. No measure of real world upper limb use was included in the study design, and it therefore remains to be explored whether the proposed therapy leads to improvements in upper limb use in daily life. While the robot-assisted therapy program could be well integrated into a subacute rehabilitation program to complement the existing therapy, only patients with mild to moderate cognitive impairment were eligible to participate, as the intense therapy program challenged some patient's cognitive abilities. This did not allow to verify up to which cognitive impairment level the proposed approach could be applied, and the included patients only had little room for cognitive recovery. However, this was not the objective of this study since both groups received the same type of treatment. As additional possible confounder, all participants received additional conventional therapy sessions as part of their standard inpatient therapy program in parallel to the intervention, which could not be entirely substituted for ethical concerns. Nevertheless, we did achieve 15 x 45-minute sessions over 4 weeks, which is comparable to other clinical trials or pilot studies on robot-assisted rehabilitation of hand function [Susanto et al., 2015, Hwang et al., 2012, Vanoglio et al., 2017]. Furthermore, the results of this study are limited by the rather small sample size and should be interpreted with respect to the provided therapy and dose level. Finally, as is the case for any clinical trial at the subacute stage post stroke and of comparable sample size, the contribution of spontaneous recovery cannot be disentangled from intervention-induced recovery.

2.4.4 Potential of neurocognitive robot-assisted rehabilitation of hand function

The therapy intensity delivered in this study typically exceeded the amount of movement practice reported in the literature for conventional physio- or occupational therapy sessions (1.45 rep/min vs 0.92 rep/min) [Lang et al., 2015]. Still, compared to the knowledge gained from animal studies and to recent high-dose clinical studies [Ward et al., 2019, McCabe et al., 2015, Daly et al., 2019], this intensity might not be sufficient. It is important to note, however, that one "repetition" using the neurocognitive approach is not directly comparable to, e.g., reaching movements as typically reported in the literature. One repetition corresponds to one complex task (e.g., sponge identification) involving several actual movements, as well as sensory processing and cognition, demanding time, effort and concentration. An open

question is whether delivering high (and potentially even higher) intensity of conventional therapy would be feasible in daily practice over several weeks, outside of a research study.

Establishing the non-inferiority in impairment reduction via robot-assisted therapy at a clinically-applicable dose is an important step towards opening new research avenues. While not all components of object manipulation (e.g., texture discrimination) can be trained with our robot, the proposed robot-assisted therapy of hand function, including sensorimotor and cognitive training, could ideally complement conventional therapy programs. Our therapy approach could further help increase the therapy dose provided to neurological patients, with the aim to positively impact functional recovery [Han et al., 2013, Veerbeek et al., 2014] with only minimal additional burden on clinical staff. This could be achieved, after appropriate adjustments to the proposed technology, through semi-supervised therapy of multiple patients in parallel [Büsching et al., 2018], minimally-supervised therapy during inpatients' spare time, or even a continuation thereof at home, as proposed in several promising pilot studies with passive devices [Hayward et al., 2015, Amirabdollahian et al., 2014]. Especially regarding the latter, we find it crucial to introduce patients to such technology at an early stage during therapist supervision, which we here (and others) have shown to be feasible. In that sense, the results of this study demonstrating that neurocognitive robot-assisted therapy is also safe and well-accepted are a positive and necessary first step.

To reach the goal of minimally-supervised robot-assisted rehabilitation, special attention should be devoted to the evaluation of usability and acceptance of rehabilitation devices, and in that sense, simple end-effector devices, such as the ReHapticKnob device used in this study, may be advantageous over upper limb exoskeletons often requiring long setup time and adjustments [Lambercy et al., 2018]. To meet user expectations and improve technology acceptance with respect to the current setup, more attention should be devoted to the design of ergonomic handles and to the adaptation of the difficulty levels of the exercises. Embedded clinical "intelligence" building on online robotic assessments, or performance metrics extracted from therapy sessions, should be further developed to provide means of accurately monitoring subjects' ability level and the evolution of their performance during treatment (or even after discharge), possibly adapting exercise difficulty autonomously to constantly challenge the user at an appropriate level [Metzger et al., 2014b]. Overall, such technology could help to increase the therapy dose subjects with stroke receive at the different stages of their rehabilitation, offer alternative solutions to enable earlier discharge of the subjects from the clinics, and provide continued and individually modulated therapy in the home environment after discharge.

2.5 Implications and outlook

This chapter presents the results of a RCT investigating the equivalence in motor recovery between dose-matched robot-assisted and conventional neurocognitive therapy of hand function after stroke. The results show that neurocognitive robot-assisted therapy can be

well integrated in the clinical routine and allows for a non-inferior motor recovery compared to conventional dose-matched neurocognitive therapy when performed during supervised inpatient rehabilitation in the subacute stage after stroke. An early familiarization of subjects with stroke to the use of such patient-tailored robot-assisted therapy program opens the doors to the use of such technology with minimal therapist supervision in the clinic, or directly at home after hospital discharge, to help increase the dose of hand therapy for persons with stroke. However, for this to be possible, the technology should be adapted to be usable with minimal supervision and portable.

3 Towards a platform for robot-assisted minimally-supervised therapy of hand function: design and pilot usability evaluation

This chapter is adapted from

Towards a Platform for Robot-Assisted Minimally-Supervised Therapy of Hand Function: Design and Pilot Usability Evaluation

Raffaele Ranzani, Lucas Eicher, Federica Viggiano, Bernadette Engelbrecht, Jeremia P.O. Held, Olivier Lambercy, and Roger Gassert

Frontiers in Bioengineering and Biotechnology, 2021.

The authors would like to thank all the volunteers that participated in the pilot study, and Dominik G. Wyser and Jan T. Meyer for their valuable insights and discussions during the writing of this work.

This work was supported by the European Project SoftPro (No.688857) and the Swiss State Secretariat for Education, Research and Innovation SERI under contract number 15.0283-1.

Raffaele Ranzani performed the data analysis and wrote the manuscript. Additionally, he contributed to the implementation of the graphical/physical user interface and exercises, definition of the study protocol and execution of the pilot study.

Final publication is available from https://doi.org/10.3389/fbioe.2021.652380.

3.1 How to increase dose

Robot-assisted therapy may offer a promising approach to increase therapy dose (i.e., number of exercise task repetitions per time unit and total therapy time) after stroke [McCabe et al., 2015, Veerbeek et al., 2017, Daly et al., 2019]. A variety of robotic devices have been proposed to train hand and wrist movements [Lambercy et al., 2007, Gupta et al., 2008, Takahashi et al., 2007, Aggogeri et al., 2019], as well as to provide sensitive and objective evaluation or therapy of motor and sensory (e.g., proprioceptive) function [Casadio et al., 2009, Kenzie et al., 2017, Mochizuki et al., 2019]. However, robot-assisted therapy has so far typically been applied with constant supervision by trained personnel, which prepares and manages the complex equipment, sets up the patient on/in the device and configures the appropriate therapy plan. As a result, most robotic devices are typically used in the context of short (frequently outpatient) supervised therapy sessions in clinical settings [Lum et al., 2012, Page et al., 2013, Klamroth-Marganska et al., 2014], and where the presence of a supervising therapist is required to prepare and manage the complex equipment, set up the patient on/in the device and configure the appropriate therapy plan. This generates organizational and economical constraints that restrict the use of the technology [Wagner et al., 2011, Schneider et al., 2016, Rodgers et al., 2019, Ward et al., 2019] and, as a result, despite claiming high intensity [Lo et al., 2010, Rodgers et al., 2019], the therapy dose achieved using robots remains limited compared to guidelines [Bernhardt et al., 2019] and preclinical evidence [Nudo and Milliken, 1996].

Minimally-supervised therapy, defined here as any form of therapy performed by a patient independently with minimal external intervention or supervision, is a promising approach to better harvest the potential of rehabilitation technologies such as robot-assisted therapy [Ranzani et al., 2020]. This could allow for the simultaneous training of multiple subjects in the clinics [Büsching et al., 2018], or for subjects to receive robot-assisted training in their home [Chi et al., 2020]. Several upper limb technology-supported therapies have been proposed for home use [Wittmann et al., 2016, Ates et al., 2017, Nijenhuis et al., 2017, Chen et al., 2019, Cramer et al., 2019, Laver et al., 2020], allowing subjects to benefit from additional rehabilitative services to increase dose [Laver et al., 2020, Skirven et al., 2020]. However, only few minimally-supervised robotic devices capable of actively supporting/resisting subjects during interactive therapy exercises have been proposed [Lemmens et al., 2014, Sivan et al., 2014, Wolf et al., 2015, Hyakutake et al., 2019, McCabe et al., 2019] and, as typically happening in conventional care [Qiuyang et al., 2019], most of them did not focus on the hand. Moreover, these devices only partially fulfilled the complex set of constraints imposed by a minimally-supervised use.

To be effective, motivating and feasible, minimally-supervised robot-assisted therapy platforms (i.e. a set of hardware and software technologies used to perform therapy exercises) should meet a wide range of usability, human factors and hardware requirements, which are difficult to respect simultaneously. Besides the necessity to provide motivating and physiologically relevant task-oriented exercises to maximize subject engagement [Veerbeek et al., 2014, Laut et al., 2015, French et al., 2016, Johnson et al., 2020] and to monitor subjects' ability

level to continuously adapt the therapy [Metzger et al., 2014a, Hocine et al., 2015, Wittmann et al., 2015, Aminov et al., 2018], ensuring ease of use is critical [Zajc and Russold, 2019]. When considering using a robot-assisted platform in a minimally-supervised way (clinical and home settings), specific hardware and software changes should be considered to allow a positive user experience and compliance with the therapy program/targets, as well as to assure safe interaction. In this sense, integrating usability evaluation during the development of rehabilitation technologies was shown to contribute to device design improvements, user satisfaction and device usability [Shah and Robinson, 2007, Power et al., 2018, Meyer et al., 2019]. Unfortunately, the usability of robotic devices for upper-limb rehabilitation is only rarely evaluated and documented in the target user population before clinical tests [Pei et al., 2017, Catalan et al., 2018, Guneysu Ozgur et al., 2018, Nam et al., 2019, Tsai et al., 2019].

In this chapter, we present the design of a platform for minimally-supervised robot-assisted therapy of hand function after stroke and the evaluation of its short-term usability in a single experimental session with 10 potential users in the chronic stage after stroke. The proposed platform builds on an existing high-fidelity 2-degrees-of-freedom end-effector haptic device (ReHapticKnob [Metzger et al., 2014b]), whose concept was inspired by the HapticKnob proposed by Lambercy et al. [Lambercy et al., 2007]. This device was successfully applied in a clinical trial on subjects with subacute stroke, showing equivalent therapy outcomes in a supervised clinical setting compared to dose-matched conventional therapy without any related adverse event [Ranzani et al., 2020]. This was a prerequisite for the exploration of strategies to better take advantage of the robot's unique features, such as potentially allowing the provision of minimally-supervised therapy. In order to make the device usable in a minimally-supervise setting, we developed an intuitive user interface (i.e., physical/hardware and graphical/software) that can be independently used by subjects in the chronic stage after stroke to perform therapy exercises with minimal supervision, either in clinical settings or at home. Additionally, two new task-oriented therapy exercises were developed to be used in a minimally-supervised scenario and complement existing exercises by simultaneously training hand grasping and forearm pronosupination, which are functionally relevant movements. The goal of this chapter is to present the hard and software modifications to the platform (i.e., robotic device with new physical and virtual user interface and therapy exercises) as well as the results of a preliminary usability evaluation with participants in the chronic stage after stroke using the device independently in a single session after a short explanation/familiarization period. This work is an important step to demonstrate that subjects with chronic stroke can independently and safely use a powered robotic device for upper-limb therapy upon first exposure, highlight key design aspects that should be taken into account for maximizing usability in real-world minimally-supervised scenarios, and thereby provide a methodological basis that could be generalized to other platforms and applications.

3.2 Platform development and pilot usability study

3.2.1 ReHapticKnob and user interface

The therapy platform (hardware and software) proposed in this work consists of an existing robotic device, the ReHapticKnob (RHK, [Metzger et al., 2011]) with a new user interface and two novel therapy exercises. The user interface is assumed to include physical components (i.e., hardware interfaces that get in contact with the user, such as the finger pads and buttons of the rehabilitation device, the ReHapticKnob) and a graphical component (i.e. software), i.e. the graphical user interface (GUI).

The RHK is a 2-degrees-of-freedom haptic device for assessment and therapy of hand function after stroke. It incorporates a set of automated assessments to determine the baseline difficulty of the therapy exercises [Metzger et al., 2014b], and allows to train hand opening-closing (i.e., grasping) and pronosupination of the forearm by rendering functionally-relevant rehabilitative tasks (e.g., interaction with virtual objects) with high haptic fidelity [Metzger et al., 2014a]. The user sits in front of the robot positioning his/her hand inside two instrumented finger pads, which slide symmetrically on a handlebar, as shown in Figure 3.1. Contact between the user's fingers and the finger pads is assured through VELCRO straps. The simple end-effector design of the robot (compared to the typically more complex donning and doffing of exoskeletons where joint alignment is critical) makes it an ideal candidate for independent use. To achieve and maintain appropriate limb positioning, patients are first instructed by the therapist on how to place their arm on the forearm support. In our previous clinical trials [Metzger et al., 2014b, Ranzani et al., 2020], we found this to be sufficient to avoid misalignments and compensatory movements when using the robot.

Considering the feedback collected from subjects and therapists within a previous clinical study under therapist supervision [Ranzani et al., 2020], we embedded the RHK into a novel therapy platform that is more user-friendly and suitable for minimally-supervised use. For this purpose, a novel GUI now directly controls the execution of the therapy program and includes two sections, one for the user and one for the therapist to customize the therapy, for example, before the first therapy session (Figure 3.1A). To configure the therapy for a subject, the therapist can log into a password protected "Therapist Section", create/update a subject profile (i.e., selected demographic data, impaired side, identification code and password consisting of a sequence of 4 colors to access the therapy plan) and select the relevant exercise parameters (i.e., derived from preliminary automated assessments) that are needed to adapt the therapy exercises to the subject ability level [Metzger et al., 2014b]. To perform a therapy session, the subject can autonomously navigate into the "Patient Section" using an intuitive colored pushbutton keyboard (Figure 3.1A). The subject can log in into his/her therapy plan by selecting his/her identification code and typing the defined colored password on the pushbutton interface. In the personal therapy plan, a graphical list of all the available therapy exercises appears. The user can then manually navigate through the exercise list and select the preferred exercise.

To maximize the usability and, consequently, the likeliness of therapists and subjects using the device, attention was devoted to the optimization of esthetics and simplicity in all virtual displays and hardware components. The design was guided by a set of usability heuristics [Nielsen, 1995], which included visibility of feedbacks (e.g., show performance feedback and unique identifiers on each user interface window), matching between virtual and haptic displays of the platform and corresponding real world tasks, user control and freedom (e.g., exit or stop buttons always available), consistency and standardization of displays' appearance, visibility and intelligibility of instructions for use of the system, fast system response, pleasant and minimalistic design, as well as simple error detection/warnings. Particular caution was directed to the placement (e.g., easily visible/retrievable), size (e.g., large to be easily selectable), logical ordering, appearance and color coding (e.g., red for quitting/exiting) of the buttons both in the colored pushbutton keyboard and in the virtual displays [Norman, 2013, de Leon et al., 2020], trying to reduce them to a maximum of five, which was needed to execute all exercises. Finally, to guarantee platform modularity, a state machine performs the low-level control of the robot (i.e., position, velocity and force control implemented in LabVIEW 2016) while the graphical user interface (Unity 5.6) guides the high-level control of the therapy session and easily allows to insert/remove different exercise types.

3.2.2 Exercises for robot-assisted minimally-supervised therapy

The RHK includes a set of seven assessment-driven therapy exercises [Metzger et al., 2014b], which were developed following the neurocognitive therapy approach formulated by Perfetti (i.e., combining motor training with somatosensory and cognitive tasks) [Perfetti and Grimaldi, 1979]. So far, these exercises only focused on the training of isolated movements (i.e., grasping or pronosupination) and were administered under therapist supervision (see Metzger et al. [2014b], Ranzani et al. [2020] for more details on existing exercises).

To complement this available set of exercises, we implemented two new exercises optimized for use in a minimally-supervised scenario and focusing on tasks that should facilitate a transition to activities of daily living. For this purpose, the exercise tasks train synchronous movements and combine complex elaborations of sensory, cognitive and motor cues.

The tunnel exercise is a functional exercise focusing on synchronous coordination of grasping and pronosupination and on sensory perception of haptic cues. The user has to move two symmetric avatars (virtually representing the finger pads of the robot as two purple triangles, see Figure 3.1B) progressing in a virtual tunnel, while avoiding obstacles and trying to collect as many rewards/points (e.g., coins) as possible. The exercise includes sensory cues, namely hand vibrations indicating the correct position to avoid an obstacle, stiff virtual walls that constrain the movement of the avatars inside the virtual tunnel, and changes in viscosity (i.e., velocity-dependent resistance) within the tunnel environment on both degrees of freedom to challenge the stabilization of the hand movement during navigation. Increasing difficulty levels linearly increase the avatars speed within the tunnel (while consecutive obstacles remain

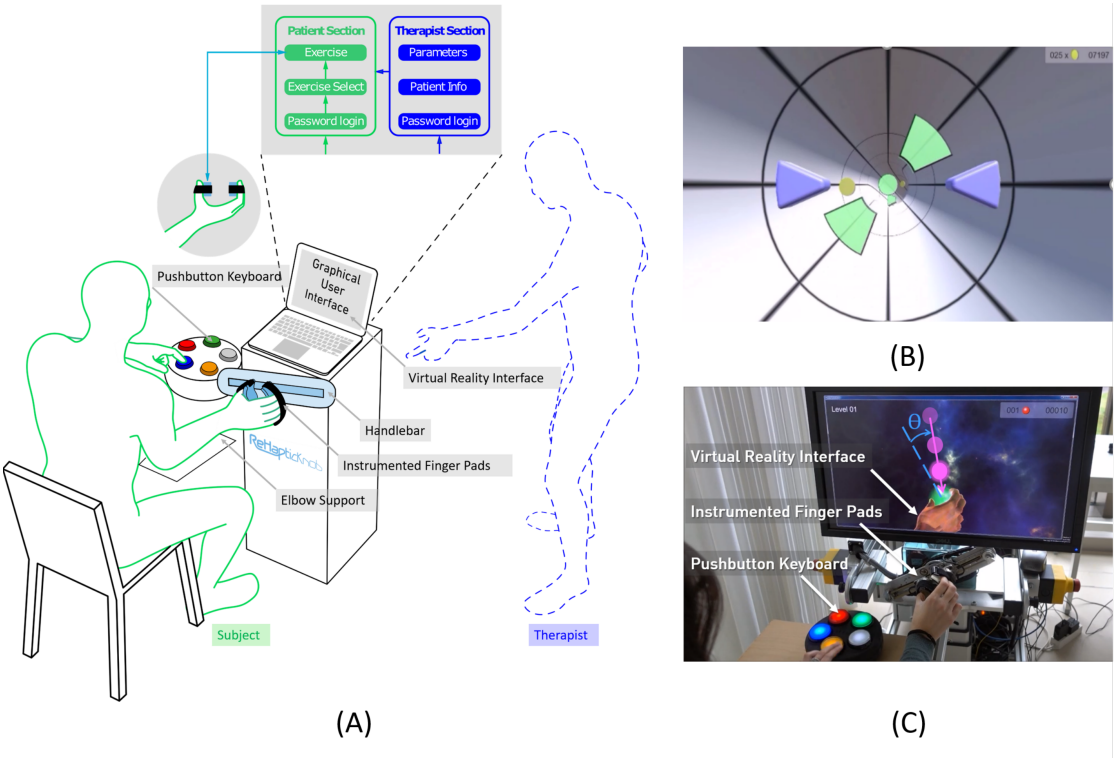


Figure 3.1: The ReHapticKnob therapy platform. (A) The platform consists of a haptic rehabilitation device - the ReHapticKnob - with physical (i.e., instrumented finger pads, colored pushbutton keyboard) and graphical user interfaces and a set of therapy exercises that can be used with minimal supervision. The graphical user interface includes a section for the therapist to initially customize the therapy plan and a patient section through which the user can autonomously perform predefined therapy exercises. (B) Virtual reality interface of the tunnel exercise. The subject has to drive a set of purple avatars by opening-closing and pronosupinating the finger pads. The goal is to avoid the green obstacles and collect as many coins as possible. (C) A subject performing the sphere exercise on the ReHapticKnob. During the testing phase shown, the subject has to catch a falling sphere halo by rotating the finger pads (pronosupination). The object is caught if the hand orientation (dotted line) is aligned with the falling direction (continuous line), within a certain angular range Θ. Once the object is caught, the subject selects the sphere stiffness he/she perceives while squeezing the object by pressing the corresponding color on the pushbutton keyboard.

at a constant distance with respect to one other), the maximum pronation and supination locations of the apertures between obstacles to promote an increase in the pronosupination range of motion (ROM) of the subject (based on an initial robotic assessment) and the changes in environment viscosity, while the space to pass through the obstacles and the haptic vibration intensity are linearly decreased. One exercise block consists of a one-minute long progression within the virtual tunnel, where up to 30 obstacles have to be avoided. One exercise session consists of a series of ten one-minute blocks.

The sphere exercise is a functional exercise focusing on hand coordination during grasping and pronosupination, with a strong focus on somatosensation and memory to identify the objects that are caught. One exercise block consists of a training phase and a testing phase. In the training phase, the user moves a virtual hand and squeezes a set of virtual spheres (i.e., three to five) to memorize the color attributed to each stiffness rendered by the robot (for more details refer to [Ranzani et al., 2019]). The user can manually switch the sphere to try/squeeze by pressing a predefined button on the colored pushbutton keyboard. In the testing phase, semi-transparent spheres (halos) fall radially from a random initial position, one at a time, towards the hand. By actively rotating the robot and adjusting the hand opening, the user has to catch the falling halo. A halo is only caught if the hand aperture matches the sphere diameter within an error band of ±10 mm, and the hand pronosupination angle is aligned with the falling direction within an error band θ (see Figure 3.1C) between ±40° and ±15° depending on the difficulty level. When a halo is caught, the participant has to squeeze it, identify its stiffness, and indicate it using the colored pushbutton keyboard. Each testing phase lasts 3 min. At increasing difficulty levels, the number of spheres and the speed of the falling halos increase, the tolerance in hand positioning to grasp the falling halos are reduced in the pronosupination degree of freedom, and the relative change in object stiffness decreases as a function of the subject's stiffness discrimination ability level (based on initial robotic psychophysical assessments). One exercise session consists of three blocks (i.e., three training phases, each followed by a testing phase) and lasts between 10 and 15 minutes.

In both exercises, an assessment-driven tailoring regulates the level of difficulty throughout the sessions (similar to the approach described in detail in [Metzger et al., 2014b]). In short, the initial difficulty level at the beginning of the first therapy session is adapted to the subject's ability based on two robotic assessments, which determine the subject's active range of motion (aROM) in grasping and pronosupination and the ability to discriminate stiffnesses on the grasping degree of freedom (expressed as "Weber fraction"). In the tunnel game, "aROM" scales the positioning and size of the virtual walls that determine the size of the tunnel, while in the sphere exercise, it scales the workspace within which the halos are falling. Additionally, the "Weber fraction" scales the initial stiffness difference between spheres in the sphere exercise. At the end of an exercise block, the achieved performance (i.e., percentage of obstacles avoided over total obstacles for the tunnel exercise, and the percentage of halos correctly caught and identified over total number of halos for the sphere exercise) is summarized to the subject through a score displayed before the next block begins. The performance in the previous block can be used to further adapt the exercise difficulty over blocks similarly to other exercises

presented in [Metzger et al., 2014b]. This allows to maintain a performance of around 70%, which maximizes engagement and avoids the frustration that could arise when performance is too low or too high [Adamovich et al., 2009, Cameirão et al., 2010, Choi et al., 2011, Lambercy et al., 2011, Metzger et al., 2014b, Wittmann et al., 2016]. However, since the work presented in this paper tested only a single session, providing only little data for evaluating performance-based difficulty adaptation, these aspects will not be discussed in the present chapter.

3.2.3 Study design and participants

A pilot study to evaluate the usability of the proposed minimally-supervised therapy platform was conducted on ten subjects with chronic stroke (>6 months), representative of potential future users of the platform. Subjects were enrolled if they were above 18 years old, able to lift the arm against gravity, had residual ability to flex and extend the fingers, and were capable of giving informed consent and understanding two-stage commands. Subjects with clinically significant non-related pathologies (i.e., severe aphasia, severe cognitive deficits, severe pain), contraindications on ethical grounds, known or suspected non-compliance (e.g., drug or alcohol abuse) were excluded from the study. The pilot study was conducted at ETH Zurich, Switzerland, over a period of two weeks. Participants took part in a single test session, as illustrated in Figure 3.2. The session consisted of a supervised and a minimally-supervised part. In the supervised part, a supervising professional therapist assessed the subject's baseline ability level through a set of standard clinical and robotic assessments, which were used to customize the difficulty levels of the therapy exercises. The therapist then instructed the subject on how to perform the exercises, and actively guided the subject in the execution of one block of each exercise. In this part of the experiment, subjects were encouraged to ask any questions they had related to the use of the device. In the subsequent minimally-supervised part, the subject had to independently use the therapy platform to perform the tunnel exercise (10 blocks) and the sphere exercise (3 blocks). During that time, the therapist sat at the back of the room and silently observed the subject's actions, recording any error or action that the subject could not perform in a checklist, and intervening only in case of risk or explicit request from the subject. The subject had to independently place his/her hand inside the finger pads, log into the therapy plan (i.e., find his/her identification code through other subject identification codes and insert the personal colored password to log in), find and start the appropriate therapy exercises from a list of all available RHK exercises, test both exercises and log out from the therapy plan. At the end of the experimental phase, subjects answered a set of usability questionnaires.

The usability evaluation was performed on the new, more complex exercises training coordinated movements as well as sensory, cognitive and motor functions for multiple reasons. These exercises present cognitive challenges (e.g., understanding the exercise structure, robot commands/instructions and feedback), which directly influence the usability of the device and thus allow to test usability under the most demanding conditions. To avoid bias in the usability evaluation with a population in the chronic stage after stroke, which already achieved

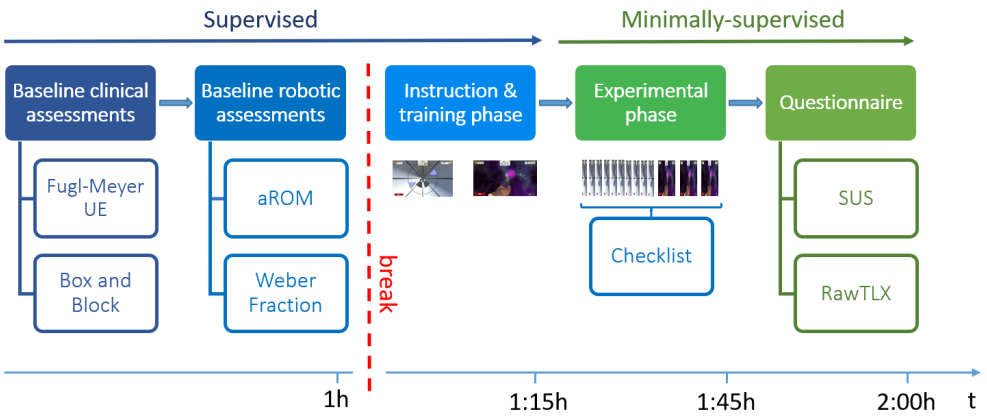


Figure 3.2: Study protocol. Abbreviations: UE – Upper Extremity. aROM – Active Range of Motion. SUS – System Usability Scale. RawTLX – Raw Task Load Index.

a good amount of recovery, we avoided simpler exercises (e.g., purely sensory, or purely motor) which are (in most cases) better suited for earlier stages of rehabilitation that would happen in a more closely supervised context. Our exercises are instead best suited for patients with mild to moderate impairments, the population that, based on our previous clinical studies [Ranzani et al., 2020], seems most suitable to train in a minimally-supervised scenario with the robot. Moreover, compared to simpler exercises, these should allow more subject engagement during minimally-supervised therapy, where there is no additional encouragement from a supervising therapist.

The study was approved by the Cantonal Ethics Committee in Zurich, Switzerland (Req-2017-00642).

3.2.4 Baseline assessments

Subjects' upper limb impairment was measured at baseline with the Fugl-Meyer Assessment of the Upper Extremity (FMA-UE) [Fugl-Meyer et al., 1975] and its wrist and hand subscore (FMA-WH). Gross manual dexterity was assessed using the Box and Block test (BBT) [Mathiowetz et al., 1985]. In addition to clinical assessments, robotic assessments (i.e., "aROM" and stiffness discrimination ability expressed as "Weber fraction") were performed and used to adapt the initial difficulty level of the therapy exercises to the subject's ability from the first block of the exercise. "aROM" assesses the subject's ability to actively open and close the hand and pronosupinate the forearm. In the tunnel game this scales the positioning and size of the virtual walls that determine the size of the tunnel, while in the sphere exercise, this scales the workspace of the falling halos. "Weber fraction" describes the smallest distinguishable difference between two object stiffnesses and scales the initial stiffness difference between spheres in the sphere exercise. For more details on the robotic assessments, please refer to [Metzger et al., 2014b].

3.2.5 Outcome measures and statistics

To evaluate the ability of chronic stroke subjects to independently use the therapy platform and identify remaining usability challenges, the main outcome measures were the percentage of items that could not be performed without external intervention and the results of two questionnaires evaluating the usability and perceived workload of the user interface and exercises. A performance checklist was used to record the tasks/actions that the subject could, or could not perform without supervision or in which therapist help was required, followed by two standardized usability questionnaires. To evaluate each component of the therapy platform separately, the performance checklist and the two questionnaires were repeated for the user interfaces (i.e., GUI and hardware interfaces such as the finger pads and pushbutton keyboard) and for the two exercises. The performance checklist includes 26 items are described in Figure 3.3 (i.e., seven about the use of the user interface, six related to the tunnel exercise, and thirteen related to the sphere exercise). The results of the checklist per subject are calculated as percentage of items that required intervention with respect to total performed items.

The standardized usability questionnaires were:

- System Usability Scale (SUS) [Brooke, 1996], a ten-item questionnaire which assesses the overall usability (i.e., effectiveness, efficiency, satisfaction) of the system under investigation (i.e., user interface and each of the two exercises separately). Two items of the SUS refer specifically to the "learnability" of a system (i.e., "I think that I would need the support of a technical person to be able to use this system", "I needed to learn a lot of things before I could get going with this system") and were considered of high importance for the evaluation of the minimally-supervised usage scenario [Lewis and Sauro, 2009]. Ideally, the total SUS score calculated from its ten items should be greater than 50 out of 100, indicating an overall usability between "OK" and "best imaginable" [Bangor et al., 2009]. To evaluate if there was any correlation between SUS scores and baseline characteristics of the subjects, we calculated the Pearson's correlation coefficients between the SUS scores (of user interface, tunnel exercise, and sphere exercise) of all the subjects and their age, FMA-UE, FMA-WH, and BBT score, resulting in a total of 12 comparisons. For these analyses, the statistical significance threshold (initially $\alpha = 0.05$) was adjusted using Bonferroni correction for multiple comparisons, leading to a corrected $\alpha = 0.05/12 = 0.0042$.

- Raw Task Load Index (RawTLX) [Hart, 2006], a six-item questionnaire which assesses the workload while using the system under investigation. The RawTLX is the widely used, shortened form of the original NASA TLX, with the difference of the six workload domains being evaluated individually without the calculation of a total workload score through domain-weighting. The workload domains assessed are: (i) mental demand (i.e., amount of mental or perceptual activity required), (ii) physical demand (e.g., amount of physical workload required), (iii) temporal demand (i.e., amount of time pressure

perceived during the use), (iv) overall performance (i.e., perceived level of unsuccessful performance), (v) effort (i.e., total amount of effort perceived to execute the task), and (vi) frustration level (i.e., amount of stress/irritation/discouragement perceived). The target workload levels differ depending on the application, thus they were defined by the investigator and therapist. For the user interface, a targeted minimal workload (i.e. ≤ 25%) was set as goal in all domains except for temporal demand, in which an intermediate workload level (i.e., between 25% and 75% included) was tolerated. The exercises should be challenging but not too difficult [Adamovich et al., 2009, Choi et al., 2011], allowing the subjects to maintain actual and perceived performance around 70%. For this reason, a target workload between 50 and 75% (included) was desired for mental, physical, temporal and effort domains, and a corresponding workload between 25% and 50% was desired in the performance domain, in which the workload axis is inversely proportional to the perceived performance. Finally, frustration should be avoided, so a workload ≤ 25% is required.

The SUS and RawTLX questionnaires were translated to German by a native speaker and rated on a 5-intervals Likert scale, which was associated with corresponding scores of 0, 25, 50, 75, and 100%.

To monitor the safety of the platform during the minimally-supervised part of the experiment, adverse events and situations that could put at risk the safety of the user (e.g., triggering of safety routines of the robot for excessive forces/movements or hardware/software errors) were recorded.

The baseline assessments, answers from SUS and TLX questionnaires and population results of the checklist are analyzed via descriptive statistics and reported as median with first and third inclusive quartiles (i.e., median (Q1-Q3)) to represent the central tendency and spread-/dispersion in subjects' characteristics/responses, respectively. These statistics were selected because of the relatively small sample size, which does not safely allow to assume normal distribution of the data, and the ordinal nature of the SUS and TLX results based on 5-intervals Likert scales [Sullivan and Artino Jr, 2013].

3.3 Usability results of the pilot study

3.3.1 Experiment characteristics

Ten subjects (4 female, 6 male) in the chronic stage after an ischemic stroke (39.5(27.0-60.5) months post event) were eligible and agreed to participate in the study. The participant age was 60.5(56.3-67.5) and there were 4 right and 6 left hemisphere lesions, while all subjects were right-handed. Most subjects showed mild to moderate [Woytowicz et al., 2017] initial upper-limb impairment with a FMA-UE of 41.5(39.3-50.0) out of 66 points, and a FMA-WH of 17.0(14.0-19.5) out of 24 points. In the BBT, subjects transported 39.5(30.0-48.8) blocks

in one minute using their impaired limb. Before enrollment, all participants were informed about the study and gave written consent. The experiment lasted 111.5(104.0-135.0) minutes, which included 79.1(67.0-86.0) minutes of robot use and 34.8(24.0-48.0) minutes for baseline clinical assessments, break time and questionnaires. Within the robot use, the subjects spent 16.0(14.0-20.0) minutes on baseline robotic assessments and 59.9(53.0-67.0) minutes to learn how to use the user interface and exercises (i.e., instruction and training phase, 27.6(22.0-38.0) minutes) and test them with minimal supervision (i.e., experimental phase, 30.6(28.0-32.0) minutes). During the experimental phase, the therapist's physical intervention (e.g., to assist hand movements or position the hand) or suggestions and further explanations (e.g., to repeat the login password or refresh the exercise rules) were required 3.5(2.0-5.0) times per subject out of the 26 checklist items (see Figure 3.3), with highest number of interventions required by the oldest subject (subject 3, 87 years old, 7 interventions). Over the duration of the study, no serious adverse event related to the robot-assisted intervention or event that would put at risk the safety of the user were observed, but the software had to be restarted two times due to the triggering of safety routines (e.g., too high forces, positions, velocities generated by the user). Two subjects reported a mild temporary increase in hand muscle tone (e.g., finger flexors and/or extensors) during the therapy exercises.

3.3.2 User interface

The user interface was ranked with a SUS score between good and excellent (85.0(75.6-86.9) out of 100) as shown in Table 3.1 and Figure 3.4A, and a learnability score of 15.0(13.1-16.9) out of 20. Nine subjects gave excellent rating and reported that they would use the RHK frequently. Most of the subjects reported that the user interface is intuitive and that the colored button interfaces are easy to use. The oldest subject (age 87) gave a score in the region of "worst imaginable" for the user interface (as well as for the sphere and tunnel exercises). The SUS results showed an inverse relationship with the age of the subjects, but no significant correlation following Bonferroni correction (correlation -0.737, p-value 0.015), and no linear relationship with their ability level as measured with the FMA-UE (0.170, 0.639), FMA-WH (-0.044, 0.904), and BBT (0.207, 0.566) scales.

The Raw TLX results are shown in Table 3.1 and in Figure 3.4B. The median perceived workload levels lie within the target workload bands in all the workload categories. However, the third quartile is outside of the target band (higher) for at least one datapoint (25%) in mental demand, physical demand and effort.

The subjects required external supervision or assistance for 14.3(0.0-14.3)% of the checklist items related to the user interface (Figure 3.3). Five subjects needed help to insert or reinsert the hand into the finger pads, as the thumb can easily slip out while moving the finger pads, particularly during the execution of active tasks within the exercises. Two subjects could not remember the colored password.

Figure 3.3: Checklist results represented as heatmap. The results averaged over subjects and items are presented on the right and on the bottom of the heat map, respectively. (Green: no problem/issue in item completion without external intervention; Red: Failure and/or external intervention required to solve the item; Av: average; U: user interface; TU: tunnel exercise, SP: sphere exercise).

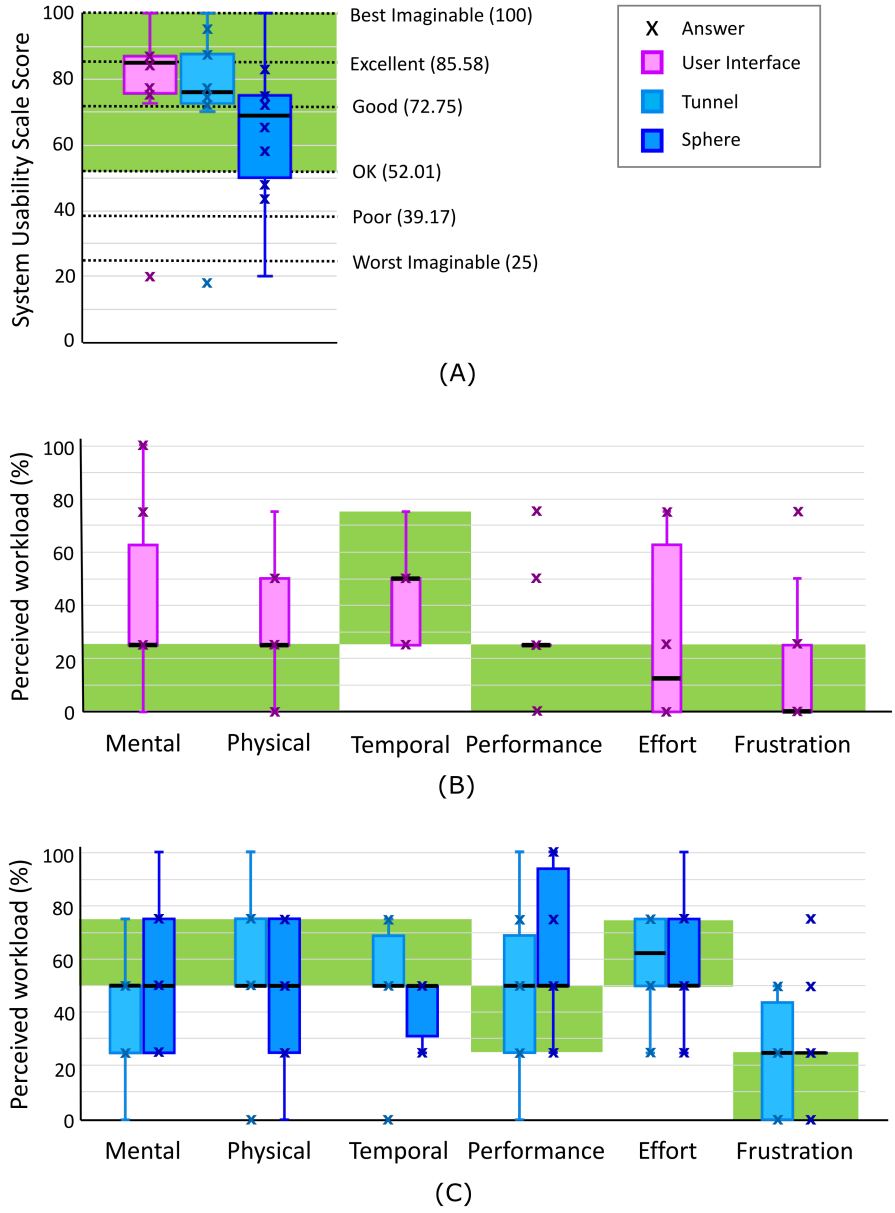


Figure 3.4: (A) System Usability Scale box-plot results for user interface (i.e., GUI, finger pads and pushbutton keyboard), tunnel exercise and sphere exercise. (B) Raw TLX box-plot results showing perceived workload levels for user interface and (C) for tunnel and sphere exercise. black line: median; green area: target usability/workload level.

Table 3.1: System Usability Scale and Raw Task Load Index results for user interface, tunnel exercise, and sphere exercise.

Questionnaire (max)	**User interface** [median (Q1–Q3)]	**Tunnel exercise** [median (Q1–Q3)]	**Sphere exercise** [median (Q1–Q3)]
System Usability Scale (SUS)			
Total (100)[1]	85.0 (75.6–86.9)	76.3 (72.5–87.5)	68.8 (50.0–75.0)
Learnability (20)[2]	15.0 (13.1–16.9)	15.0 (10.0–19.4)	10.0 (10.0–14.4)
Raw Task Load Index (Raw TLX)			
Mental (%) *How mentally demanding was the task?*	25.0 (25.0–62.5)	50.0 (25.0–50.0)	50.0 (25.0–75.0)
Physical (%) *How physically demanding was the task?*	25.0 (25.0–50.0)	50.0 (50.0–75.0)	50.0 (25.0–75.0)
Temporal (%) *How hurried/rushed was the pace of the task?*	50.0 (25.0–50.0)	50.0 (50.0–68.8)	50.0 (31.3–50.0)
Performance (%) *How successful where you in accomplishing what you were asked to do?*[3]	25.0 (25.0–25.0)	50.0 (25.0–68.8)	50.0 (50.0–93.8)
Effort (%) *How hard did you have to work to accomplish your level of performance?*	12.5 (0.0–62.5)	62.5 (50.0–75.0)	50.0 (50.0–75.0)
Frustration (%) *How insecure, discouraged, irritated, stressed and annoyed were you?*	0.0 (0.0–25.0)	25.0 (0.0–43.8)	25.0 (25.0–25.0)

[1] Based on ten items: (1) I think that I would like to use this system frequently, (2) I found the system unnecessarily complex, (3) I thought the system was easy to use, (4) I think I would need the support of a technical person to be able to use this system, (5) I found the various functions in this system were well integrated, (6) I thought there was too much inconsistency in this system, (7) I would imagine that most people would learn to use this system very quickly, (8) I found the system very cumbersome to use, (9) I felt very confident using the system, and (10) I needed to learn a lot of things before I could get going with this system.

[2] Based on items (4) and (10) from [1].

[3] In this question low workload corresponds to "Perfect" and high workload to "Failure".

3.3.3 Tunnel exercise

The usability of the tunnel exercise was ranked between good and excellent (76.3(72.5-87.5) out of 100) on the SUS (Table 3.1, Figure 3.4A). Three subjects reported that the exercise is entertaining and motivating. As for the user interface, the SUS scores showed an inverse relationship with the age of the subjects, although without significant correlation after Bonferroni correction (correlation -0.681, p-value 0.030), and no linear relationship with FMA-UE (0.342, 0.333), FMA-WH (0.019, 0.958), and BBT (0.335, 0.344) scores.

The Raw TLX results are shown in Table 3.1 and 3.4C. The median perceived workload levels lie within the target workload bands in all the workload categories. However, the first quartile is lower than the target workload band for at least one datapoint (25%) in mental demand.

The subjects required external supervision or assistance in only 0.0(0.0-16.7)% of the checklist items related to the tunnel exercise (Figure 3.3). Six out of ten subjects could perform the entire exercise independently without any therapist intervention. One subject could not independently perform the calibration at the beginning of the exercise as she did not understand the instructions provided by the robot (i.e., the robot was asking to open the hand to a comfortable position and the subject tried to open the hand as much as possible). Two subjects could not independently perform either the calibration or the hand opening/closing tasks of the exercise, as they could not actively open the hand beyond of the minimum position of the robot (i.e., approximately 4 cm between thumb and index finger tip) due to their motor impairment level (i.e., FMA-UE below 38 out of 66 points, FMA-WH below 15 out of 24 points). One subject only completed 8 out of 10 blocks, as the robot went into a safety stop (i.e., too high forces, position or velocity). Two subjects required further explanations of the scope and rules of the exercise (e.g., tried to hit the obstacles instead of avoiding them). As additional comments,

one subject reported that the tunnel speed was too fast for her, and another subject reported that the depth perception of the virtual reality should be improved. The median performance (i.e., number of obstacles avoided versus total number of obstacles) of the subjects within the ten blocks was 71.7(59.1-79.9)%, which is very close to the desired 70% performance.

3.3.4 Sphere exercise

The usability of the sphere exercise was ranked between OK and good (68.8(50.0-75.0) out of 100) at the SUS (Table 3.1, Figure 3.4A). Two subjects reported that the game was too challenging and more boring compared to the tunnel exercise and would recommend this game for a mildly impaired population. As for the user interface and tunnel exercise, the SUS scores showed an inverse relationship with the age of the subjects without a significant correlation after Bonferroni correction (correlation -0.739, p-value 0.015), and no linear relationship with FMA-UE (0.092, 0.800), FMA-WH (0.014, 0.970), and BBT (0.081, 0.825).

The Raw TLX results are shown in dark blue in Table 3.1 and Figure 3.4C. The median perceived workload levels lie within the target workload band for mental demand (50.0(25.0-75.0)%), physical demand (50.0(25.0-75.0)%), temporal demand (50.0(31.3-50.0)%), performance (50.0(50.0-93.8)%), effort (50.0(50.0-75.0)%) and frustration (25.0(25.0-25.0)%). However, the first quartile is lower than the target workload band for at least one datapoint (25%) in mental and physical demand, and the third quartile is higher than the target workload band in performance.

The subjects required external supervision or assistance in 11.5(7.7-15.4)% of the checklist items related to the sphere exercise (Figure 3.3). Only one subject could perform the entire exercise without any therapist intervention. During the training phase, the subjects pressed a "next" button to go to the next sphere presented in the exercise. However, two subjects found this button confusing because the color of the button represented both the action of moving on to the next sphere to explore and one of the spheres that could be selected as answer. This issue could not be avoided with the current button interface with only five buttons for five possible objects/spheres to select from. The subjects suggested to avoid this issue by always having a unique mapping between button color and function/object, both in the training and in the test phase of the exercises. One subject did not understand how to repeat the training phase. During the testing phase, only four subjects learned how to catch and identify the falling halos, due to difficulties in understanding the catching strategy (six out of ten subjects), controlling and maintaining the grip aperture during catching or squeezing (three out of ten), perceiving the stiffness differences (five out of ten). The median performance (i.e., number of halos caught and identified versus total number of halos) of the subjects within the three blocks was 27.0(16.4-31.5)%.

3.3.5 Additional spontaneous feedback

During the trial, the subjects reported additional spontaneous feedback. Three subjects recommended to modify the elbow support of the RHK. They asked to simplify the adjustment of the elbow support height with respect to the finger pads, which is currently done manually with two levers, and to constrain the forearm to the elbow support with straps to avoid large elbow movements during active pronosupination tasks (e.g., in the tunnel exercise). Two subjects reported mild/moderate pain in the fingers due to the finger straps, which were tightened to avoid finger slippage out of the thin handle surface. It was also reported that such finger pads might not allow a subject with high motor impairment to accurately control and perceive finger forces, as the contact between fingers and finger pads occurred only at the fingertips. Finally, the supervising therapist reported that to increase the safety of the device, all the mechanical parts of the robot (e.g., mechanical transmissions) that could get in contact with the user should be covered to avoid snag hazards (e.g., of the fingers).

3.4 Discussion

This chapter presented the design and rigorous preliminary usability evaluation of a therapy platform (i.e., end-effector haptic device with new physical and graphical user interfaces and two novel therapy exercises) that aims to enable minimally-supervised robot-assisted therapy of hand function after stroke. This approach promises to be a suitable solution to increase the therapy dose offered to subjects after stroke either in the clinic (e.g., by allowing the training of multiple subjects in parallel, or additional training during the subject's spare time in an unsupervised robotic gym), or at home after discharge, with the potential to maximize and maintain long-term therapy outcomes. A careful and quantitative pilot usability evaluation allows to preliminarily assess if the platform could be applicable in minimally-supervised conditions and which modifications are necessary to increase the feasibility of this therapy approach in a real-world minimally supervised scenario (e.g., in the clinic).

3.4.1 Minimally-supervised therapy is possible upon short-term exposure

Through the development of a modular graphical user interface and novel therapy exercises, we proposed a subject-tailored functional therapy platform that could be used upon first exposure by subjects after stroke in a single session with minimal therapist supervision. The platform was developed to meet a tradeoff between different requirements, namely to provide active task-oriented exercises similar to conventional exercises [Ranzani et al., 2020], while guaranteeing ease of use and subject compliance to the therapy program (motivation) while requiring minimal supervision both from a clinical (therapist) and technical (operator of the device) point of view [Zajc and Russold, 2019]. Particular attention was dedicated to the optimization of the virtual reality interfaces, both in the graphical user interface and in the exercises to be easily usable/learnable, efficient (in terms of workload) and motivating, since it was shown that enriched virtual reality feedback might facilitate an increase in therapy dose

and consequent improvements in arm function [Laut et al., 2015, Laver et al., 2015, Johnson et al., 2020].

In clinical settings, minimally-supervised therapy has rarely been investigated and documented [Büsching et al., 2018, McCabe et al., 2019]. Starting from Cordo et al. 2009, few robotic devices have been proposed for minimally-supervised upper limb therapy at home [Cordo et al., 2009, Zhang et al., 2011, Lemmens et al., 2014, Sivan et al., 2014, Wolf et al., 2015, Hyakutake et al., 2019, McCabe et al., 2019]. Only one device includes a virtual reality interface to increase subject motivation, and most of these devices only provide basic adaptive algorithms to customize the therapy plan to the subject needs. The device settings (e.g., lengths, sizes, finger pads) and exercise parameters are mostly manually tuned by the therapist at the beginning of the therapy protocol, while the subject performance is either ignored, telemonitored, or minimally-supervised by the therapist. Typically, these devices were evaluated in research settings in terms of clinical efficacy, but they lacked usability evaluations, which would have been more informative and better correlated with their real-world adoption in a minimally-supervised scenario [Turchetti et al., 2014], as well as with their safety and feasibility. To obtain meaningful usability results that can be transferred to real-world use, therapy goals and use environment should be precisely defined.

3.4.2 The platform was attributed high usability, with suggestions for minor improvements

We achieved very positive usability results with our therapy platform, with system usability scores between good and excellent (i.e., between 70 and 90 out of 100) for the user interface and tunnel exercise, between OK and good (i.e., between 50 and 80 out of 100) for the sphere exercise, as well as TLX scores within the target workload boundaries. This study revealed that, even with only few minutes of instruction, it is easy to learn how to use the platform, use the colored pushbutton keyboard, navigate through the graphical user interface, insert the hand into the device finger pads and perform the exercises (i.e. particularly the tunnel exercise). Overall, the time needed to learn how to use the platform (instruction and training phase) and perform the experiment with minimal supervision (experimental phase) seems adequate for a first use of the platform (i.e., less than 60 min). The time required for testing under minimal supervision corresponded to our expectation (i.e., approximately ten minutes for the test phase of each exercise, and ten additional minutes for training phases and setting up). The instructions and learning phases were relatively short for a first exposure (i.e., approx. 30 minutes). These results indirectly support the feasibility of the minimally-supervised use of the platform and seem to indicate that future users could be introduced to the platform within a single to two therapy sessions. The usability results showed an inverse trend with age but not with the impairment level of the subjects (either global, distal, or related to manual dexterity), reaching worst results for the oldest subject (age 87). However, this result is not significant, particularly with our small user sample size.

Usability evaluations of rehabilitation robots reported in literature yielded scores between 36 and 90 out of 100 using different usability questionnaires, including the SUS [Pei et al., 2017], "Cognitive Walkthrough" and "Think Aloud" methods [Valdés et al., 2014], custom-made questionnaires or checklists [Chen et al., 2015, Smith et al., 2015], which can be based on the Technology Acceptance Model [Davis, 1985]. Only Sivan et al. 2014 proposed a basic evaluation of the usability of a minimally-supervised robotic platform considering the time needed to learn how to use the device independently and the total time of use of the device, and based on the experiments and user feedback identified design aspects that could be improved [Sivan et al., 2014]. Human-centered designs based on usability evaluations have become best-practice in the medical field in recent years [Wiklund and Wilcox, 2005, Oviatt, 2006, Shah and Robinson, 2006, Blanco et al., 2016, for Standardization, 2019], but the elicitation of standardized usability requirements and evaluations is still particularly challenging due to the heterogeneity of user groups, needs and environments (e.g., clinic or home) [Shah and Robinson, 2006], and the small sample sizes typically considered in this type of studies [van Ommeren et al., 2018]. Therefore, it is generally difficult to compare the usability evaluations among different platforms.

The usability evaluation proposed in this work allows to quantify different aspects of usability, such as platform usability and learnability, perceived workload for the user, and ability to independently perform the tasks required during a minimally-supervised use of the platform. Our usability evaluation methods and results are not limited to the specific therapy platform proposed in this work, but can be generalized to most robotic therapy platforms. The early identification of usability aspects with a small sample population during the development of the platform allows to improve design points that could bias the clinical applicability and testing of the platform with patients, and ultimately help reducing pilot testing duration and associated costs. These points might otherwise only be noticed in longer and resource-demanding clinical studies and would then require corrections and additional retesting. For instance, through our detailed usability analysis, we highlighted key aspects regarding the physical and graphical user interfaces (e.g., handle size and shape, as well as button shape and color coding), and the exercise architecture (e.g., catching/grasping strategies closer to activities of daily living). These aspects would not affect the feasibility of using the platform in clinical settings but would certainly impact the adoption of this device, as well as other similar upper-limb robotic devices, in minimally-supervised settings. Finally, the GUI and pushbutton interface proposed in this work achieved very good usability at first exposure, suggesting that they are a valid approach to achieve minimally-supervised therapy with most (mono-lateral) upper-limb robotic devices and therapy exercises.

3.4.3 Therapy Exercises are functional, motivating and respect target workload levels

The mental, physical and effort workloads in the exercises were rather high while frustration and performance workloads were rather low. The overall usability was high for both exercises.

This is a promising result, underlining that the two new functional/synchronous exercises are engaging without being overly frustrating. Improvements would be needed to slightly increase the mental/cognitive workload required in the tunnel exercise and the physical workload in the sphere exercise. In the latter, however, the task complexity should be slightly reduced, since the performance achieved in the exercise is still too low with respect to the target performance level (i.e., 70%) and requires a too high performance workload. Detailed descriptions of minimally-supervised task-oriented exercises (e.g., requiring the functional training of multiple degrees of freedom) are rarely presented in literature [Lemmens et al., 2014, Sivan et al., 2014, Wolf et al., 2015]. These exercises are often lacking engaging interfaces to enhance subject motivation [Zhang et al., 2011, McCabe et al., 2019] and are typically focused on pure motor training tasks, neglecting sensory and cognitive abilities. Based on the level of task complexity and on the usability results, our therapy exercises could be recommended for late stages of rehabilitation in a mildly/moderately impaired population. They could well complement the previously available exercises implemented on the rehabilitation robot that train either grasping or forearm pronosupination during passive proprioceptive tasks or active manipulation tasks [Metzger et al., 2014a].

3.4.4 The platform is safe and could be exploited for a continuum of robot-assisted care

After a guided instruction phase, our test tried to emulate a minimally-supervised environment in which the therapist intervened only in case help was required by the subject, as done in other studies performed in real-life minimally-supervised conditions [Lemmens et al., 2014, Sivan et al., 2014, Hyakutake et al., 2019]. Throughout the test, the therapist intervention was needed on average less than 4 times per subject out of the 26 checklist items, mostly due to misunderstanding of the instructions or small software inconsistencies (e.g., unclear feedbacks, unclear color-function relations) without critical safety-related problems that would affect the applicability of the system with minimal supervision. These errors are expected to not occur anymore if the subjects were given a longer time for instructions and training. A continuum of use (over a larger time span) of our platform from supervised to minimally-supervised conditions would allow the user to familiarize with the system during the supervised sessions in the clinic and further continue the therapy seamlessly once the therapist is confident that the subject can safely train independently. Intervention minimization is useful to use the platform in the clinic, where a single therapist could supervise multiple subjects, and is essential in home environments, where external supervision is not always available or would require additional external communication channels (e.g., telerehabilitation [Wolf et al., 2015]). Safety and customization could be further increased through additional integrated robotic assessments. For example, two subjects reported a mild temporary increase in muscle tone, which can be physiologically induced by the active nature of the robotic assessments and exercises [Veerbeek et al., 2017]. An increase in hand muscle tone may cause pain and negatively affect recovery, but could be monitored online throughout the therapy using robotic assessments incorporated into the therapy exercises [Ranzani et al., 2019].

3.4.5 Limitations

The results of this pilot study should be interpreted with respect to the relatively small sample size tested, which is, however, considered sufficient to identify the majority of the usability challenges [Virzi, 1992]. The results reflect the usability of the platform for a mildly/moderately-impaired population in the chronic stage after stroke, which arguably is the target population for such a minimally-supervised therapy platform, but could also be validated in different stages after stroke (e.g., subacute). The reported usability results are applicable to a population that does not suffer from color blindness, since most of the user interfaces rely on color perception. Numbers or symbols could be added for people with color blindness. The experiment lasted only one session, so it was not possible to evaluate how the subjects could learn to use the system in a longer term and in real-world minimally-supervised conditions, e.g. to assess if their motivation level would eventually drop after few sessions. For the same reason, the performance-based difficulty adaptation algorithms will be further investigated in the context of multi-session experiments. Moreover, the scales proposed to evaluate the usability and workloads required by our platform can only partly capture the overall user experience, which should also account for user emotions, preferences, beliefs, physical and psychological responses before and after a longer use of the platform [Petrie and Bevan, 2009, for Standardization, 2019, Meyer et al., 2019]. Additionally, within this pilot study, it was not possible to implement the necessary usability adjustments that were identified and re-test the usability of the platform after modifications, but this should be assessed in the future. Finally, the presence of the technology developers during parts of the study (e.g., instruction and training phase) might have indirectly biased the usability evaluation performed by the subjects.

3.4.6 Future directions

Future research should investigate how to equip rehabilitation robots with further intelligence to automatically propose therapy plans and settings based on objective measures, and provide comprehensive digital reports to remote therapists to monitor and document subjects' progress. To be usable in a real-world minimally supervised scenario, the therapy platform would require minor adjustments identified throughout this study. Regarding the hardware, the finger pads should be wider to avoid finger slippage, and the pushbutton keyboard should include more buttons to allow consistent color-function and color-object mapping in GUI and exercises (e.g., insert one or two buttons uniquely for exercise control or quitting, to avoid color overlapping in difficulty levels requiring five objects/colors, such as in the sphere exercise). All the mechanical parts of the robot should be covered to avoid snag hazards, and an optical fingerprint reader could be added to the platform to simplify the access of multiple users to their therapy programs without the need to remember colored passwords. Regarding the software, based on the successful proof of concept with our new minimally-supervised exercises, the available assessment-driven supervised therapy exercises proposed by Metzger (Metzger et al., 2014b) will be redesigned to be usable with minimal supervision. As for the

sphere exercise, attention should be devoted to the optimization of instructions/feedbacks clarity, and of task complexity and matching to real-world actions. The GUI should provide feedback to the therapist (e.g., subject performance and statistics) and possibilities to further customize the exercises (e.g., simplify graphical content for subjects with attention or cognitive deficits). Finally, a long-term study is required to evaluate the feasibility and usability of a continuum of robot-assisted care from supervised to minimally supervised conditions, and a mobile/portable device should be developed to allow the application of this approach also in the home environment.

3.5 Implications and outlook

The goal of this work was to develop and evaluate, in a single-session pilot study, the usability of a minimally-supervised therapy platform, allowing to perform functional, personalized and motivating task-oriented exercises at the level of the hand. Our findings demonstrate that a powered robot-assisted therapy device respecting usability and perceived workload requirements can be safely and intuitively used in a single session with minimal supervision by chronic stroke patients. This preliminary evaluation allowed us to identify further design improvements needed to increase the platform usability and acceptance among the users. Our results open the possibility to use active robotic devices with minimal supervision to complement conventional therapies in real-world settings, offer increased dose with the existing resources, and create a continuum of care that progressively increases subject involvement and autonomy from the clinic to home. The integration of this technology in the home environment will require a more portable therapy device and additional integrated robotic assessments that could autonomously monitor the patient conditions online during the exercises and, if needed, adapt the therapy to maintain appropriate user tailoring and/or safety.

4 Online monitoring of patient's ability and physical conditions during robot-assisted therapy after stroke

This chapter is adapted from

Method for Muscle Tone Monitoring During Robot-Assisted Therapy of Hand Function: A Proof of Concept

Raffaele Ranzani, Federica Viggiano, Bernadette Engelbrecht, Jeremia P.O. Held, Olivier Lambercy, and Roger Gassert

2019 IEEE 16th International Conference on Rehabilitation Robotics (ICORR).

The authors would like to thank all the volunteers that participated in the pilot study, and Mike Domenik Rinderknecht for his MATLAB Toolboxes.

This work was supported by the European Project SoftPro (No.688857) and the Swiss State Secretariat for Education, Research and Innovation SERI under contract number 15.0283-1.

Raffaele Ranzani performed the data analysis and wrote the manuscript. Additionally, he contributed to the implementation of the graphical/physical user interface and monitoring exercise, the definition of the study protocol and the execution of the pilot study.

Final publication is available from https://doi.org/10.1109/ICORR.2019.8779454.

4.1 The risk of unforeseen adverse events during minimally-supervised therapy

Upper limb robot-assisted therapy has become an established method to complement conventional therapy after neurological injury, with therapy outcomes that are comparable to intensive conventional therapy [Mehrholz et al., 2018, Veerbeek et al., 2014, Lambercy et al., 2018]. Recently, there is increasing interest in exploring the minimally-supervised use of robotic technology (e.g., for home rehabilitation), which may promote recovery by increasing the overall amount of therapy offered to the patients [Veerbeek et al., 2014]. In chapter 2, we presented an assessment-driven therapy method, which can patient-tailor the exercise difficulty based on patient ability and performance [Metzger et al., 2014b]. These adaptive algorithms allow to replace one important part of the therapist supervision, related to the execution and adaptation of the single therapy exercise. However, they do not replicate the same high-level control of the therapy session as a whole, particularly in the event of adverse situations. Therefore, during minimally-supervised therapy, unforeseen events or changes (e.g., in patient health conditions or device functioning) could significantly compromise the therapy outcomes or put at risk the safety of the patient. To overcome these limitations, it is of utmost importance to introduce additional autonomous monitoring algorithms. These algorithms could detect changes in patient health parameters (e.g., pain, muscle tone, attention levels [Rinderknecht et al., 2018]) or in the device behavior (e.g., device errors, damage). Such information could be used in different ways. First, the monitoring data could be used longitudinally to investigate the therapy execution (e.g., assess patient compliance) and the evolution in patient conditions. Second, the platform could automatically react (e.g., automatically adjust the therapy, call for help) to continuously guarantee appropriate and safe tailoring of the therapy.

Given their potentially intensive therapy regime, robots may promote an increase in muscle tone, which is often already abnormally increased after stroke in the form of spasticity, with an incidence rate of 19-43% at 3-18 months after the event [Lundström et al., 2010, Veerbeek et al., 2017, Urban et al., 2010]. Based on the potential frequency of this problem, and to exploit the fine interaction control and sensing capabilities of our robotic device, the ReHapticKnob, we decided to start exploring autonomous monitoring strategies with an online muscle tone monitoring algorithm. This type of monitoring requires the robot to actively perturb the patient's hand during a therapy exercise, and to analyzes the force reactions induced at the level of the fingers [Katz and Rymer, 1989].

4.1.1 Spastic muscle tone abnormalities and assessment

Spasticity is a motor disorder characterized by a velocity and direction dependent increase in tonic stretch reflexes during resting state (i.e., "muscle tone"), which affects mostly flexors in the upper limb [Lance, 1980]. Limb joint stiffness is increased due to reduced stretch reflex thresholds and to alterations in mechanical properties of muscles developing over time

[O'dwyer et al., 1996]. Although the etiology of spasticity is still widely unknown, according to some rehabilitation approaches a prompt detection of spasticity is desired to adapt the therapy such that the patient can re-learn muscle tone control and avoid possible long-term negative consequences of spasticity (e.g., pain, reduced functional ability and recovery) [Bobath and Bobath, 1950, Perfetti and Wopfner-Oberleit, 1997, Kong et al., 2012, Formisano et al., 2005]. Unfortunately, in particular within minimally-supervised therapy sessions, current rehabilitation robots do not consider or monitor alterations in muscle tone during the course of a rehabilitation session.

Clinically, muscle tone is assessed using passive movements around a joint to determine the amount of muscle resistance encountered. The most frequently used scales for spasticity assessment are the Ashworth Scale (AS), the Modified Ashworth Scale (MAS) and the Tardieu Scale [Tardieu, 1954]. AS and MAS are still commonly used for their reliability and simplicity, but they are subjective and suffer from low sensitivity [Katz and Rymer, 1989]. The Tardieu Scale might be a valid alternative in differentiating spasticity, since it is evaluated at three different speeds. Using robotic devices, impedance estimation methods are commonly adopted to quantify muscle tone using force or position perturbations [Przuntek et al., 2012]. Only few robotic devices have been used to investigate upper-limb tone changes at the level of the hand, applying different types of ramp position perturbations to the finger joints (e.g., metacarpophalangeal joint) or to the fingers and wrist simultaneously but these approaches have so far only been applied in dedicated assessment sessions before and/or after therapy [Gäverth et al., 2014, Orihuela-Espina et al., 2016, Höppner et al., 2017, Kamper et al., 2001]. To avoid contributions from voluntary reactions, participants typically were in static (i.e., not moving) and passive (i.e., not exerting force) conditions when the perturbation was applied [Gäverth et al., 2014, Orihuela-Espina et al., 2016, Kamper et al., 2001]. Unfortunately, these studies mainly used a single movement speed and often only a single perturbation direction [Gäverth et al., 2014, Orihuela-Espina et al., 2016, Höppner et al., 2017, Kamper et al., 2001]. To the best of the authors' knowledge, no device or study has ever assessed both the speed-dependent and direction-dependent (opening-closing) changes in hand muscle tone (i.e., fingers flexors and extensors), nor was this information assessed online during the execution of a therapy protocol involving hand movements (i.e., where potential changes in muscle tone could be expected over time).

In this chapter, we present and evaluate a novel method implemented on a robotic device to objectively evaluate hand muscle tone online during the execution of a therapy exercise including the synchronous training of grasping and pronosupination. While both the exercise and the assessment embedded into it have been newly developed, the assessment paradigm could also be applied in other robot-assisted exercises. The exercise includes an online assessment of hand muscle tone evaluated with a ramp-and-hold perturbation-based approach (at different velocities and direction) to detect potential changes in spasticity. Given the repeated active hand movements required in the exercise, we hypothesized that muscle tone might increase even in participants that are non-spastic at rest. Therefore, we tested the exercise in a pilot study with healthy participants and non-spastic participants with stroke to evaluate

the extent of physiologically natural change in muscle tone caused by such an active training. This information could be used for remote monitoring, or to develop strategies for online adaptation of difficulty and intensity of robot-assisted therapy to minimize physiological fluctuations in muscle tone.

4.2 Method for online muscle tone assessment

4.2.1 Muscle tone monitoring exercise

The proposed exercise includes a series of therapy blocks during which small perturbations are applied at the level of the hand to assess online for the presence of a spastic muscle tone change (i.e., speed and direction dependent) over therapy time while training on an end-effector robotic gripper (i.e., the ReHapticKnob). The user sits in front of the robot and places his/her hand inside two instrumented finger pads with straps, as shown in Fig. 4.1. A 6-DOF force/torque sensor is mounted beneath each of the two finger pads, and allows to precisely measure the interaction force between user and device. To allow independent use of the robot, the patient uses an intuitive colored pushbutton keyboard to access his/her therapy plan and participate in the exercise tasks (e.g., select objects or provide answers when prompted by the exercise; Fig. 4.1), as described in Chapter 3.

The exercise embeds somatosensory and cognitive training aspects together with synchronous motor training of grasping and pronosupination in order to promote functional recovery [Perfetti and Wopfner-Oberleit, 1997]. The exercise structure is shown in Fig. 4.2 and follows a series of blocks (i.e., one guided block supervised by the therapist and 3 experimental blocks without supervision). Each block is divided into two parts, a training phase and a test phase.

In the training phase, a variable number of virtual objects (i.e., 3 to 5 spheres) are displayed one by one to the tested participant. The spheres have different colors, each associated with a different stiffness value. Through the finger pads, the user controls a virtual hand and has to squeeze the spheres one by one and memorize their stiffness. Position perturbations at the finger pads are applied during the switch between consecutive spheres, while the participant is passive.

In the test phase, semi-transparent spheres (halos) fall radially from a random initial position, one at a time, towards a position fixed at the center of the hand. The participant has to actively rotate the arm and adjust the hand aperture to catch the falling halo. The halo is caught if the hand aperture matches the diameter of the sphere and if the hand is properly rotated towards the falling direction within an alignment range Θ, shown in Fig. 4.1. If the halo is caught, the participant has to squeeze the halo and identify its stiffness/color using the colored pushbutton keyboard. Each test phase lasts 3 min. At the end, the score collected during the current test phase is presented, and a new block (i.e., training phase followed by test phase) begins. One session with the exercise, includes three blocks (i.e., 3 training phases, each followed by a test phase) and lasts between 10 and 15 minutes.

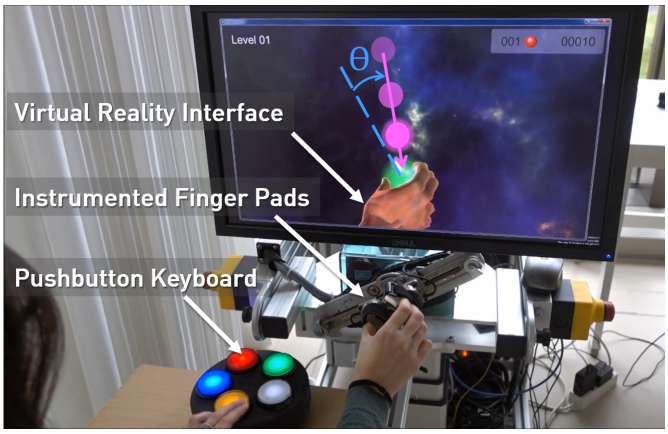


Figure 4.1: A participant performing the therapy exercise on the ReHapticKnob. A virtual reality interface displays the objects in the exercise, while their mechanical properties are rendered through active instrumented finger pads (held and manipulated by the participant). During the test phase shown, the participant has to catch a falling sphere. The object is caught if the hand orientation (dotted line) is aligned with the falling direction (continuous line), within an angular range Θ. Once the object is caught, the participant explores the mechanical properties by squeezing and selects the color corresponding to the identified stiffness by pressing a pushbutton on a dedicated colored keyboard.

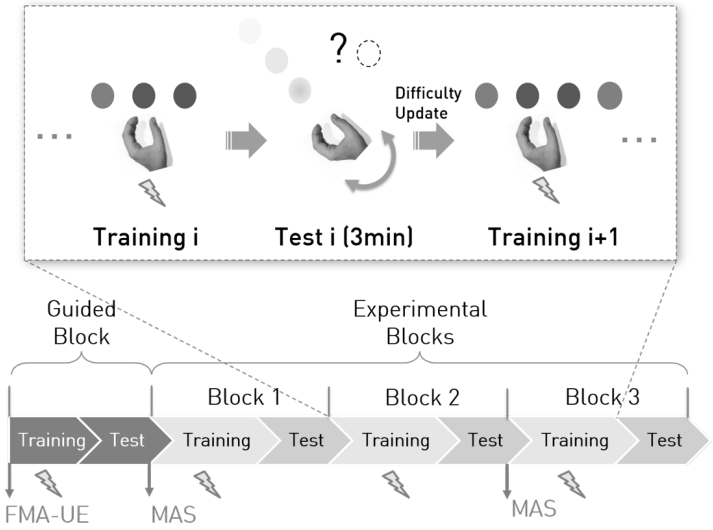


Figure 4.2: Exercise description and pilot study protocol. Top: detail of the exercise structure. A block i consists of a training phase and a test phase. In the training, four opening/closing fast/slow perturbations (thunderbolt icon) are applied during sphere switches, while the participant is inactive. In the test phase, the participant is instructed to catch falling spheres and to identify their color/stiffness. Bottom: The pilot study includes a supervised familiarization block, followed by three blocks in which the patient independently performs the exercise. The Fugl-Meyer of the Upper Extremity (FMA-UE) is evaluated at the beginning of the experiment, while the Modified Ashworth Scale (MAS) of finger flexors and extensors is evaluated at the beginning of blocks one and three.

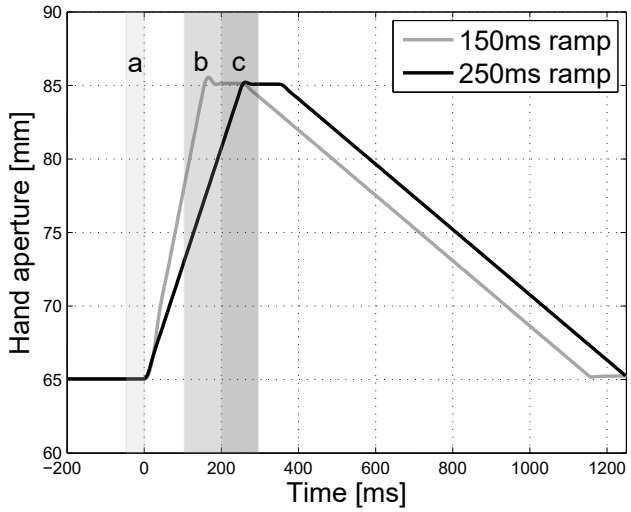


Figure 4.3: Representative fast (grey) and slow (black) 20 mm (thumb to index tip distance) ramp-and-hold perturbations in opening direction. (a) 50 ms window in which the average baseline force (F_{base}) is calculated before the ramp onset. (b)-(c) 100 ms window in which the maximum force peak induced by the perturbation (F_{pert}) is evaluated for the fast and slow perturbations, respectively.

To achieve robust control of the robot behavior during perturbations, displacement perturbations were chosen. Ramp-and-hold perturbations of 20 mm (i.e., 10 mm per finger) were implemented to not excessively perturb the participant, starting from a baseline hand aperture of approximately 65 mm (i.e., thumb to index tip distance). This is comparable to the range of values found in other studies (i.e., 7.5 to 58 mm [Höppner et al., 2017, Kamper et al., 2001]). To verify to which extent the change in muscle tone is direction and speed dependent, the perturbations are applied both in finger flexion and extension, and with two different ramp durations of 150 ms and 250 ms, respectively. These time windows allow to include reflex reactions that are relevant in the control of muscle tone and happen within 100 ms after perturbation onset (i.e., monosynaptic/short-loop and transcortical/long-loop reflexes), and to exclude steady state voluntary control, which typically starts 750 ms after perturbation onset [Davidoff, 1992, Hammond et al., 1956, Pruszynski et al., 2009]. Examples of opening perturbations are shown in Fig. 4.3. In total, three sets of perturbations are applied over the session time (i.e., one per block) during the training phase. Each set includes four perturbations (i.e., slow/fast and opening/closing) applied in randomized order so that the participant cannot predict them. Following the adaptation protocol described in [Metzger et al., 2014b] and to maintain an engaging and challenging training level, the difficulty of the exercise (e.g., number of spheres, stiffness difference between spheres) is adapted at the end of each block depending on the participant's performance (i.e., percentage of correctly identified spheres).

4.2.2 Pilot study

A pilot study was conducted at ETH Zurich, in collaboration with the University Hospital, Zurich. Five chronic ischemic stroke patients (>6 months) and five age-matched healthy participants (i.e., >50 years old) were enrolled to participate in a single experimental session. To be able to measure the amount of physiological muscle tone change induced by active training, patients were excluded if they had clinically significant concomitant diseases or a baseline MAS above 1 in hand finger flexors and extensors. As shown in Fig. 4.2, the experimental session consisted of a guided block in which participants were instructed on how to use the robot and perform the exercise, followed by an experimental stage in which participants performed the exercise independently (i.e., 3 blocks, without the intervention of the supervising therapist). Patients were tested on their impaired hand, while the control participants were tested using their dominant hand. To differentiate the upper limb impairment level of the patients, a baseline assessment of the Upper Extremity Fugl-Meyer (FMA-UE) was performed [Fugl-Meyer et al., 1975]. To compare the force changes in the robot-assisted muscle tone assessment with a reference clinical scale, the MAS of the finger flexors and extensors was performed before the beginning of the first and third block (Fig. 4.2). An experienced physiotherapist guided the experiment and performed the clinical assessments. The participants gave written informed consent in accordance with the declaration of Helsinki. The study was approved by the Cantonal Ethics Committee in Zurich, Switzerland (Req-2017-00642).

4.2.3 Outcome measures

For each perturbation in the training phase of a certain block i, the change between the force before the perturbation and after the perturbation is computed as:

$$\Delta F_{x,y}(i) = F_{pert}(i) - F_{base}(i) \tag{4.1}$$

where x is the perturbation direction (i.e., o = open, c = close), and y is the perturbation speed (i.e., s = slow, f = fast). The baseline grasping force before the perturbation (F_{base}) is calculated as the average force over the 50 ms before the ramp onset, the force after the perturbation (F_{pert}) is calculated as the peak force reached between 50 ms before and 50 ms after the ramp end. These time intervals, depicted in Figure 4.3, were empirically chosen based on the physiological duration of reflexes and after visual inspection of pilot data, as they are long enough to capture both baseline forces and force changes due to the perturbation without including voluntary reactions. To verify if muscle tone is speed and direction dependent, at each block i the following metrics are calculated on the perturbation-induced force reactions:

$$\Delta F_{o,spd}(i) = \Delta F_{o,f}(i) - \Delta F_{o,s}(i) \tag{4.2}$$

$$\Delta F_{dir,f}(i) = \left|\Delta F_{o,f}(i) - \Delta F_{c,f}(i)\right| \tag{4.3}$$

$\Delta F_{o,spd}(i)$ is used to evaluate speed dependency and corresponds to the difference in force change at two speeds in opening direction, which is the direction that predominantly elicits

Table 4.1: Baseline characteristics

Category	Stroke	Healthy	P^a
Gender (M,F)	3F, 2M	2F, 3M	1.000
Hand Dominance (L,R)	5R	5R	1.000
Impaired/Test Hand (L,R)	4R, 1L	5R	1.000
Age (mean±std)	67.20±12.01	58.60±4.04	0.168 (t(8)=1.52)
Months Post Stroke (mean±std)	57.60±63.47	-	-
FMA-UE (mean±std)	48.40±10.14	-	-
MAS (mean±std)	0.20±0.45	0.00±0.00	1.000 (U=30)

[a] P values are associated with the Fisher's exact test for categorical variables, while Wilcoxon rank sum test or two-sample t-test are used for continuous variables (independent samples). Abbreviations: FMA-UE, Fugl-Meyer Assessment of the Upper Extremity (range 0-66). MAS, Modified Ashworth Scale (i.e., sum of finger flexor and extensor scores).

spastic behavior [Katner and Kasarskis, 2014]. $\Delta F_{dir,f}(i)$ is used to evaluate the direction dependency (i.e., open-close) in force change at fast speed, since spastic force reactions increase with perturbation speed [Davidoff, 1992].

4.2.4 Data analysis

The Wilcoxon Rank Sum Test or the two-sample t-test were used to assess homogeneity between groups at baseline for continuous variables, while the Fisher's exact test was used for categorical variables. The force changes were compared in a 2x3 aligned rank transform for nonparametric analyses of variance (ART-ANOVA) (i.e., group x block, perturbation speed x time/block, statistical significance $\alpha = 0.05$) to analyze between and within-group differences [Wobbrock et al., 2011].

4.3 Assessment results

All participants completed the full protocol and no adverse event related to the use of the robot was observed. The baseline demographics and clinical characteristics of the two groups are described in Table 5.2. Most patients showed mild to moderate initial upper-limb impairment (FMA-UE 48.40 ± 10.14 (mean±std)) and the two groups were homogeneous in terms of non-stroke related parameters.

4.3.1 Speed dependency in force changes

Figure 4.4 shows the average force changes induced in participants with stroke and healthy participants by the slow and fast perturbations in opening direction with 80% confidence

intervals. In the stroke group (Figure 4.4.a), the force changes with the fast and slow perturbation start from a similar range of 3.25 ± 0.32 N and 3.76 ± 2.50 N at block 1, respectively. The force change with slow perturbation remains approximately constant over time, while the change after fast perturbation increases over the blocks, reaching a value of 6.29 ± 6.59 N (max 15.98 N) in block 3. Thus, the difference $\Delta F_{o,spd}$ increases over blocks and reaches a peak of 4.48 ± 7.78 N (max 13.08 N) in block 3. In the healthy group (Figure 4.4.b), the force change with fast perturbation is on average always higher than the force change with slow perturbation, but their value remains approximately the same between block 1 (3.37 ± 2.17 N, 4.31 ± 1.89 N, respectively) and block 3 (3.14 ± 1.29 N, 4.32 ± 2.00 N, respectively). The difference $\Delta F_{o,spd}$ is on average always smaller than 1 N, but mildly increases over blocks and reaches a peak of 0.96 ± 0.94 N (max 2.05 N) at block 3. In both groups, the change in force with respect to block and perturbation speed was not statistically significantly different according to ART-ANOVA (Block: F(2,45)=0.131, P=0.877; speed: F(1,45)=3.320, P=0.075). The force change with respect to block and subject group was also not statistically significantly different both at high speed (Block: F(2,16)=0.204, P=0.818; group: F(1,8)=0.106, P=0.753) and low speed (Block: F(2,16)=0.927, P=0.416; group: F(1,8)=0.030, P=0.867).

4.3.2 Direction dependency in force changes

Figure 4.5 shows the average difference between force changes induced in opening and in closing directions, in both the stroke (black) and healthy participants group (gray). In the stroke group, the force differences with fast perturbation $\Delta F_{dir,f}$ between opening and closing are on average always below 5 N. The difference is higher in block 2 (4.09 ± 3.90 N), and below 1.5 N in blocks 1 and 3. In the healthy group, the difference is on average always smaller than in the stroke group, and its value remains constantly closer to zero between block 1 (0.67 ± 0.68 N) and block 3 (1.36 ± 0.78 N), meaning that the force change is direction independent. The directional force difference with respect to block and participant group is not statistically significantly different (Block: F(2,16)=0.7642, P=0.482; group: F(1,8)=3.107, P=0.116).

4.3.3 Comparison with Modified Ashworth Scale

Four patients and the healthy volunteers that participated in the study had an initial muscle tone level of 0 on the MAS (beginning block 1), which remained the same throughout the test session (beginning block 3). Only one patient had an initial MAS of 1 in the finger extensors, which faded to 0 towards the end of the test session (beginning of block 3). This was reflected by the fast closing perturbation at block 1, where the patient reacted with a 22 N force. Given these MAS ranges, theoretically, the force changes measured in this work in opening direction and at the end of the exercise can be associated with physiological hand muscle tone changes happening during exercise.

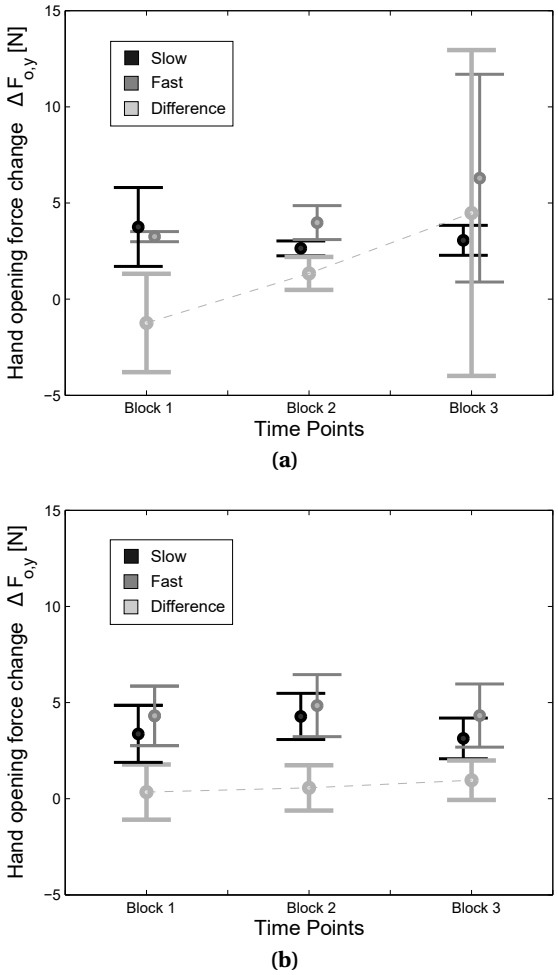


Figure 4.4: Average speed-dependent force changes induced by fast (gray, $\Delta F_{o,f}$) and slow (black, $\Delta F_{o,s}$) ramp perturbations (20 mm, 250 and 150 ms) in opening direction over 3 test blocks. The light gray dotted line is their average difference $\Delta F_{o,spd}$. (a) five chronic stroke patients, (b) five healthy participants.

4.4 Discussion

This chapter presented the development of a method to assess online finger muscle tone level in a stroke population within the execution of a minimally supervised robot-assisted therapy exercise of hand function. The muscle tone level is determined using an online perturbation-based force estimation method. A preliminary pilot study was conducted on chronic stroke patients and age-matched unimpaired participants to determine which are the physiological force changes developed within an exercise session. In view of independent, robot-assisted therapy, this information could be used to adapt the difficulty level of exercises not only based on the patient's performance but also considering muscle tone fluctuations, to minimize undesired increases in muscle tone, which could result in pain or injury. To the best of the authors' knowledge, no other robotic device for robot-assisted therapy allows to

test the evolution of hand muscle tone online during the execution of an exercise. Moreover, most robotic devices typically only test muscle tone reactions in opening direction and do not allow to evaluate the directional muscle tone-dependency [Gäverth et al., 2014, Höppner et al., 2017, Kamper et al., 2001].

The results of the pilot study showed that the muscle tone level during hand opening is higher with high perturbation speed in both groups, and corresponds to a force change of approximately 4-5 N. The two groups did not show statistically significant differences, but over the three blocks, the force change at slow speed remained constant, while at high speed it progressively increased in the stroke group, reaching an average of 6.3 N with a peak of 16.0 N in block 3. Thus, in the stroke group, the force change became more speed-dependent over exercise time/blocks. This slight increase would be in line with a recent review reporting that robot-assisted therapy can lead to increased muscle tone [Veerbeek et al., 2017]. Additionally, as expected from non-spastic participants, the observed force levels (i.e., below 6.5 N) are below the force range presented in the work of Kamper and colleagues, in which stiffness and force changes in finger flexors where determined on 8 chronic stroke patients with spastic hemiplegia (MAS>1) [Kamper et al., 2001]. Their max developed torque change ranged approximately between 9-35 N at the fingertip (assuming a finger length of 7.5 cm) depending on the degree of spasticity. This is not surprising given the almost zero MAS scores in our population.

Despite being a standard clinical assessment, the accuracy of the MAS assessment is debatable as shown in several analyses both at a clinical level or performed through robotic devices [Katz and Rymer, 1989, Melendez-Calderon et al., 2013]. Therefore, it seems reasonable to adopt a robotic assessment to accurately complement the evaluation of muscle tone and continuously monitor muscle tone during the execution of unsupervised therapy exercises. There are several differences though between the MAS and our robotic assessment. First, our exercise records force peaks at 1 kHz, while humans discriminate different muscle tone levels via tactile or proprioceptive perception, which elicit cortical activation within 5-50 ms (i.e., max frequency 20-200 Hz) [Hatsopoulos and Suminski, 2011]. Second, the MAS is performed by moving the joint over 1 sec and can therefore activate also voluntary control, while a robotic assessment can reach much higher perturbation speeds. In our pilot study, the MAS did not detect any increase in finger flexor tone over blocks, indicating that all the force measurements that we recorded reflect clinically non-meaningful changes in muscle tone over the exercise blocks. However, given the scale limitations and force ranges found in literature [Kamper et al., 2001], it is questionable whether the patient that showed a force change around 16 N in block 3 could have been in a voluntary contracted status when the perturbation was applied, or had a spastic contraction that was not detected in the MAS.

The results on direction dependency show that, as could be expected in a healthy population, the difference in force changes induced by opening and closing perturbations are smaller in the healthy group (i.e., tending to zero) compared to the stroke group. However, the two groups did not show statistically significant differences, and in the stroke group, no definite

conclusion on the force-direction dependency can be made due to the oscillatory direction-dependent force changes in different blocks. A larger sample size would be needed for this analysis, which would be key in discriminating spasticity from other pathologies that are direction independent (e.g., rigidity).

The pilot study and the tested exercise have the following limitations. The results of the study present rather small force changes but this is not surprising given the non-spastic population tested and the moderate exercise intensities (i.e, number of repetitions and forces required by the squeezing/catching task). Future experiments could achieve higher exercise intensities (both force and repetitions) and include more than one session, to verify the muscle tone evolution over longer time. Moreover, to capture intra-subject variability, the perturbations could be repeated multiple times within the same block. The test should be extended to a wider patient population including also spastic patients. This would be useful to identify speed and direction dependent force thresholds that could be used to characterize a spastic muscle tone change and adapt the difficulty level of the exercise accordingly. Finally, to further quantify changes in muscle tone, electromyography of forearm muscles and other electrophysiological or clinical scales (e.g., Tardieu Scale) could be recorded. However, while these approaches could help validate the proposed method in laboratory settings, they would not be applicable in view of unsupervised applications.

To summarize, in the future the experiments will be repeated in a larger population including spastic participants and will test higher exercise intensities over more than one session. To capture intra-subject variability the perturbations will be repeated multiple times in the same block.

4.5 Implications and outlook

The proposed method to evaluate muscle tone online during a therapy exercise opens up new avenues for the use of robotic devices with limited supervision, as they would allow for accurate, objective and quantitative remote monitoring of muscle tone fluctuations during robot-assisted therapy. Used within a robot-assisted rehabilitation program that starts in the clinic and continues after discharge, this method could help documenting muscle tone changes over time, which could be useful to investigate how to optimize the therapy strategy for each patient, and will allow to promptly adapt the therapy exercise in order to prevent pathological increases in muscle tone, as well as their possible effects on recovery. This monitoring method, could be further generalized to other forms of online autonomous assessment and monitoring, which will be particular important to guarantee user safety during the continuation of the therapy with a portable device in the home environment.

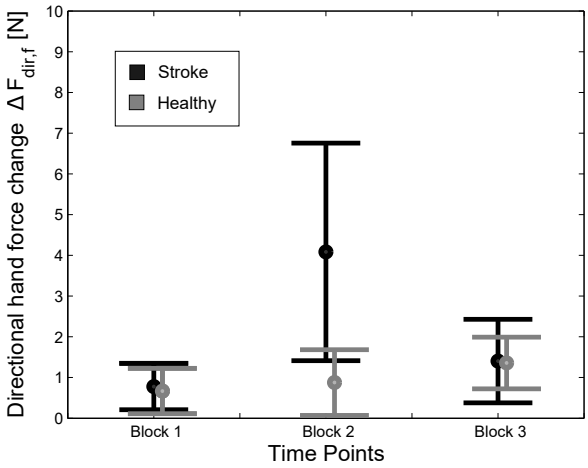


Figure 4.5: Average direction-dependent difference in force changes between opening and closing fast ramp perturbations (20 mm, 150 ms) in five chronic stroke patients (black) and five healthy participants (gray).

5 Design, characterization and preliminary usability testing of a portable robot for minimally-supervised therapy of hand function

This chapter is adapted from

Design, characterization and preliminary usability testing of a portable robot for minimally-supervised therapy of hand function

Raffaele Ranzani, Martin Albrecht, Claudia Haarman, Emily Koh, Giada Devittori, Jeremia P.O. Held, Freek Tönis, Olivier Lambercy, and Roger Gassert

Manuscript in preparation for *Journal of NeuroEngineering and Rehabilitation*.

The authors would like to acknowledge Ricardo Beira for his inputs on the device mechanics, and the medical doctors and therapists of the Clinica Hildebrand Centro di Riabilitazione Brissago, who helped in defining the design requirements and testing preliminary kinematic prototypes. Special thanks go to David Fisch, Jiri Danihelka and Cherelle Connor who participated in the development of the graphical user interface and exercises, and Kevin Sin, who evaluated the device compliance with respect to safety norms for medical devices.

This work has received funding from the European Union Horizon 2020 research and innovation programme under grant agreement No. 688857 (SoftPro) and from the Swiss State Secretariat for Education, Research and Innovation (SERI; contract number 15.0283-1).

Raffaele Ranzani designed the hardware and developed the low-level firmware for the control of HandyBot, performed performance evaluation tests and data analysis, and wrote the manuscript. Additionally, he contributed to the implementation of the graphical/physical user interface and exercises tested in the manuscript, the definition of the study protocol and the execution of the pilot study.

5.1 Towards a continuum of hand therapy after stroke

Almost two third of stroke survivors suffer from long-term upper limb impairment and are permanently disabled in the execution of activities of daily living (ADL) [Adamson et al., 2004, Broeks et al., 1999]. There is evidence that increasing therapy dose (i.e., number of exercise task repetitions and total therapy time) might promote an increase in upper limb sensorimotor recovery, even long time after the stroke [Veerbeek et al., 2014, Schneider et al., 2016, Ward et al., 2019]. Unfortunately, in clinical practice, the therapy dose that can be achieved is often constrained by financial and organizational limitations [Schneider et al., 2016, Ward et al., 2019]. As a result, patients after stroke typically receive suboptimal amounts of upper limb therapy both during inpatients rehabilitation programs in the clinic, and most importantly when back home after discharge. Robotic devices could be viable tools to offer high-dose functional therapies that are relevant for ADL [Hung et al., 2017]. These devices offer motivating task-oriented therapies that allow comparable therapy outcomes compared to dose-matched conventional therapies [Klamroth-Marganska et al., 2014, Lo et al., 2010, Mehrholz et al., 2018, Rodgers et al., 2019] and, in the case of haptic devices, realistic/accurate sensorimotor interactions that could support upper limb recovery [Perfetti and Grimaldi, 1979]. Unfortunately, the use of robotic devices is currently mainly limited to short therapy sessions in the clinics under constant supervision of specialized therapists, which limits their potential as a vector to increase therapy dose. One way to achieve this objective could be to use such technology within minimally-supervised robot-assisted therapy programs, which could start in the clinic [Büsching et al., 2018, Broderick et al., 2021] and continue at home after discharge [Chen et al., 2019, Hyakutake et al., 2019, McCabe et al., 2019].

Unfortunately, to make the step into the home environment of neurological subjects, robotic devices should be rethought to guarantee simplicity of use, adaptability to different users and ergonomics, affordability and scalability, safety and portability [Hung et al., 2017, Lu et al., 2011, Story, 2010]. These are critical aspects that should be considered early during design phases as recommended by the Food and Drug Administration [Food et al., 2012]. Meeting these requirements is a challenge [Chen et al., 2019] and, as a result, only few robotic devices for the upper limb have been proposed and tested for home use [Hyakutake et al., 2019, McCabe et al., 2019, Lemmens et al., 2014, Sivan et al., 2014, Wolf et al., 2015], often without reporting their technical evaluation. Furthermore, little is known about their usability, which is fundamental to optimize the device development, as well as increase acceptance and user compliance to a therapy plan [Lu et al., 2011, Lee et al., 2005, Ranzani et al., 2021, Just et al., 2018, Meyer et al., 2019].

In this chapter, we present the design and evaluation of HandyBot (Figure 5.1), a portable haptic device to perform task-oriented therapy of hand function under minimal supervision. This work builds on the knowledge gained from two haptic end-effector devices for hand therapy, the HapticKnob (HK, [Lambercy et al., 2007]) and the ReHapticKnob (RHK, [Metzger et al., 2011]). These devices train hand opening-closing and forearm pronosupination through sensorimotor functionally-relevant therapy tasks, which are particularly important for hand

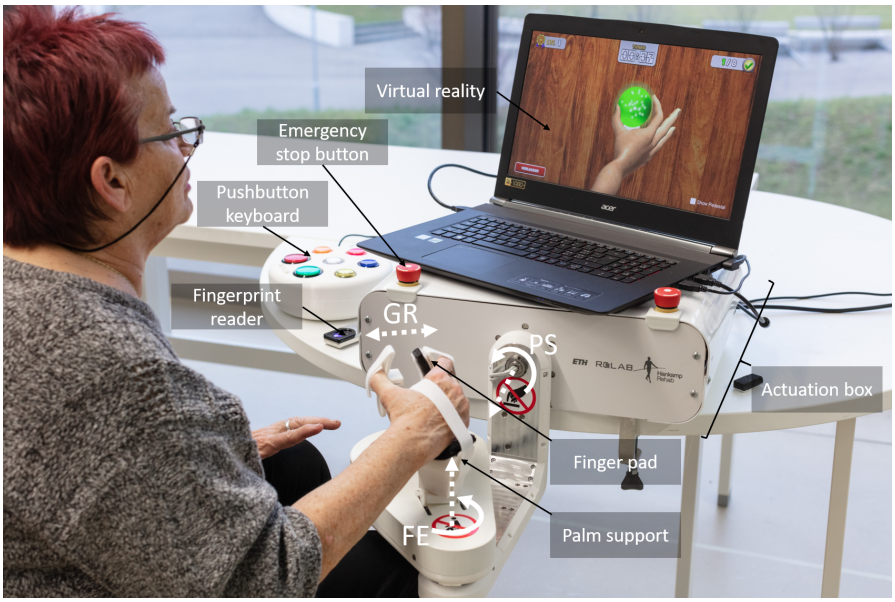


Figure 5.1: A subject performing a therapy exercise (WristCatch) on the HandyBot, a portable table-top end-effector robot for the assessment and therapy of grasping, forearm pronosupination and wrist flexion-extension tasks. Virtual tasks are haptically reproduced through two pads that get in contact with the fingers of the user, and visually rendered in a virtual reality environment presented on a computer screen. The user can start his/her therapy by logging-in via a fingerprint reader or inserting a colored password through a pushbutton keyboard, which also serves as a input interface to interact with the virtual reality of the exercises. Two easily reachable emergency stop buttons are embedded in the actuation box of the device, which includes the actuators as well as electronics and safety components.

rehabilitation [Metzger et al., 2014b], and already proved their efficacy in terms of motor impairment reduction in supervised clinical settings [Ranzani et al., 2020, Lambercy et al., 2011]. Unfortunately, they did not make the step out of the clinic due to the device size, cost and technology complexity.

The current work has two objectives. First, to develop HandyBot (Figure 5.1) and evaluate its technical characteristics in terms of workspace, sensing, dynamics and haptic performance to guarantee good rendering of therapy exercises focusing on sensorimotor tasks that are key to hand rehabilitation. Second, a pilot study should evaluate the usability of HandyBot in subjects after chronic stroke, which are the target population for home use of the device.

5.2 Device design and usability evaluation

5.2.1 Requirements

We previously proposed two haptic end-effector therapy devices, the HK [Lambercy et al., 2007] and the RHK [Metzger et al., 2011], which train hand grasping (GR) and forearm prono-

supination (PS) by rendering functionally-relevant rehabilitative tasks (e.g., interaction with virtual objects) that can be reproduced with high haptic accuracy through active instrumented pads that get in touch with the fingers, and are visualized in virtual reality through a computer screen [Metzger et al., 2014b]. These devices offer a combined sensorimotor and cognitive training, as proposed by Perfetti [Perfetti and Grimaldi, 1979], and showed equivalent therapy outcomes compared to dose-matched conventional therapy [Ranzani et al., 2020]. The RHK was recently embedded into a novel therapy platform (i.e., haptic device with a graphical/physical user interface and a set of therapy exercises) that allows to perform minimally-supervised therapy in controlled settings [Ranzani et al., 2021, 2019].

Building on this knowledge, our approach is to develop HandyBot as a portable haptic device that could offer the same type of sensorimotor therapy as the HK and the RHK in minimally-supervised conditions, with the long-term objective of independent training in the home environment. To guarantee the compatibility with therapy exercises previously developed and clinically validated and, at the same time, guarantee a training in conditions similar to interaction with real objects, the same movements (i.e., grasping and forearm pronosupination) should be trained through an end-effector approach. Moreover, given its relevance in ADL tasks [Reissner et al., 2019, Nelson et al., 1994] and its synergies with grasping functions [Pezent et al., 2017], it was decided to add a third degree of freedom (DOF) to also train wrist flexion-extension (FE). Very few robotic devices support these three DOFs, and they either do not allow their simultaneous training, which is essential for typical ADL or rehabilitation exercises, or require external help to change the hand interfaces to select the movement/-task to train [Tong et al., 2015, Khor et al., 2014]. Also, in most cases, the hand mechanism is embedded in complex and/or expensive multi-DOF therapy platforms [Just et al., 2018, Pezent et al., 2017, Loureiro and Harwin, 2007]. To make a powered device suitable for home rehabilitation and potential private use (e.g., on a pay-per-use policy directed by the clinic), its cost should be at least halved compared to the RHK and other robot-assisted upper limb therapy devices that cost more than 40000 euro [Just et al., 2018, Loureiro and Harwin, 2007, Huang et al., 2018], while ease of use and portability should be ensured [Lu et al., 2011]. User comfort and ergonomics should also be optimized [Hung et al., 2017] and safety during the use and interaction with the device should be ensured [Story, 2010]. As learned during a previous study with the RHK [Ranzani et al., 2020], the parts interacting with the user (e.g., finger pads, straps, supports) should be adaptable in size/positioning and prevent hand slippage, while arm supports should be positioned not too far from the hand fixations to reduce pressure marks on the fingers. Thumb motion during grasping is complex and would require simultaneous flexion-extension and adduction-abduction for a natural grasping [Bützer et al., 2020]. Based on data from previous studies with the RHK [Ranzani et al., 2020] (see Table 5.1) and biomechanical considerations on the human hand, the maximum hand aperture between thumb and middle finger during typical therapy exercises should be 110mm, the maximum pronation (or supination) of the forearm is 90° and the maximum flexion (or extension) of the wrist is smaller than 80° [Norkin and White, 2016]. The maximum force at the fingertip (i.e., thumb or four fingers) should be 50N to successfully simulate typical object manipulations in

Table 5.1: Mean and maximum forces and maximum reachable positions (in grasping GR, and pronosupination PS) during the execution of neurocognitive robot-assisted exercises with the ReHapticKnob (for more details on the exercises refer to [Metzger et al., 2014b]). Mean and maximum forces have been derived using the data of 14 patients that performed robot-assisted therapy in the randomized controlled trial described in [Ranzani et al., 2020]. Maximum reachable positions are the positions needed to render necessary therapy objects or tasks of the exercise.

Exercise	**Force**$_{GR}$ [mean (max)]	**Torque**$_{PS}$ [mean (max)]	**Position** [max$_{GR}$,max$_{PS}$]
E_1(bars): Proprioception	1.3 (33.2) N	-	102mm, -
E_2(arches): Proprioception	1.4 (20.8) N	2.0 (2.6) Nm	-, ±60°
E_3(sponges): Haptic perception	2.9 (43.8) N	-	102mm, -
E_4(springs): Haptic perception	2.0 (44.0) N	-	140mm, ±90°
E_5(grip memory): Sensorimotor memory	1.1 (33.4) N	-	102mm, -
E_6(pronosupination memory): Sensorimotor memory	2.6 (49.8) N	1.6 (1.9) Nm	102mm, ±60°
E_7 (postcards): Sensorimotor coordination	3.6 (44.9) N	0.1 (1.9) Nm	102mm, ±60°

ADL and therapy tasks (see Table 5.1). The maximum PS and FE torques relevant to simulate daily tasks are below 1.2Nm [Lambercy et al., 2007, Williams et al., 2001]. Respecting a tradeoff between electromechanical components quality and cost, accurate haptic renderings (ranging from transparency to high impedances) should be reproduced under a stable closed-loop behavior in particular in the grasping DOF, where they are perceived by the hand with maximum sensitivity [Skedung et al., 2013].

5.2.2 Design concept and kinematics

Several design concepts and existing design solutions [Tong et al., 2015, Bouri et al., 2013] have been evaluated for the development of our 3-DOF robot HandyBot before achieving a design that could maximize structural stiffness and compactness, while providing suitable ranges of motion and forces, and a complete decoupling between the three DOF (Figure 5.2). The first rotational DOF is the forearm pronosupination θ_{PS}, which is controlled by a geared motor $M_{PS} - G_{PS}$ rotating an aluminum L-shape structure (yellow). Two motors M_j drive the rotational DOF for wrist flexion-extension (j=FE, blue) and the linear DOF for grasping (j=GR, green) through a series of capstan drive stages with 0.69mm tungsten cables (section 7x7x7x0.025mm, Baird Industries). As recommended in literature [Beira et al., 2010, Nef et al., 2007], a transmission based on capstan drives (i.e., cable transmission) was selected since it allows to reduce friction and backlash, while maintaining high structural stiffness and allowing for the rendering of a wide range of control impedances. To pass through the coaxial joints J_i avoiding cable cross-over conflicts, coaxial pulleys $P_{j,i}$ (in the form of coaxial tubes of different lengths) are used, as proposed by [Beira et al., 2018]. To avoid cable slippage, each tungsten cable is constrained to the driver/load pulleys via ball beads (3mm) and drives inside grooves on the pulley surfaces. The pulley $P_{FE,2}$ directly drives the flexion-extension plate (light blue) generating a rotation θ_{FE} around the L-shape structure. The rotation of its

coaxial pulley $P_{GR,2}$ is transformed in the simultaneous linear motion x_{GR} of custom made aluminum carriages mounted on linear guides (Misumi miniature guides SELB8), one moving horizontally the finger pad and two (in lighter green) driving symmetrically the (left- or right-hand) thumb pad with an inclination of 15°, which allows the simultaneous flexion-extension and adduction-abduction of the thumb during grasping [Bützer et al., 2020]. To change the left/right hand side, the finger pad can be rotated around its axis, while the thumb pad can be connected to the respective inclined slider. The pads and the palm support include Velcro straps that maintain hand and fingers in place during active movements, and can be rapidly exchanged and/or manufactured on a 3D printer in different hand sizes for men, or for women. Additionally, to ensure user comfort, the palm support (Figure 5.1) can slide to different fixed positions depending on the hand size and shape. Positions of the end-effector are measured in joint space with encoders E_j attached to the motor shafts, which measure relative angles $\delta\theta_{j,0}$ (j=PS,FE,GR). The position of the end-effector in task space [θ_{PS}, θ_{FE}, x_{GR}] can be described with respect to joint space coordinates (and the initial end-effector absolute position measured through the potentiometers) by three linear equations.

$$\theta_{PS}(t) = \frac{1}{i_{PS}}\delta\theta_{PS,0}(t) + \theta_{PS}(0) \tag{5.1}$$

$$\theta_{FE}(t) = -\frac{1}{i_{PS}}\delta\theta_{PS,0}(t) - \frac{d_{FE,0}}{d_{FE,1}}\delta\theta_{FE,0}(t) + \theta_{FE}(0) \tag{5.2}$$

$$x_{GR}(t) = \frac{d_{GR,2}d_{FE,0}}{2d_{FE,1}}\delta\theta_{FE,0}(t) + \frac{d_{GR,0}d_{GR,2}}{2d_{GR,1}}\delta\theta_{GR,0}(t) + x_{GR}(0) \tag{5.3}$$

The derivatives of these equations result in the following forward kinematics:

$$\begin{bmatrix} \dot{\theta}_{PS}(t) \\ \dot{\theta}_{FE}(t) \\ \dot{x}_{GR}(t) \end{bmatrix} = \begin{bmatrix} 1/i_{PS} & 0 & 0 \\ -1/i_{PS} & -\frac{d_{FE,0}}{d_{FE,1}} & 0 \\ 0 & \frac{d_{GR,2}d_{FE,0}}{2d_{FE,1}} & \frac{d_{GR,0}d_{GR,2}}{2d_{GR,1}} \end{bmatrix} \begin{bmatrix} \dot{\theta}_{PS,0}(t) \\ \dot{\theta}_{FE,0}(t) \\ \dot{\theta}_{GR,0}(t) \end{bmatrix} \tag{5.4}$$

Where i_{PS} is the gear ratio of the gear G_{PS} and $d_{j,i}$ are the diameters of the pulleys $P_{j,i}$. The determinant of the Jacobian matrix is not equal to zero, thus the system has no singularities for any given state. The motion is only constrained by the mechanical range limits of the device.

5.2.3 Electronics, control and safety

The architecture of HandyBot is shown in Figure 5.3. A portable reconfigurable I/O device with an embedded processor running LabVIEW Real-Time 2018 (National Instruments myRIO-1900) performs the low-level control of HandyBot. The low-level control (frequency 1kHz) reads the sensors, performs safety routines and data saving, and sends commands to the actuators through a state machine including position and impedance (feedforward for PS and

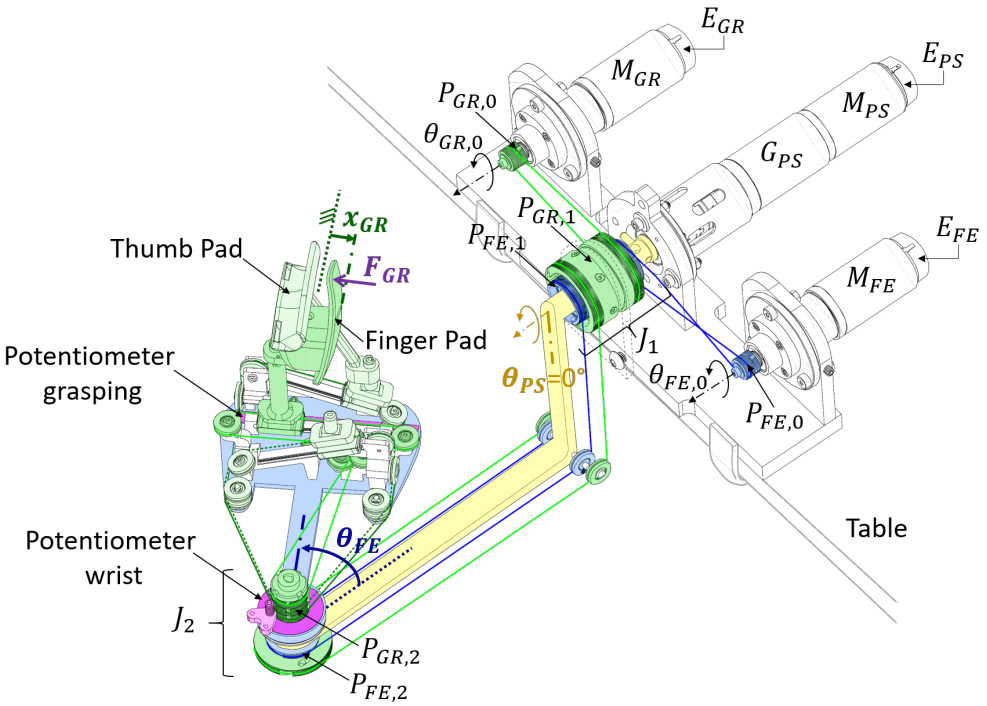


Figure 5.2: Simplified model of the HandyBot: The geared motor $M_{PS} - G_{PS}$ rotates the ball bearing supported yellow L-shape structure, which allows to perform forearm pronosupination with an angle θ_{PS}. Two motors M_{FE} and M_{GR} drive the wrist flexion-extension (light blue plate, angle θ_{FE}) and the grasping DOF (thumb and finger pads in light green and green, displacement x_{GR}) through a series of capstan drives with tungsten cables. To allow the transmission of the power through the coaxial joints J_i, coaxial pulleys $P_{FE,i}$ and $P_{GR,i}$ (concentric tubes of different lengths) are used for each DOF. Linear guides allow the transformation of the rotational displacement of the idler pulley $P_{GR,2}$ to a symmetric displacement x_{GR} of both the thumb and finger pads. The position of each DOF is measured through rotational encoders E on the motor shafts, and redundant potentiometers (pink) for safety and calibration. The force exerted on the finger pad F_{GR} is measured through a 1-DOF load cell embedded in the pad support. Note: The figure shows the right-hand configuration. The thumb pad could be connected to the 3^{rd} unplugged linear slider to allow left-hand use of the device.

FE, with force feedback for GR [Metzger et al., 2012, Hogan and Buerger, 2005]) control modes. MyRIO can be connected via USB2.0 to any portable laptop (e.g., ACER Aspire VN7-792G, Intel Core i7-6700HQ, 32GB RAM), which performs the high-level control of the therapy exercises in Unity 2018.2.18f1 at 60Hz, communicates via UDP with the low-level control, and provides interactive graphical/physical interfaces with the user.

1. Actuation: The actuators were dimensioned to meet the force/torque requirements. All motors are brushed DC motors (RE40, GB, 150W, Maxon Motor) controlled in current mode by servo controllers (Escon 50/5, Maxon Motor). The motor MPS has a gearbox GPS with gear ratio 21:1, while the gear ratios achieved through the pulleys in the FE and GR DOF are approximately 2:1 and 3:1, respectively. These small gear ratios (i.e., smaller than 30:1) lend the system a medium backdrivability, which guarantees a tradeoff between system transparency and safety in case of power shut down [Perret and Vercruysse, 2014].

2. Sensors: Robot positions are measured through optical encoders (HEDL 5540, 500 counts per turn for PS; MR Type L, 1024 counts per turn for FE and GR, Maxon Motor) mounted on the motor shafts. For redundant measurement of the end-effector position (in case of failure of the cable transmission) and initial calibration, one rotational soft potentiometer is mounted between the L-shape structure and the wrist flexion-extension plate (Rotary ThinPot, 351° travel, 3% linearity, Spectra Symbol) and one linear soft potentiometer (ThinPot, 100mm travel, 1% linearity, Spectra Symbol) is placed on the side of the linear guides on which the finger pad is mounted. The PS DOF does not require any redundant potentiometer for calibration as the L-shape structure passively stays in a 0° position (i.e., vertical position shown by θ_{PS} in Figure 5.2) through gravity. A 1-DOF load cell (Thin-Beam load cell, weight capacity 178N, Omega) is mounted between the finger pad and the aluminum carriage supporting it. This enables precise measurement of forces applied by/to the fingers during grasping movements, which can be reasonably expected to match thumb forces during symmetric grasping [Lambercy et al., 2014].

3. Interactive Physical User Interfaces: In order to operate HandyBot, the user can directly login into the graphical user interface, in particular into his/her therapy plan, with an optical fingerprint reader (Digital Persona 4500, HID) (Figure 5.1). An intuitive colored pushbutton keyboard (Xin-Mo 1 player controller interface, Arcade World UK) allows the user to autonomously navigate in his/her therapy page, select and perform therapy exercises. Both interfaces are connected with the laptop via USB2.0.

4. Safety: To fulfill safety norms required for electronic medical devices, the following safety features were implemented:

    - To fulfill the European Standard safety requirement for medical electrical equipment (Norm IEC 60601-1:2005:AMD1:2012), all active parts are disconnected from the mains using a medically certified isolated power supply (VMS 550W, CUI). All

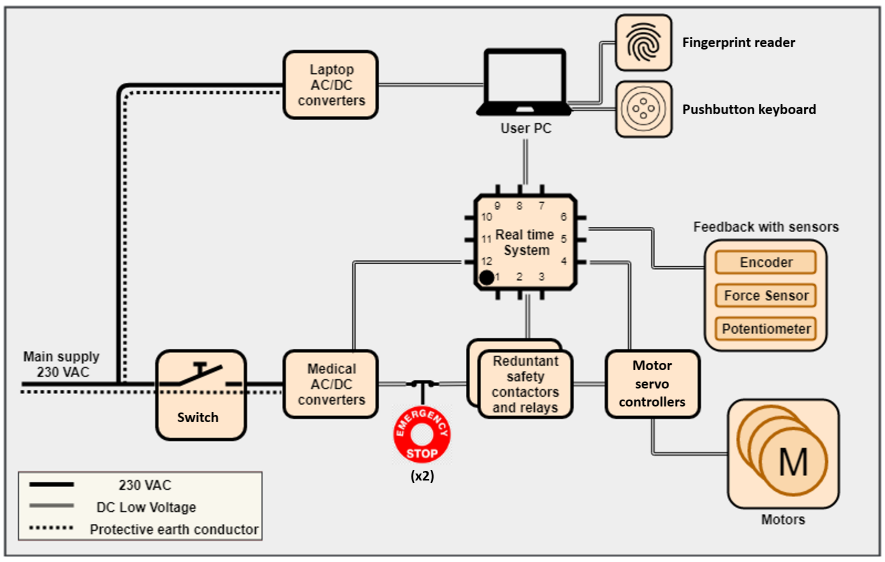


Figure 5.3: System architecture of the HandyBot.

the components in contact with the user do not carry mains voltage and have leakage currents below the limits imposed by the norm. All metallic parts are connected to each other and to the earth conductor of the isolating transformer.

- In case of emergency during interaction with the robot, the user can press either of the two emergency buttons located on top of the robot. This activates a safety relay (PNOZ s1, Pilz), which operates two power contactors connected in series to redundantly cut the power supply to the servo controllers without cutting the power to the sensors. This setup fulfills the highest safety level of the European Norm EN ISO 13849–1 on safety of machinery.
- To prevent any harm to the user, maximum positions, velocities and forces are limited by the software, and the range of motion (ROM) of each DOF is constrained by mechanical stops. Additionally, if a mismatch between the redundant positions sensors is detected, the power to the electronic system is cut.

Furthermore, the design of the device complies with the Council Directive for medical devices (93/42/EEC:2007), respects labeling and symbols for medical devices (ISO 15223:2015) and has acceptable residual risks for the user during its operation according to our risk analysis (DIN EN ISO 14971:2018).

5.2.4 Performance evaluation

The general performance of HandyBot was assessed through workspace (i.e., ROM), sensing and dynamics performance measures, in order to provide a direct comparison with the HK and RHK [Metzger et al., 2011], as well as with other state of the art rehabilitation robots. The sensing measures directly affect the control performance and stability, and include:

- *Encoder position resolution*: minimal displacement/rotation of the end-effector that can be captured by the encoder.
- *Velocity resolution*: minimal detectable displacement (i.e., position resolution) divided by the sampling interval of 0.001s.
- *Maximum measurable force and force resolution*: reflect the ranges provided by the sensor manufacturer. The resolution is calculated based on the force amplifier and the analogue to digital conversion of the signal.

The following dynamics measures reflect mechanical and actuation properties of the device:

- *Maximum velocity and acceleration*: estimated using offline lowpass filtered (20Hz) position measurements from the encoders when giving a maximum current step (for velocity estimation) or a maximum current impulse (10ms long, for acceleration estimate) to the motors [Hayward and Astley, 1996].
- *Uncompensated static friction*: computed by increasing the motor current by small steps until a movement (i.e., 2° and 0.2mm for rotational and translational DOF, respectively) of the end-effector was detected.
- *Maximum and continuous end-effector force*: calculated based on the stall and continuous torques provided in the motor data sheet and transformed from joint to task space.

Additional measures allow to evaluate the haptic performance of the device when using impedance control during human-robot interactions.

- *Transparency planes* describe the lower apparent impedance of the device [Tagliamonte et al., 2011]. The transparency plane visually indicates, through its flatness, whether the haptic display is transparent or resists active movements of the user. To construct the transparency plane on the grasping DOF, the end-effector was moved by hand at different velocities during transparency rendering, while interaction force F_{GR} and position x_{GR} were recorded with the corresponding force sensor and encoder. Raw position data were then differentiated and filtered with a zero-phase lowpass filter with a cut-off frequency of 15Hz to obtain velocity $\dot{x}_{GR}$ and acceleration $\ddot{x}_{GR}$ values. Thereafter, the interaction force exerted was plotted with respect to velocity and acceleration values, and through multiple linear regression the following plane was fitted:

$$F_{GR} = m_{app}\ddot{x}_{GR} + b_{app}\dot{x}_{GR} \tag{5.5}$$

  where m_{app} and b_{app} are the apparent inertia and damping felt by the user during human-robot interaction. The linearity of the transparency plane model can be validated if the trajectory points lie close to the fitted plane (i.e., the residuals of the multiple linear regression fit are small).

- *Fidelity of rigid contact* analyzes the ability of the device to render a sharp transition from transparency to high-impedance renderings (e.g., virtual wall), which can be often used to display virtual objects. The transition is implemented through a virtual spring-damper element that varies with the position x_{GR}:

$$F_d = \begin{cases} 0 & x_{GR} < x_{wall} \\ \mathrm{k}_d(x_{GR} - x_{wall}) + b_d \dot{x}_{GR} & x_{GR} \geq x_{wall} \end{cases} \tag{5.6}$$

  During this test, one of the highest combinations of stiffness k_d and damping b_d that can be stably rendered was identified, while the resulting controlled stiffness at the end effector k_{ctrl} was calculated using force and encoder signals. The ability of the device to render a rigid contact was quantified as controlled stiffness fidelity (i.e., ratio between k_{ctrl} and k_d).

- *KB plots*, as described by Colgate and Brown [1994], display the curve of stable k_d and b_d combinations that are at the edge with an unstable behavior of the system when a human interacts with a virtual wall described by 5.6. For instance, the stability limit can be identified when increasing the stiffness k_d for a fixed damping b_d until a stable impact with the virtual wall is not possible anymore. The area underneath the curve can be seen as an estimate of the Z-width [Colgate and Brown, 1994] and represents the stable parameter combinations.

The performance measures were computed for each DOF, excluding maximum measurable force, force resolution, rendering of rigid contact and transparency planes, which could only be computed for GR, as it is the only DOF equipped with a force sensor for high haptic fidelity. To enable a fair comparison between devices, device size, cost and weight were also considered.

5.2.5 Usability evaluation

To achieve the goal of minimally-supervised robot-assisted therapy, the robotic platform (i.e., haptic device with user interface and therapy exercises) should meet a wide range of human factors and mechatronics requirements. In addition, its usability should be assessed early during development to ensure positive user experience and compliance to the therapy program, as well as identify necessary design improvements [Meyer et al., 2019, Shah and Robinson, 2007, Power et al., 2018]. The minimally-supervised user interface and therapy exercises developed in Unity for the RHK were positively evaluated in our previous work [Metzger et al., 2014b] and [Ranzani et al., 2021], and were therefore selected as a starting point for HandyBot. To verify the usability of HandyBot with minimal external supervision, a pilot usability study was performed with four subjects in the chronic stage after stroke (>6 months). This typically corresponds to the target population for minimally-supervised exercises in home settings for which HandyBot has been designed. Participants took part in a single test session, which consisted of a supervised and a simulated minimally-supervised part conducted in laboratory settings.

In the *supervised part*, a supervising therapist assessed the subject's baseline ability level through the Fugl-Meyer of the Upper Extremity (FMA-UE) and a robotic assessment (ROM), which was used to customize the difficulty level of the therapy exercises. After that, the therapist instructed the subject on how to use two exercises (i.e., Tunnel and WristGrasp exercise), and actively guided the subject in a preliminary guided execution. In the Tunnel exercise, the subject had to coordinate GR and PS to navigate inside a virtual tunnel during one-minute blocks, while avoiding obstacles and reacting to viscous perturbations (for more details please refer to [Ranzani et al., 2021]). The WristGrasp exercise was a novel sensorimotor exercise, developed to take advantage of the new features of HandyBot and train wrist FE in simultaneous coordination with GR (Figure 5.1), which would be relevant for ADL [Pezent et al., 2017]. In this exercise, the subject had to grasp a glass sphere and release it onto an invisible pedestal, located at random wrist flexion-extension positions within the subject ROM. The location of the pedestal could only be identified through haptic cues (i.e., changes in wrist FE force field around the target position). One exercise block lasted three minutes. Both exercises have different levels of difficulty, which are adapted after each block based on performance.

In the *minimally-supervised part* of the study, each subject had to independently use the therapy platform to perform the Tunnel exercise (i.e., ten blocks) and the WristGrasp exercise (i.e., three blocks). During this time, the therapist sat at the back of the room, silently observed the subject's actions and intervened only in case of risk or explicit request from the subject. In particular, the subject had to independently position his/her hand on the finger/thumb pads, log into the graphical user interface, find and start the appropriate therapy exercises from a graphical list of exercises, test both exercises and log out from the graphical user interface. At the end of the experiment, the subject answered four System Usability Scale (SUS) questionnaires, which are the main outcome measure of the study: two for the exercises, one on the graphical user interface, and one on the device itself. The SUS assesses the overall usability of the system under investigation. Two items of the SUS refer specifically to the "learnability" of a system (i.e., "I think that I would need the support of a technical person to be able to use this system", "I needed to learn a lot of things before I could get going with this system") and were considered of high importance for a minimally-supervised usage scenario [Lewis and Sauro, 2009]. Ideally, the total SUS score calculated from its ten items should be greater than 50 out of 100, indicating an overall usability between "OK" and "best imaginable" [Bangor et al., 2009], and the learnability subscore should be greater than ten out of 20. The study was approved by the ETH Zurich Ethics Commission, Switzerland (2020-N-16). Given the small sample size tested, the results of the experiment are reported as median with first and third quartile (i.e., median (quartile 1 - quartile 3)). These results will allow to verify if the usability of the platform (i.e., robot, exercises and user interface) remains comparable with the results achieved with the RHK [Ranzani et al., 2021].

Table 5.2: Performance measures of HandyBot and comparison with HapticKnob and ReHapticKnob.

Performance Measure	**HapticKnob**		**ReHapticKnob**		**HandyBot**		
DOF	Grasping	Pronosupination	Grasping	Pronosupination	Grasping (x_{GR})	Pronosupination (θ_{PS})	Flexion-Extension (θ_{FE})
ROM	15-75mm	±180°	15-100mm	±159°	5-55mm	±90°	±90°
Position Resolution	0.115mm/count	0.021°/count	0.0012mm/count	0.009°/count	0.0063mm/count	0.0086°/count	0.0427°/count
Velocity Resolution @1kHz	115mm/s	21°/s	1.23mm/s	9°/s	6.28mm/s	8.57°/s	42.7°/s
Max Velocity	-	-	520mm/s	1728°/s	688mm/s	651°/s	330°/s
Max Acceleration	-	-	13.25m/s^2	44640°/s^2	11.73m/s^2	2314°/s^2	2075°/s^2
Uncompensated Static Friction	9N	0.02Nm	6N	<0.4Nm	<5.5N	<0.75Nm	<0.3Nm
Max End-Effector Force (continuous)	50N	1.5Nm	1181N (88N)	12.18Nm (0.98Nm)	125N (23N)	21.42Nm (3.97Nm)	2.1Nm (0.39Nm)
Max Measurable Force (resolution)	30N (0.2N)	-	80N (0.02N)	4Nm (0.0005Nm)	151N (73.73mN)	-	-
Control Frequency	100Hz		1kHz		1kHz		
Cost	-		>40000 euro		<15000 euro		
Device Size	-		800x1400x1200 mm		445x605x200 mm		
Weight	-		>100 kg		<15 kg		
Abbreviations: ROM=Range of Motion, DOF=Degree of Freedom							

5.3 Results

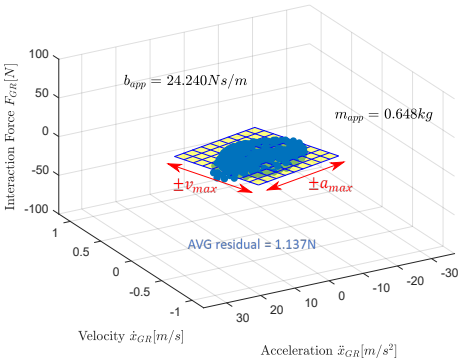
5.3.1 Performance evaluation

HandyBot resulted in compact table-top design with an actuation metal box (i.e., including actuation, electronics and safety components, 445x305x135mm) and an end-effector (150x300x200mm) (Figure 5.1). The performance of HandyBot in terms of workspace, dynamics and sensing was evaluated and is reported in Table 5.2, together with overall device size, cost and weight. In addition, these metrics are compared with the previously developed HapticKnob and ReHapticKnob to show the similarity in performance despite the scalability and compactness of the new device. Some of the performance metrics can also be compared with three other portable robot-assisted therapy devices, namely the ReachMAN [Yeong et al., 2009], the CR2-Haptic [Khor et al., 2014] and the OpenWrist [Pezent et al., 2017], which train (singularly and/or simultaneously) at least two of the DOF trained by HandyBot. In these devices, the ROM is 25-90mm in GR [Yeong et al., 2009], between ±85° and ±180° in PS [Yeong et al., 2009, Pezent et al., 2017, Khor et al., 2014], and between ±70° and ±135° in FE [Pezent et al., 2017, Khor et al., 2014], generating maximum end-effector forces/torques up to 10.8N, 3.5Nm and 3.6Nm, respectively. Their static friction is below 2N in GR [Yeong et al., 2009], and below 0.4Nm and 0.11Nm in PS [Yeong et al., 2009, Pezent et al., 2017, Khor et al., 2014] and FE [Pezent et al., 2017, Khor et al., 2014], respectively. On the grasping DOF, transparency planes were identified for the uncontrolled device and when the device is controlled to render a transparent impedance via impedance control with force feedback (Figure 5.4). The uncontrolled device showed an apparent mass of 0.65kg and an apparent damping of 24.24Ns/m with aver-

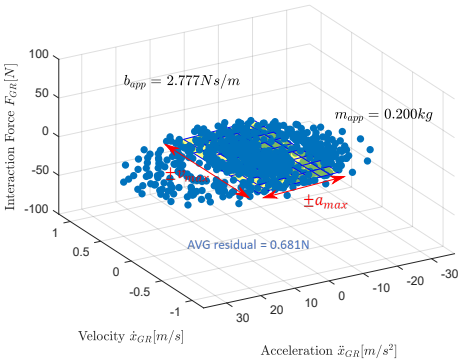
age residuals above 1N, while the impedance control with force feedback during transparency rendering reduced the apparent mass by 69.14% (to 0.20kg), the apparent damping by 88.54% (to 2.78Ns/m) and the residuals below 0.7N. The dynamic human-robot interaction movements achieved during the transparency rendering test reached large velocity and acceleration values close to or above the maximum velocity and acceleration of the actuated HandyBot (Figure 5.4.c). This indicates that the control allows the user, with little additional effort, to push the system above its limits, and that, despite reaching their saturation, the motors are still supporting transparency. A combination of $k_d = 25kN/m$ and $b_d = 0.02kN*s/m$ was selected to test the control fidelity in rendering a rigid contact. The virtual wall transition is shown in Figure 5.5 in comparison with the RHK [Metzger et al., 2012] and the commercially available Phantom Premium 1.5 [Massie and Salisbury, 1994]. Similarly to these devices, HandyBot can render transparency with resistances <1N but, as shown in Table 5.3, can reach a controlled stiffness accuracy of 94% compared to the accuracies of 92% and 80% of the RHK and Phantom Premium 1.5, respectively. Figure 5.6.a shows the KB plots for HandyBot and RHK in the grasping DOF [Metzger et al., 2012]. The maximum stable rendered stiffness k_d and damping b_d are 30kN/m and 0.1kNs/m for HandyBot, and 150kN/m and 1.55kNs/m for RHK, respectively. The estimates of the Z-width (i.e., area underneath the KB curve) of the two devices are 2.1 and $150.1kN^2s/m^2$, respectively. The KB plots of the forearm pronosupination and wrist flexion-extension DOF controlled via feedforward impedance control are shown in Figure 5.6.b and Figure 5.6.c, respectively. The maximum stiffness and damping in the pronosupination DOF are 17.5 Nm/deg and 0.075 Nm*s/deg for HandyBot, and 6 Nm/deg and 0.045 Nm*s/deg for RHK, respectively, while they are 0.4 Nm/deg and 0.0025 Nm*s/deg in the wrist flexion-extension DOF for HandyBot.

Table 5.3: Desired and achieved parameters for a virtual wall (shown in Figure 5.5) rendered in the grasping DOF of HandyBot, ReHapticKnob [Metzger et al., 2012], and Phantom Premium 1.5 [Massie and Salisbury, 1994].

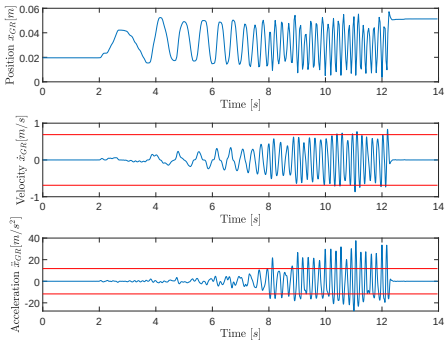
Device	**Desired virtual wall**		**Controlled stiffness**	**Controlled stiffness fidelity**
	k_d [kN/m]	b_d [N*s/m]	k_{ctrl} [kN/m]	$1-\frac{\lvert k_d-k_{ctrl}\rvert}{k_d}$
HandyBot (impedance control with force feedback)	25	20	26.47	0.94
ReHapticKnob (impedance control with force feedback)	50	50	54	0.92
Phantom Premium 1.5 (impedance control)	2	20	2.4	0.8



(a)



(b)



(c)

Figure 5.4: Transparency planes: user experienced transparency (apparent dynamics) during physical human-robot interaction in the grasping degree of freedom when HandyBot is uncontrolled (a), and when it is controlled via impedance control with force feedback (b) and perturbed with motion patterns shown in (c). Recorded force-motion trajectories (blue dots) are plotted over velocity and acceleration to indicate the damping and inertia components of the apparent impedance. A linear fit (yellow plane) and the identified model parameters of the apparent damping b_{app} and mass m_{app} allow a qualitative and quantitative comparison between the performance of the different control approaches. The plane size represents the range of maximum actuated velocity and acceleration reachable by HandyBot. The averaged (AVG) residuals indicate the fitting accuracy of the transparency planes.

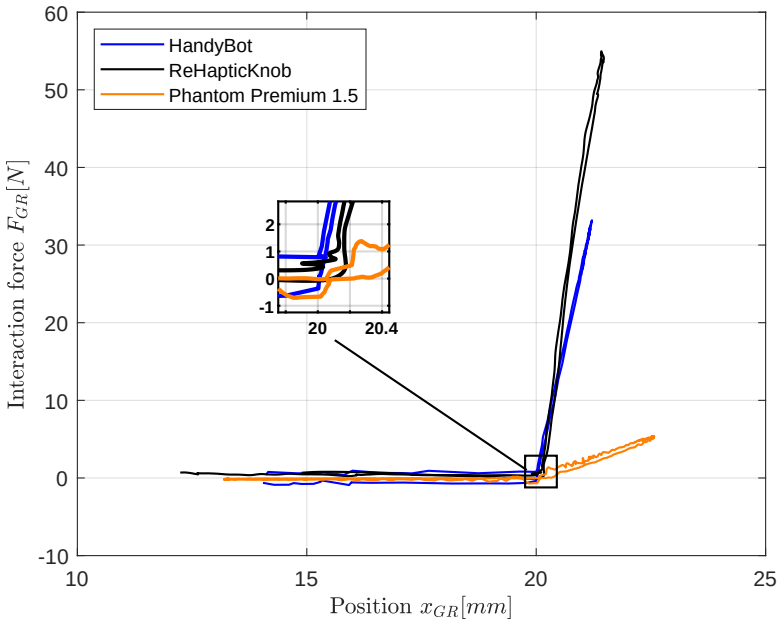
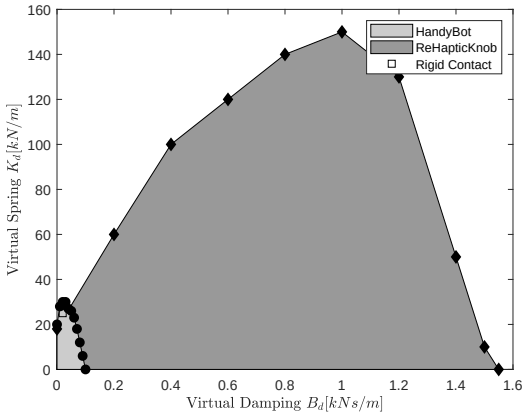


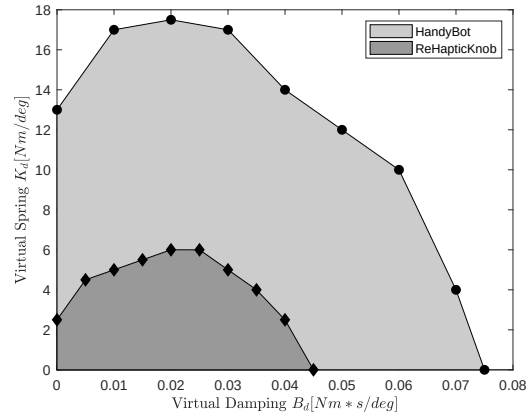
Figure 5.5: Rendering a virtual wall (unidirectional stiff spring-damper combination) with HandyBot (blue). The interaction with a virtual wall rendered with the ReHapticKnob (black, [Metzger et al., 2012]) and with the commercially available Phantom Premium 1.5 (orange, [Massie and Salisbury, 1994]) is shown for comparison.

5.3.2 Usability evaluation

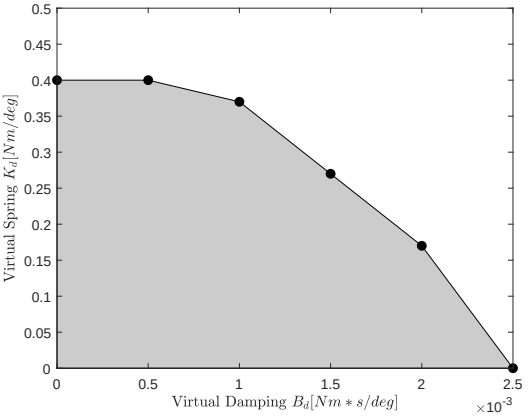
Four subjects (1 female, 3 male) in the chronic stage after an ischemic (3) or haemorrhagic (1) stroke (71.00(61.00-107.50) months post event) were eligible and agreed to participate in the study. The participant age was 64.50(62.50-67.00) and there were two right and two left hemisphere lesions, while all subjects were right-handed. Most subjects showed mild to moderate [Woytowicz et al., 2017] initial upper-limb impairment with a FMA-UE of 48.50(41.25-55.50) out of 66 points. During the minimally-supervised part of the study, the subjects could independently position their hand in the finger/thumb pads, and operate the device to start and perform the appropriate therapy exercises. No serious adverse event related to the use of the robot, nor any event that would put at risk the safety of the user was observed. However, one subject (FMA-UE of 39 out of 66) required external help in both exercises as they could not autonomously open the hand due to high hand muscle tone. Regarding the hardware, minor usability limitations were identified for all users. The 3D printed palm support and its strap fixation were too weak to maintain the hand and arm in place with respect to the device, which has a perceivable residual inertia (after impedance control) in the PS DOF. The issue with the straps led to difficulties for the users in maintaining their anatomical axes (i.e., mainly the forearm pronosupination axis) aligned with the respective robot axes. Moreover, the wrist FE actuator resulted to be too weak to maintain the hand in place during rapid pronosupination rotations in the Tunnel exercise, in which gravity directly acted on the wrist



(a)



(b)



(c)

Figure 5.6: KB plots: Stable desired spring-damper combinations renderable as rigid contact (described by 5.6) via impedance control with force feedback by HandyBot (K_f=5) or ReHaptic-Knob (K_f=10), in grasping (a), pronosupination (b) and flexion-extension (c, HandyBot only). The area underneath the curve (Z-width estimate) describes all the possible stable parameter combinations.

FE DOF. Regarding the software, the subjects had difficulties in understanding the rules of the WristCatch exercise mainly due to difficulties in perceiving haptic cues at the level of the wrist or coordinating grasping forces to not break the sphere while moving. HandyBot was ranked with a SUS score between OK and excellent (76.25(58.13-91.25) out of 100) and a learnability subscore of 11.25(9.38-13.75) out of 20, while the graphical user interface was ranked with a SUS score between good and excellent (85.00(73.75-91.25) out of 100) and a learnability subscore of 13.75(7.50-18.13) out of 20. The Tunnel and WristGrasp exercises were ranked with SUS scores between good and excellent (78.75(70.00-83.75) out of 100) and between OK and good (67.50(61.25-74.38) out of 100), and learnability subscores of 13.75(8.75-17.50) and 12.50(9.38-16.25) out of 20, respectively.

5.4 Discussion

5.4.1 The potential of a portable platform for minimally supervised therapy

This chapter presents the design, as well as performance and preliminary usability evaluations of HandyBot, a novel portable end-effector haptic device for minimally-supervised robot-assisted therapy of hand function after stroke. HandyBot builds on the sensorimotor robot-assisted therapy concept developed on two haptic devices, HapticKnob and ReHapticKnob, whose efficacy was successfully validated in clinical environments when used by subjects after stroke either with [Ranzani et al., 2020, Lambercy et al., 2011]. HandyBot strives to provide a similar therapy platform (i.e., end-effector haptic device with user interface and sensorimotor therapy exercises) than the one previously validated on the RHK [Ranzani et al., 2021], and to extend it to use in different environments (e.g., start in the clinic and continue at home), to further promote minimally-supervise use. This would allow to complement conventional therapies, and increase therapy dose and subject autonomy.

5.4.2 HandyBot is compact and demonstrates good performance

HandyBot is significantly more compact and portable than HK and RHK, and still allows to actively train grasping and forearm pronosupination, and an additional movement (i.e., wrist flexion extension), following the same validated sensorimotor therapy concept [Metzger et al., 2014b, Lambercy et al., 2011]. Excluding hand gloves and exoskeletons, only few powered portable devices focus on the training of hand function [Pezent et al., 2017, Tong et al., 2015, Khor et al., 2014, Hesse et al., 2008] and allow to actively assist/resist the patient movements and/or to reproduce sensorimotor therapy tasks. Compared to these portable devices and its non-portable predecessors, HandyBot maintains similar performance in terms of workspace, dynamics and sensing, despite achieving a significant cost reduction with respect to the RHK (i.e., price above 40000 euro). Respecting therapy and biomechanical requirements, the robot workspace has been adapted to now allow for smaller minimum grasping apertures for fine object manipulation, while it is similar for PS and FE. Maximum achievable movement/force

dynamics and sensor resolution are in the same order of magnitude of the other devices except for PS, which achieves slightly lower accelerations and has an increased static friction, probably due to the high weight and inertia of the metal L-shape structure necessary to align the robotic wrist FE axis with the user anatomical axis. Such high weight and inertia reduce the device acceleration and exert a high unidirectional load on the rotational bearings of joint J_1, generating friction. Maximum generated grasping forces are in line with other rehabilitation devices [Lambercy et al., 2007, Yeong et al., 2009] except for the RHK, which achieves a range of maximum forces that is not needed in the therapy exercises and in ADL [Lambercy et al., 2007]. While PS can achieve torques higher than average [Pezent et al., 2017, Khor et al., 2014, Yeong et al., 2009], the FE DOF achieves maximum torques that, after overcoming the robot inertia, only allow to assist/resist/perturb the user's movements, but cannot passively hold the limb of the user in different positions particularly against gravity (i.e., when the user is in extreme pronation or supination positions).

Through a single low-cost force sensor, HandyBot allows to maintain good haptic control performance in terms of rigid contact rendering fidelity, and span between maximum achievable impedances and transparencies, particularly at the level of hand grasping, which is characterized by the finest sensorimotor control of the human body [Röijezon et al., 2017, Radman, 2013].

The transparency rendering performance is better than the RHK, achieving a quarter of the apparent mass (i.e., 0.2 kg compared to 0.8 kg in RHK) and similar apparent damping (i.e., 2.78 Ns/m compared to 2.7 Ns/m in RHK). The accuracy in rendering high stiffnesses/impedances is also better than the Phantom Premium 1.5 and RHK, but the range of maximum achievable impedances (i.e., K, B, Z-width) is lower in GR when compared to the RHK. Still, the range of impedances that can be rendered is sufficient for the available therapy exercises [Metzger et al., 2014b].

The differences in impedance rendering between HandyBot and RHK could be explained by the lower quality of the low-cost components of HandyBot (e.g., force sensor in GR), which may negatively affect the control performance, and by the nature of their mechanical transmissions. A geared transmission (e.g., gearboxes and/or timing belts, as in the case of RHK and PS in HandyBot) allows to stably render a wide range of impedances, but significantly increases size, weight and inertia of end-effector designs, proportionally to the number of DOF. Additionally, it can reduce transparency mainly due to backlash and/or high gear ratios. A cable transmission (GR and FE in HandyBot) has instead the potential to reduce the size, weight and inertia of the end-effector, improve transmission transparency, but it can reduce the range of stable renderable KB combinations depending on the level of cable tensioning, which alters the friction in idler pulleys, on the mismatch in cable tensioning within a transmission chain, which generates cable vibration/resonance similarly to backlash, and on the elasticity of the mechanical structures, all factors that contribute to the instability of the system [Posa et al., 2015, Lu and Fan, 2013, Bottin et al., 2020]. Furthermore, in GR, HandyBot has approximately a 3:1 gear ratio, which is four time less compared to the 12:1 gear ratio of the RHK with the

same motor. This significantly reduces the maximum range of impedances that HandyBot can render in GR. On the contrary, in PS, HandyBot has a higher gear ratio of 21:1 compared to the 14:1 gear ratio of the RHK, which may contribute to the higher impedances rendered by HandyBot despite differences in, for examples, actuators (i.e., the RE35 90W Maxon motor used in RHK is slightly less powerful than the RE40 150W Maxon motor used in HandyBot) and end-effector inertia (i.e., higher in HandyBot).

5.4.3 The platform is safe and maintains the positive usability of ReHapticKnob

We achieved promising positive usability results with our therapy platform, showing that HandyBot is usable with minimal supervision and learnable during a first exposure. After a supervised instruction phase, our test tried to emulate minimally-supervised therapy conditions in which the therapist intervened only in case help was required by the subject, as done in under minimally-supervised training in clinical settings [Hyakutake et al., 2019, Lemmens et al., 2014, Sivan et al., 2014]. Throughout the test, the therapist intervention was only required for one subject that had an increase in hand muscle tone during the experiment. Robotic assessments incorporated into the therapy exercises could allow to monitor hand muscle tone throughout the therapy, to avoid negative consequences such as pain that could affect recovery [Ranzani et al., 2019]. The device respects safety norms for medical devices, as well as ergonomics and adaptability design requirements, and did not show safety-related problems. Minimization of issues requiring external intervention and safety are fundamental for the use of the therapy platform in the home environment, where supervision is not always available or would require additional communication channels (e.g., telerehabilitation [Wolf et al., 2015]). The usability results of HandyBot, GUI and Tunnel exercise are between good and excellent (i.e., approximately between 70 and 90 out of 100), which is aligned with the usability results achieved when using the RHK with minimal supervision [Ranzani et al., 2021], meaning that the change of device did not affect the user experience during therapy. The WristGrasp exercise obtained lower but positive usability scores (i.e., above "OK"), probably associated with the difficulty of the exercise, which requires good sensorimotor functions to hold the glass sphere without breaking it or to identify target wrist flexion-extension positions based on haptic cues. The usability results are positively aligned with other technology-assisted therapy platforms [Sivan et al., 2014, Pei et al., 2017, Chen et al., 2015, Smith et al., 2015], although only one of these assessed the SUS with an average score of 71.8 out of 100 [Pei et al., 2017].

5.4.4 Necessary improvements

Our evaluation allowed to identify important design improvements that should be considered before testing the device in real-world minimally-supervised conditions (e.g., home). Hand/arm supports and maximum torques generated at each DOF (e.g., FE) should be optimized to allow precise control of the limb positioning (e.g., avoid compensatory movements) and prevent misalignments between anatomical and robot joints, which could obtrude the movements of the subject in positions that are at the limit of the robot workspace. Completely

eliminating these issues is a challenge, particularly in an end-effector device when patients try to control multiple DOF simultaneously. Therefore, exercises that train maximum two DOF simultaneously should be considered with an end-effector approach. Furthermore, as recommended in literature [Perfetti and Grimaldi, 1979], to avoid visual compensation in solving sensorimotor therapy tasks, the hand of the subject should be covered during therapy.

5.4.5 Limitations

Our preliminary usability results should be interpreted with respect to the small sample size tested, although this size can be considered sufficient to identify the major usability challenges of the platform [Virzi, 1992]. However, the results should be further validated over a longer time horizon and in real-world minimally-supervised conditions (e.g., in the home environment), to verify the feasibility of this therapy approach, how the subject could learn to use the system, and if their motivation to use the device would eventually drop.

5.5 Implications and outlook

Our positive performance results in terms of haptic rendering and usability, with the same minimally-supervised therapy framework than the RHK, open the door to the use of HandyBot in different settings (e.g., clinic or home) after an appropriate supervised learning period in the clinic. This could help increase therapy dose for the patients and reduce limb non-use after discharge, decrease therapy-associated costs (e.g., therapist time during minimally-supervised use in the clinic) and progressively increase patient independence in daily-life settings. Future investigations should verify the feasibility and usability of our portable therapy platform within a clinical trial in home settings. To make the step into the home environment, clear protocols will have to be defined to decide when the patient is ready to perform such training at home and how family members and therapists should be instructed to assist the patient (when needed). Once this is established, it will be important to perform cost-utility analyses to quantify the benefits in cost and therapy outcomes of this novel robot-assisted therapy approach.

6 General discussion

The potential of robot-assisted therapy for neurorehabilitation of the upper-limb after stroke is established in research and industry [Maciejasz et al., 2014]. Among several positive features, one of the most exciting opportunities of robot-assisted therapy could be to increase therapy dose (i.e., number of exercise repetitions per time unit and therapy time), which is often considered insufficient in clinical practice and after discharge, especially with respect to hand function [Lambercy et al., 2018, Qiuyang et al., 2019, Gillen, 2015]. Unfortunately, currently available robotic devices for rehabilitation of hand function are not exploited at their maximum potential. On the one hand, they require constant supervision of trained personnel, which contributes to a cost increase and limits the maximum dose achievable using this technology. On the other hand, they are only used to perform selective types of training (e.g., pure motor therapy) that neglect important functions for the hand, such as somatosensation and cognition [Veerbeek et al., 2017, Bertani et al., 2017, Aprile et al., 2020, Fasoli and Adans-Dester, 2019].

This work aimed at evaluating whether robot-assisted therapy of hand function following a sensorimotor therapy approach is feasible and produces equivalent therapy outcomes compared to dose-matched conventional care. This served as necessary basis to investigate and develop the elements necessary to create a portable robot-assisted therapy platform (i.e., a haptic device to train hand and forearm function, a patient-centered user interface and a battery of therapy exercises and assessments), which could offer the same therapy approach with minimal supervision and potentially enable a therapy dose increase in different environments (e.g., clinic, home). To achieve this goal, the following steps were undertaken.

First, a robotic platform and therapy concept were developed and the equivalence of robot-assisted and dose-matched conventional therapy was established in supervised conditions in a randomized controlled trial with 27 inpatients in the subacute stage after stroke. This necessary result opened the way to use such platform to complement conventional care with non-inferior therapy outcomes.

Second, to increase therapy dose, physical and graphical user interface and therapy exercises

have been redesigned to be usable with minimal supervision, and their usability was verified in a pilot study with ten chronic stroke patients.

Third, to increase safety and monitor unforeseen adverse events (e.g., abnormal increase in hand muscle tone) without supervision, novel concepts for online monitoring based on robotic metrics collected during therapy exercises were proposed and tested in five unimpaired subjects and five subjects after chronic stroke.

Finally, to allow the use of the therapy platform in different environments (e.g., at home), a novel compact, scalable and portable haptic device training grasping, forearm pronosupination and wrist flexion-extension was developed and preliminarily tested with minimal supervision on four subjects after chronic stroke using the developed user interface and therapy exercises. The usability insights from the pilot study allowed to identify usability challenges that led to the development of a second improved portable device.

6.1 Neurocognitive robot-assisted therapy of hand function is feasible and results in equivalent recovery

It has been shown that focusing therapy on task-oriented sensorimotor interactions and cognitive tasks Jayasinghe [2019], Chen et al. [2018], French et al. [2016], Yoo and Park [2015a], Aprile et al. [2020], Fasoli and Adans-Dester [2019], as well as increasing therapy dose [Ward et al., 2019, Schneider et al., 2016, McCabe et al., 2015], are important strategies to promote recovery. In our robot-assisted platform, we decided to establish a therapy concept following the neurocognitive therapy approach proposed by Perfetti [Perfetti and Grimaldi, 1979]. We selected this therapy approach since it is one of the few therapy approaches strongly focused on somatosensation and cognition, based on their importance for hand function and on strong neurophysiological assumptions. The method supports a therapy progression from sensory tasks (e.g., identify hand/finger positions without watching) to multi-DOF sensorimotor tasks (e.g., perform 3D manipulations), and requires constant cognitive involvement (e.g., memorize, correct, identify a gesture) to progressively reteach the patient how to analyze, plan and execute a task and progressively regain autonomy.

With our RCT, we could show for the first time that neurocognitive robot-assisted care is feasible and can complement conventional care achieving equivalent dose-matched therapy outcomes. Unlike the majority of the clinical studies in literature [Lang et al., 2015], our study respected an accurate definition, reporting and matching of dose (i.e., total scheduled therapy time, frequency over sessions/days/weeks, number of repetitions per effective exercise time, clear definition of a task repetition). Our approach goes beyond the movement practice proposed by most robot-assisted hand therapy devices [Lambercy et al., 2018, Lum et al., 2012]. Our structured sensorimotor therapy plan takes advantage of the capabilities of robotic technology (e.g., assessment accuracy, haptic rendering, therapy adaptability, engagement), while training dynamic interactions with the environment, which are essential hand functions

[Kamper, 2016]. Showing equivalence in therapy outcomes required extensive resources (i.e., more than 860 hours of supervised robot-assisted or conventional neurocognitive therapy performed by 27 inpatients) and represents an important contribution of this thesis, as it is a necessary step to demonstrate the therapy effects (per dose unit) that can be safely achieved with our technology, and support its further exploitation. In fact, the potential of robotic technologies is wider and should be further explored to achieve, for instance, higher therapy dose [Duret et al., 2019, Pila et al., 2017, McCabe et al., 2015], which were not allowed by our study design.

6.2 Minimally-supervised therapy is possible with a robotic therapy platform

A dose increase could be achieved when robot-assisted therapy is used with minimal supervision to complement conventional care, as recently shown in literature with self-directed exergaming [Broderick et al., 2021]. Based on this assumption, we collected patient and therapist inputs and started a user-centered redesign of our therapy platform (i.e., ReHapticKnob with physical/graphical user interface and therapy exercises). We could successfully show that the redesigned platform is usable with minimal supervision in controlled settings, while maintaining the same therapy approach. This is important to establish a continuum of care that could start in the clinic and continue after discharge in different environments (e.g., home), facilitating a dose increase in the long term. Additionally, through these pilot usability tests, we could early identify further technical challenges and, before the end of the thesis, already correct them within a new design iteration.

In the hardware, we made the finger pads wider and more ergonomic to reduce finger slippage [Metzger, 2014, Ranzani et al., 2020], symmetrical to allow left and right hand use and scalable in five male (or female) anthropometric sizes [Chengalur et al., 2004, Buryanov and Kotiuk, 2010]. We also inserted new covers (e.g., of the mechanical transmissions) to avoid snag hazards. The virtual reality screen was fixed in a predefined position to guarantee correct virtual reality scaling and prospective, and its function to cover the user hand was substituted by an adjustable hand cover. An optical fingerprint reader was added to simplify user login, such that patients with memory problems do not have to remember a password. Furthermore, we increased the number of buttons in the pushbutton keyboard to allow a logical color-function and color-object mapping in all the interfaces (e.g., green always for confirmation buttons, red always for exit/emergency buttons), as recommended by Norman [2013] and the IEC 60601-1:2005 [Commission et al., 2005]. The resulting therapy platform is shown in Figure 6.1.

In the software, the appearance of the graphics, consistency and clarity of instructions/feedbacks, and matching between virtual and real-world tasks were improved in all the graphical user interfaces and exercises. A new framework (i.e., template with a library of predefined functions) was developed in Unity (C#) to allow easy and rapid creation/customization of

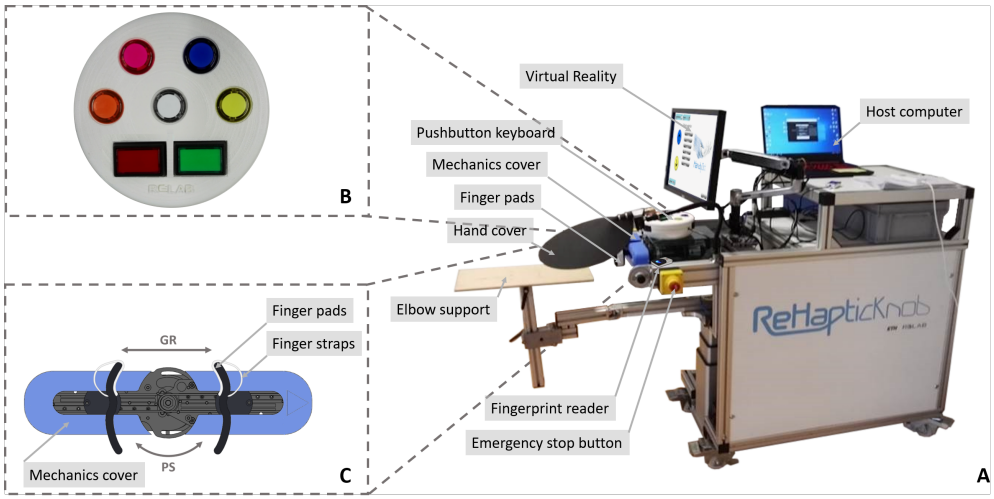


Figure 6.1: (A) Latest design of the ReHapticKnob platform for minimally-supervised therapy of hand grasping (GR) and forearm pronosupination (PS). The user can login into the platform via an optical fingerprint reader, and interact with graphical interfaces and exercises via a new pushbutton keyboard (B). The user arm is positioned on the elbow support, while thumb and index and middle fingers are inserted into symmetrical finger pads with straps (C). To reduce the risk of snag hazards, plastic covers isolate the mechanical transmission. The virtual reality screen is placed in a fixed position, while the patient hand can be covered via an adjustable hand cover.

additional exercises or functionalities. Furthermore, thanks to this framework, the platform can be used on different devices (e.g., on RHK or on the new portable devices) and automatically performs anonymized data storage and/or retrieval (e.g., of received therapy dose). Additionally, in the therapist panel, we added the possibility to simplify the graphical content of the therapy exercises (e.g., remove environment and leave only objects necessary for the exercise) for subjects with attention or cognitive deficits. Based on the successful proof of concept with our new minimally-supervised exercises, we redesigned the therapy exercises tested in our RCT ([Metzger et al., 2014b]) to make them usable with minimal supervision and improve their difficulty adaptation when needed Ranzani et al. [2020]. Summary descriptions of the currently available exercises in our therapy platform are shown in Figure 6.2 (grade 1 exercises, which train attention and conscious perception), Figure 6.3 (grade 2 exercises, which train attention, conscious perception and single-DOF movements), and Figure reffig:Figure2c (grade 3 exercises, which train multi-DOF actions requiring complex sensorimotor control). All the exercises follow a patient-tailored adaptation from the first exercise session based on three baseline robotic assessments, which assess grasping and pronosupination ROM (aROM), proprioception (i.e., assessing the just noticeable difference (aJND) in length discrimination) and haptic perception (i.e., assessing smallest detectable stiffness difference expressed as Weber fraction (aWF)). More details on the proposed assessment-driven therapy concept can be found in Metzger et al. [2014b].

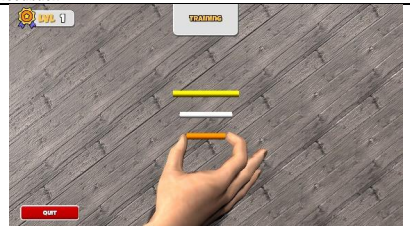
6.3 Online monitoring of the patient condition is necessary for customization, safety and research

Our therapy platform presents assessment-driven algorithms that allow to replace one important part of the therapist supervision, related to the execution and adaptation of single therapy exercises. Moreover, the software safety features implemented in our device (e.g., to detect sensor errors, or abnormal forces/movements) and our positive preliminary usability tests, seem to demonstrate that the platform can be safely used. However, these features do not replicate the same high-level control that a therapist could perform during therapy, particularly in the event of adverse situations. During minimally-supervised therapy, unforeseen events or changes (e.g., in patient health conditions or device functioning) could significantly compromise the therapy outcomes and patient safety. To overcome these limitations, it is of utmost importance to introduce new autonomous monitoring algorithms.

We started the evaluation of autonomous monitoring strategies from a online muscle tone monitoring method, which takes advantage of the robot ability to physically interact with the patient in a controlled way. Through this method, we could successfully demonstrate that it is feasible to automatically assess and keep track of patient conditions during therapy. This proof of concept seems to suggest that other abilities of a robotic device, such as performing online robotic assessments that require physical interaction, could become fundamental in minimally-supervised therapies in two ways. First, they could detect the onset of adverse events or variations in patient health conditions (e.g., abnormal muscle tone changes, fainting, worsening in patient pathology). This could be used to trigger an automatic reaction of the platform ranging from tailoring the therapy plan/exercises, to undertaking emergency actions (e.g., emergency calls external intervention) in case of severe problems. Second, they could be used to continuously monitor the patient progress over time. This could serve as basis to significantly extend the amount of information on the impairment evolution, which could be used in research to investigate neurophysiological recovery processes. During the PhD, we worked on three monitoring strategies: online muscle tone monitoring, online haptic perception assessment, and precision grip control assessment. The first two are applicable online within the therapy exercises (e.g., on a trial-by-trial basis, or on a block-by-block basis), while the last is a standalone assessment that can be applied less frequently (e.g., on a session-per-session basis, or more rarely). The frequency at which the monitoring strategy is applied depends on the biomarker measured (i.e., a measurement of muscle tone abnormalities or safety-critical conditions should take place more frequently compared to a functional measurement such as the grip control assessment) and on the practicability of the assessment strategy chosen within the execution of a therapy exercise. Embedding a monitoring strategy online inside a therapy exercise could allow to maintain higher levels of motivation compared to standalone assessments and allows faster reactions to unexpected changes, which are particularly critical in minimally-supervised settings.

<table>
<tr><th colspan="5">Grade 1
Exercises focused on attention and conscious perception (i.e., tactile perception, proprioception) to recover sensory deficits and control of muscle stretch reactions. No motor training.</th></tr>
<tr><th>Exercise description</th><th>Visual feedback</th><th>Difficulty levels</th><th>Performance</th><th>Difficulty adaptation</th></tr>
<tr>
<td>Bars
(Proprioception: passive grip aperture identification)

3 blocks i, including:
<u>Training:</u> The robot moves the hand at least twice to N different target apertures (within the linear aROM) that differ by δd increments. The patient needs to memorize which colour corresponds to which position.

<u>Test (3min):</u> The robot opens the hand to one of the learned apertures (randomly selected), and the patient needs to select the corresponding colour (i.e., pushing the corresponding button on the pushbutton keyboard).</td>
<td> 
N bars indicate the N grasping apertures that differ by δd mm. A virtual hand is shown only in Training to simplify task explanation and embodiment. Identification feedback: a green halo (correct ans.) or a red halo (wrong ans.) is displayed on the selected bar with a correct/wrong sound, while remaining bars become semitransparent. If selected bar is wrong, correct bar appears blinking.</td>
<td>5 difficulty levels L, which scale:

• Number of target apertures
N = {3,4,4,5,5}

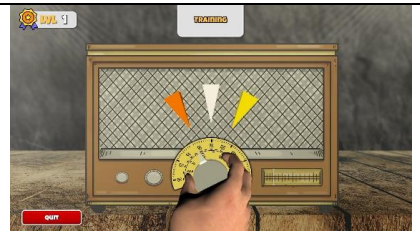
• Target aperture difference
δd = {4.8,4.4,4.0,3.6,3.2}*aJND/IF_{bar}

aJND = baseline distance JND assessment limited to the range [2,10]mm

IF_{bar} = intelligent factor of this exercise
Default =1
Range = [0.1 and 2] (increments of 0.1)

Max aperture scaled to be within aROM</td>
<td>P_i = percentage of correct identification trials (in therapy block i)</td>
<td rowspan="2">$L_{i+1} = \begin{cases} L_i + 2 & P_i = 100\% \\ L_i + 1 & 70 \le P_i < 100\% \\ L_i & 40 \le P_i < 70\% \\ L_i - 1 & 10 \le P_i < 40\% \\ L_i - 2 & 0 \le P_i < 10\% \end{cases}$</td>
</tr>
<tr>
<td>Arches
(Proprioception: passive pronosupination angle identification)

3 blocks i, including:
<u>Training:</u> The robot moves the hand at least twice to N different target angles (within the rotational aROM) that differ by δφ increments. The patient needs to memorize which colour corresponds to which angle.

<u>Test (3min):</u> The robot moves the hand to one of the learned angles (randomly selected), and the patient needs to select the corresponding colour (i.e., pushing the corresponding button on the pushbutton keyboard).</td>
<td> 
N triangles indicate the N target angles that differ by δφ °. A virtual hand and a radio knob shown only in Training to simplify task explanation and embodiment. Identification feedback: a green halo (correct ans.) or a red halo (wrong ans.) is displayed on the selected triangle with a correct/wrong sound, while remaining triangles become semitransparent. If selected triangle is wrong, correct triangle appears blinking.</td>
<td>5 difficulty levels L, which scale:

• Number of target apertures
N = {3,4,4,5,5}

• Target aperture difference
δφ = {30°,25°,20°,15°,10°}/IF_{arc}

IF_{arc} = intelligent factor of this exercise
Default =1
Range = [0.1 and 2] (increments of 0.1)

Max angles scaled to be within aROM</td>
<td>P_i = percentage of correct identification trials (in therapy block i)</td>
</tr>
</table>

Figure 6.2: Grade 1 neurocognitive patient-tailored exercises: detailed description. These exercises are focused on attention and conscious perception (i.e., tactile perception, proprioception) to recover sensory deficits and control of muscle stretch reactions during 1-DOF movements, without requiring any active motor control. In all the grades, the exercise difficulty is adapted from the first therapy session based on a set of robotic assessments, and at the end of each exercise block based on patient performance. The "clinical artificial intelligence" can be used to vary the intelligent factors IF and correct the difficulty levels in case they reach upper or lower saturation.

Grade 2

Exercises focused on attention, conscious perception, and motor control of few motor units (e.g., 1DOF movements) to recover haptic perception and basic voluntary control of motor efferencies in simple (2D) motor tasks.

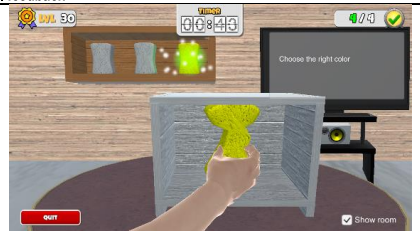
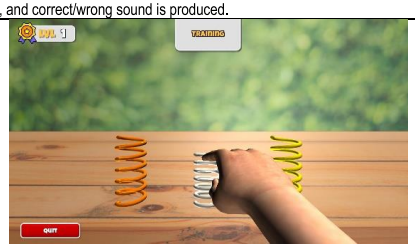
Exercise description	Visual feedback	Difficulty levels	Performance	Difficulty adaptation
Sponges (Haptic perception: stiffness identification during grasping) Blocks *i*, including: Training: The robot renders 3 sponges (different spring-damper combinations) on a shelf, and proposes each of them twice to the patient. The patient needs to squeeze them and memorize which color corresponds to which resistance. Stiffness and damping pairs vary by WF percent from one to another. Test: The robot randomly presents a virtual sponge in a black box. The patient needs to feel the resistance by grasping the virtual sponge and then identify the right color (i.e., selected via the pushbutton keyboard).	 N sponges are displayed on a shelf, and either of them is presented to the patient (hidden in a box during Test). *Identification feedback*: the box opens to show the sponge inside. On the shelf, a green halo (correct ans.) or a red halo (wrong ans.) is displayed on the selected sponge with a correct/wrong sound, while remaining sponges become semitransparent. If selected sponge is wrong, correct sponge appears blinking.	Approximately 100 levels L, which scale: • Relative stiffness/damping difference between the sponges *s*, expressed as Weber Fraction (WF) $K(s,i) = f(WF_i) * K_{medium}$ $B(s,i) = f(WF_i) * B_{medium}$ $f(WF_i) = \begin{cases} (1 + WF_i)^{-1} & s = 1 \\ 1 & s = 2 \\ 1 + WF_i & s = 3 \end{cases}$ WF is initially 0.8 for all patients, and is adapted online using Parameter Estimation by Sequential Testing (PEST) depending on patient performance [Taylor & Creelman, 1967]	Performance in PEST is a function of number and sequence of correct identification trials with respect to the total trials	L_i = (1-WF)*100 WF updated after each block following Parameter Estimation by Sequential Testing (PEST) [Taylor & Creelman, 1967]
Neon (Sensorimotor memory: teach and reproduce grip aperture) 3 blocks *i* of 3 minutes, including repetitions of: Teach: The robot moves the patient's hand from an initial open position (within the linear aROM) to a randomly selected target grasping aperture d_T. This position is kept for 2 seconds, then the robot opens the hand to the initial position. Reproduce: The patient has to actively close the hand back to the target position taught in the teach phase, and confirm the selection either by holding the position for 2 sec or pressing the green pushbutton. A trial is correct if the selected position lies within the error band [d_T-δe/2, d_T+δe/2]. A damped force field B helps to smoothen the movement of the patient.	 A neon of varying length indicates the target position in the Teach phase. In the Reproduce phase, the neon is fully covered by a strong light and the virtual hand representing the patient disappears. *Reproduce feedback*: The strong light disappears, revealing the actual neon length with respect to the selected hand position. The neon lights up in green if the trial was correct, or red if the trial was wrong, and correct/wrong sound is produced.	5 difficulty levels L, which scale: • Error band δe = {2.4,2.2,2.0,1.8,1.6}*aJND/IF_{neo} • Damping support: B = {1.2,1.1,1.0, 0.9,0.8}*0.7kNs/m aJND = baseline distance JND assessment limited to the range [2,10]mm IF_{neo} = intelligent factor of this exercise Default =1 Range = [0.1 and 2] (increments of 0.1) Initial position scaled to be within aROM	P_i= percentage of correctly reproduced apertures (in therapy block *i*)	$L_{i+1} = \begin{cases} L_i + 2 & P_i = 100\% \\ L_i + 1 & 70 \le P_i < 100\% \\ L_i & 40 \le P_i < 70\% \\ L_i - 1 & 10 \le P_i < 40\% \\ L_i - 2 & 0 \le P_i < 10\% \end{cases}$
Springs (Haptic perception: stiffness identification during pinching) 3 blocks *i*, including: Training: The robot renders N springs (different spring-damper combinations) and proposes each of them twice to the patient. The patient needs to pinch them vertically and memorize which color corresponds to which resistance. Stiffness and damping pairs vary by η percent from one to another. Test (3min): The robot presents a single grey (neutral) spring. The patient has to feel the resistance by actively pinching the virtual spring, and identify the right color (i.e., selected via the pushbutton keyboard).	 All N springs are displayed during Training and animated on a table by a virtual hand representing the patient to simplify task explanation and embodiment. In Test, only a single grey spring is animated in the middle of the table, without the hand. *Identification feedback*: a green halo (correct ans.) or a red halo (wrong ans.) is displayed on the neutral spring, which turns from grey to its color, and a correct/wrong sound is produced.	5 difficulty levels L, which scale: • Number of springs N = {3,4,4,5,5} • Relative difference between viscoelasticities η = {2.4,2.2,2.0,1.8,1.6} *aWF/IF_{spr} aWF = baseline stiffness WF assessment IF_{spr} = intelligent factor of this exercise Default =1 Range = [0.1 and 2] (increments of 0.1)	P_i= percentage of correct identification trials (in therapy block *i*)	

Figure 6.3: Grade 2 neurocognitive patient-tailored exercises: detailed description. These exercises are focused on attention, conscious perception, and motor control during simple (2D) motor tasks.

Grade 3

Exercises focused on generalizing the sensorimotor skills acquired in grade 1 and 2 to achieve fine control of multi-DOF sensorimotor actions in terms of timing, positioning and intensity

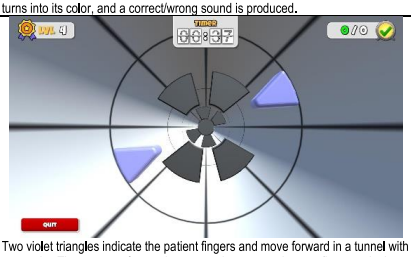
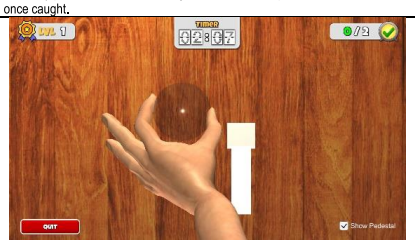
Exercise description	Visual feedback	Difficulty levels	Performance	Difficulty adaptation
Spheres (Haptic perception and motor function: synchronous forearm rotation and object catching, stiffness identification during grasping) 3 blocks *i*, including: Training: The robot renders N spheres (different spring-damper combinations) and present each of them twice to the patient. The patient needs to squeeze them and memorize which color corresponds to which resistance. Stiffness and damping pairs vary by η percent from one to another. Test (3 min): One neutral sphere at a time falls down from the top of the screen. The patient needs to align the orientation of the hand to the trajectory of the sphere to catch it. Once caught, the patient has to squeeze the sphere and identify the right color (i.e., selected via pushbutton keyboard).	 N spheres are displayed during Training, and either of them is proposed for squeezing to the patient virtual hand. In Test, the patient moves the virtual hand to catch a falling neutral sphere and squeeze it. *Identification feedback*: a green halo (correct ans.) or a red halo (wrong ans.) is displayed on the sphere, which turns into its color, and a correct/wrong sound is produced.	10 difficulty levels L, which scale: • Number of spheres N = {3,3,4,4,4,4,5,5,5,5} • Relative difference between viscoelasticities η = {2.4,2.3,2.2,2.1,2.0,1.9,1.8,1.7,1.6,1.5} *aWF/IF_{sph} aWF = baseline stiffness WF assessment IF_{sph} = intelligent factor of this exercise Default =1 Range = [0.1 and 2] (increments of 0.1)	P_i= percentage of correct catch&identify trials (in therapy block *i*)	$L_{i+1} = \begin{cases} L_i + 2 & P_i = 100\% \\ L_i + 1 & 70 \le P_i < 100\% \\ L_i & 40 \le P_i < 70\% \\ L_i - 1 & 10 \le P_i < 40\% \\ L_i - 2 & 0 \le P_i < 10\% \end{cases}$
Tunnel (Haptic perception and motor function: synchronous forearm rotation and grasping, haptic perception of notches (rotational), avatar stiffness or barrier collision (linear), viscosity (both DOF)) 10 blocks *i* of 1 min, including: Test: The patient needs to navigate two triangles through a tunnel without touching the grey obstacles, which are randomly presented. To avoid them, the patient has to open or close the fingers and to rotate the forearm. In terms of haptic perception, the diameter of the tunnel is constrained by the aROM with virtual walls. A viscous field (with damping η) resisting any movement is randomly applied inside the tunnel and varies between tunnel segments to challenge the stabilization of hand movements during navigation. A notch (i.e., converging force field with force constant k) in the rotational DOF indicates the correct forearm rotation φ to overcome an obstacle. A vibration in the linear DOF is generated once a collision with an obstacle is detected.	 Two violet triangles indicate the patient fingers and move forward in a tunnel with a speed v. Three types of grey obstacles exist: center-obstacle (i.e., wall in the center, passed if the fingers are open), circle-obstacle (i.e., circular barrier outside, passed only if the fingers are closed), any-obstacle (i.e., obstacle can be passed either in the center or outside). The outer opening in the center- and any-obstacles is centered around the rotational position φ and has an amplitude δ. *Identification feedback*: If the obstacle is passed, it becomes transparent, otherwise it becomes red with a wrong sound during collisions. Floating coins are randomly placed in the tunnel and generate additional points and a correct sound once caught.	10 difficulty levels DL=L/10, which scales: • Triangles velocity v = min_v + (max_v-min_v)*DL*IF_{tun} • Target position φ φ = min_φ + rand(0,1)*(max_φ-min_φ) *Note: max_φ and min_φ are f(RF). RF = min_{RF} + (max_{RF}-min_{RF})*DL* *RF [0.75,1.1] is the aROM fraction within which the patient's fingers can move* • Obstacle aperture amplitude δ δ = ($aROM_{PS,max}$-$aROM_{PS,min}$)* rand($min_{barrierRange}$, $max_{barrierRange}$) *Note: min and $max_{barrierRange}$ are ∝DL and ∝(IF_{tun}^{-1})* • Notch intensity k = min_k + (max_k-min_k)*(1-DL) • Tunnel viscosity η = min_η + rand(0,1)*(max_η-min_η)*DL forced position FP∝(DL) are the rates at which circle-obstacles • Obstacle type *Note: Forced position FP∝(DL) is the rate at which either center-obstacles or circle-obstacles are presented. Center fraction CF∝(1-DL) is the ratio of center-obstacles.* IF_{tun} = intelligent factor of this exercise Default =1, Range = [0.1 and 2] (increments of 0.1)	P_i= percentage of obstacles passed without collision (in therapy block *i*)	
Glass (Haptic perception and motor function: synchronous wrist flexion-extension (FE) and grasping), haptic perception of notches (wrist FE), sphere stiffness (grasping) 3 blocks *i*, including: Test (3min): the robot presents a glass sphere at a fixed starting position. The patients has to grasp the sphere, adjusting the grasping force so that the sphere neither breaks nor falls. The patient has to flex the wrist to move the sphere and place it on the pedestal, which is located at a random position d_φ within the flexion-extension aROM of the patient. The pedestal is invisible, but two haptic cues (converging force fields separated by δe degrees) indicate its outer edges. The sphere has to be released between the two cues, otherwise it will fall and break. A trial is correct if the selected position lies within the error band [d_φ -δe/2, d_φ +δe/2]. The intensity of the force field is represented by the constant k. A damped force field B helps to smoothen the flexion-extension movement of the patient.	 A transparent sphere is presented to the patient, who can grasp it and move it by flexing the wrist towards an invisible pedestal. *Identification feedback*: the pedestal appears. If it is identified correctly, the sphere turns green and a "correct" sound is generated. If it is not identified correctly, the sphere falls. In this case, or if the hand squeezes beyond x [mm], the sphere breaks with a crashing sound.	5 difficulty levels L, which scale: • Error band δe = {6,5,4,3,2}° • Damping support B = {1.0,0.75,0.5, 0.25,0.0} kNmms/° • Force field intensity k = {0.22,0.18,0.14,0.10,0.06} Nmm/° • Sphere breaking penetration x = 1.2*{10,8.33,6.67,5,3.33}*aWF/IF_{gls} mm aWF = baseline stiffness WF assessment IF_{gls} = intelligent factor of this exercise Default =1 Range = [0.1 and 2] (increments of 0.1) Target positions d_φ scaled to be within aROM	P_i= percentage of spheres correctly placed on the pedestal without breaking (in therapy block *i*)	

Figure 6.4: Grade 3 neurocognitive patient-tailored exercises: detailed description. These exercises are focused on fine control of multi-DOF sensorimotor actions in terms of timing, positioning and intensity. They aim to be more motivating than grade 1 and 2, and train tasks that are closer to daily life activities.

6.3.1 Online muscle tone monitoring

Our muscle tone monitoring method represents a first example of online detection of variations in health conditions. An important motivation for implementing this method were the inputs from our clinical partners from the Clinica Hildebrand Centro di Riabilitazione Brissago during our randomized controlled trial. They supported the hypothesis that highly intensive robot-assisted training could promote muscle hypertonia and compromise the patient recovery. We therefore implemented a perturbation-based approach to investigate the evolution of patient muscle tone during the execution of robot-assisted therapy tasks.

Most state of the art robotic devices test muscle tone reactions at different speeds in opening direction (i.e., on flexor muscles), and do not allow to evaluate directional muscle tone-dependencies [Gäverth et al., 2014, Höppner et al., 2017, Kamper et al., 2001]. Instead, our approach allows to study both the speed-dependency and the direction-dependency of the force reactions, which are equally important characteristics of spasticity (i.e., higher force reactions at higher speed, and in finger flexor muscles compared to extensor muscles). Our method allowed us to preliminarily identify that finger flexors' force reactions after ramp-and-hold perturbations may become more speed dependent over exercise blocks even in a non-spastic population after chronic stroke. In particular, the difference in force reaction between fast (150 ms) and slow (250 ms) ramp-and-hold hand opening perturbations of 20 mm ($\Delta F_{o,spd}$) can reach up to $4.48 \pm 7.78N$. In the population tested, this change derives most likely from a physiological mild increase in muscle tone induced by the training, and would be in line with a recent review reporting that robot-assisted therapy might lead to increased muscle tone [Veerbeek et al., 2017]. However, this should be carefully distinguished from an abnormal increase in muscle tone, frequently affecting the upper limb after stroke [Sommerfeld et al., 2012].

According to different rehabilitation approaches [Bobath and Bobath, 1950, Perfetti and Grimaldi, 1979, Paget-Blanc et al., 2019], a prompt detection of abnormal muscle tone increase is desired to adapt the therapy such that the patient can re-learn muscle tone control and avoid possible long-term negative consequences of spasticity (e.g., pain, reduced functional ability, recovery and independence) [Formisano et al., 2005, Kong et al., 2012, Sommerfeld et al., 2012]. The identified difference in force reaction between fast and slow perturbations could be used to define a threshold (e.g., mean+0.5std = 8.4 N) that differentiates a physiological muscle tone increase (i.e., small speed dependency of opening stretch reflexes, $\Delta F_{o,spd} < 8.4N$) from a pathological increase (i.e., increased speed dependency of opening stretch reflexes, $\Delta F_{o,spd} > 8.4N$). Based on this assumption, we extended our perturbation-based tone monitoring method from the sphere exercise to other two exercises (e.g., bars, neon). To make the assessment more reliable, we programmed the randomized execution of three opening fast and three opening slow perturbations per block, and used the threshold to verify if there is an abnormal increase in the speed-dependency of tonic stretch reflexes. If this happens, the platform could react by reducing the physical effort required in the therapy exercises (e.g., reduce velocities or forces, stop motor actions) or terminating them. To the

best of the authors' knowledge, no other robot-assisted therapy platform allows to monitor the evolution of hand muscle tone online during the execution of a therapy exercise and/or to use such information for online tailoring of the therapy difficulty.

6.3.2 Online haptic perception assessment

We developed an online assessment that allows to integrate the use of monitoring for investigation purposes and for therapy adaptation after detecting changes in patient ability. The assessment aims to embed the haptic perception assessment (aWF) proposed by Metzger et al. [2014b] into the therapy exercises that require stiffness identification. As a proof of concept, we implemented the aWF adaptive algorithm (i.e., based on Parameter Estimation by Sequential Testing, (PEST) [Taylor and Creelman, 1967]) into one of our therapy exercises (i.e., sponge exercise, see Figure 6.3). In this exercise, the smallest detectable difference in stiffness (Weber Fraction, WF) is used to scale the stiffness of the therapy object (i.e., sponges). To respect the identification paradigm required in the exercise, we could not maintain a two-alternative forced choice (2AFC) paradigm, but we had to introduce a minimum of three stiffnesses/sponges. The introduction of this assessment directly into the exercise has several potential advantages. First, it could allow to reduce problems in difficulty settings that can rise when the assessment results are not easily transferable into a therapy adaptation (e.g., due to different exercise paradigms). Second, it could reduce the time dedicated to the assessments, which are less motivating. Third, it will allow to better tune the difficulty of the exercise depending on the patient performance. However, this approach has some limitations. Preliminary results with healthy subjects showed that the PEST convergence to a meaningful WF takes longer than the standalone robotic assessment. This is due to the necessity in the therapy exercise to repeat the training phase every time the WF varies. The time increase could prolong the convergence even across multiple sessions, opening concerns about the reliability of the results. Finally, the results of the two assessments cannot be directly compared, as a user is more sensitive while doing a comparative task (e.g., 2AFC) than a discriminative task (e.g., identification) [Chaudhuri and Bhardwaj, 2018]. The exercise is currently under clinical investigation with stroke patients. In the future, the validity and reliability of this assessments (as well as of the others presented in this section) should be investigated.

6.3.3 Precision grip control

As example of assessment to investigate neurophysiological impairment or recovery mechanisms, we started studying on the ReHapticKnob the possible applications of a robotic assessment of precision grip control after stroke. Precision grip control is among the essential functions of the hand in daily life [Ingram and Wolpert, 2011, Kilbreath and Heard, 2005]. In particular, the manipulation of objects with unknown mechanical properties is a complex task relying on the integration of sensorimotor predictions and sensory feedbacks from the hand [Johansson and Flanagan, 2009], and on the adaptation of the grip strategy [Lambercy et al., 2014]. Rapid adaptations are based on fast error-based and strategy-based corrections, which

adapt the gesture based on the cognitive elaboration of sensory feedbacks [Spampinato and Celnik, 2020]. Long term adaptations are instead generalizable to the application and based on reinforcement learning, which contributes to the feedforward control of the gesture. We hypothesized that stroke could greatly impact these processes through different combinations of sensory, motor and cognitive impairments and that therapy interventions could reduce the gap between grip control adaptations in unimpaired and stroke subjects.

To verify our hypotheses, we replicated a symmetric grip task proposed by Lambercy on the RHK [Lambercy et al., 2014], in which the user has to symmetrically close the thumb and finger pads by 20 mm within $500 \pm 100 ms$ to reach a visual target displayed on the screen. During the task, the movement is perturbed by a viscoelastic force field defined by a parallel spring damper arrangement with two possible mechanical impedances (i.e., $K_1 = 0.3 N/mm, B_1 = 0.02 Ns/mm; K_2 = 0.2 N/mm, B_2 = 0.1 Ns/mm$). Given its fast timing, this task is dominated by feedforward control and adaptation of long-term internal motor control models. During the randomized controlled trial described in Chapter 2, 17 subacute stroke patients tested this robotic assessment at baseline (T0), after 4 weeks of intervention (T1), and at 8 weeks (T2) and 8 months (T3) after baseline. The patients were 8 male and 9 females, 11 ischemic, 5 hemorrhagic, 1 both, 71.4 ± 11.7 years old, and with a FMA-UE and a BBT of 55.5 ± 33.2 points and 19.2 ± 21.1 blocks per minute, respectively. In each session, the subjects repeated the task 20 times per viscoelasticity. To evaluate differences in grip control adaptation, the results were compared with an available pool of data from nine healthy subjects (5 male and 4 females, 37.5 ± 10.1 years old) that performed only a single session of the assessment.

We introduced four monodimensional metrics. Within a single task trial, we evaluated:

- *Closing time (CT)*: time to reach the target closing of $20 \pm 1 mm$. This metric directly reflects the performance in the task but does not reflect pure feedforward sensorimotor control (i.e., it is influenced by voluntary/cognitive control).
- *Spectral Arc Length (SAL)*: smoothness of the velocity profile following the approach of Balasubramanian et al. [2015]. In fast movements, this metric can be more directly linked to sensorimotor control and impairment [Rohrer et al., 2002].

To investigate the adaptation patterns, we evaluated the evolution of CT and SAL within a session of 20 trials, introducing:

- *Adaptation Time (AT)*: number of trials needed for CT/SAL to decrease below their average over all trials
- *Performance Plateau (PP)*: average CT/SAL achieved in the trials after the adaptation time

A graphical description of AT and PP is given for CT in Figure 6.5.

Preliminary results on the evolution over one session of CT and SAL in the stroke and unimpaired groups are summarized in Figure 6.6. Our results show that stroke patients have worse CT and SAL from the beginning to the end of the session. This confirms their impairment in grip control [Raghavan, 2015, Bleyenheuft and Gordon, 2014] and might also reflect less adaptation in internal models. Furthermore, the variance in CT and SAL is higher, probably due to the different levels of impairment within the patients. On the contrary, adaptation times are not significantly different, which may indicate that the given stroke population has limited cognitive impairment (e.g., in attention, motor planning) [Rinne et al., 2018, Cumming et al., 2012], as confirmed by positive Frontal Assessment Battery and Mini Mental Scale results (see Chapter 2), and intact cerebellar pathways [Krakauer et al., 2011, Bond and Taylor, 2015, Taylor et al., 2014].

Regarding the influence of the different viscoelasticities, only the performance of the stroke patients is significantly different depending on the viscoelasticity. Higher stiffness leads to higher spread of the CT and SAL performance, while high damping stabilizes and simplifies the execution of the task. On one hand, this supports the use of adaptable viscous force fields to simplify task execution and/or alter force/motion profiles and muscle recruitment in therapy exercises, as typically done in assist-as-needed or adaptive approaches [Oscari et al., 2016, Abdelhameed et al., 2015, Emken et al., 2007]. On the other hand, it underlines the potential use of highly elastic fields, within robot-assisted haptic assessments or therapy exercises, to differentiate impairment types among the patients. For instance, it could discriminate gross and fine motor impairment depending on the ability of the patients to generate symmetrical thumb and finger forces, or could determine whether stroke affected the high-level (e.g., internal models) or low-level motor control (e.g., muscle control), which would result in a worse performance in the highly elastic field.

Furthermore, we could prove that our performance metrics capture the effects of the therapeutic intervention in the stroke group. Both SAL and CT performance plateaus show significant improvements after four weeks of treatment (as most of the conventional scales, described in Chapter 2) and maintain the recovery over time up to T2. The performance plateaus slightly decrease only in T3, probably as a result of reduced familiarity with the RHK due to the long time between sessions, or of reduced use of the hand in daily life after discharge [Raghavan, 2015].

The proposed assessment strategy has the potential to study and discriminate different impairment modalities in stroke patients, evaluate their evolution over time, and adapt the therapy task (e.g., characteristics of the force field) to challenge the patient at an appropriate level. Given the strong link to the sensorimotor impairment of the patient, which is slowly adapting, this monitoring approach could be embedded in minimally-supervised therapy exercises that are rarely performed (e.g., maximum once a week). The therapy task could for instance require fine grip control to catch falling fragile bodies (e.g., egg or chick fallen from the nest) without injuring them.

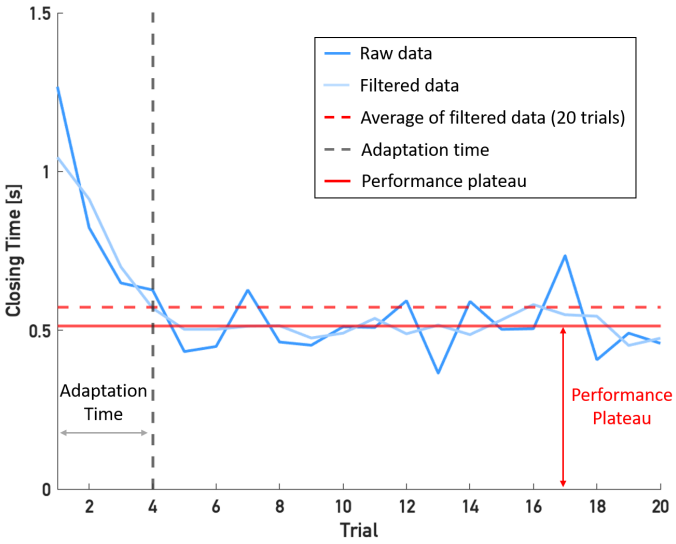
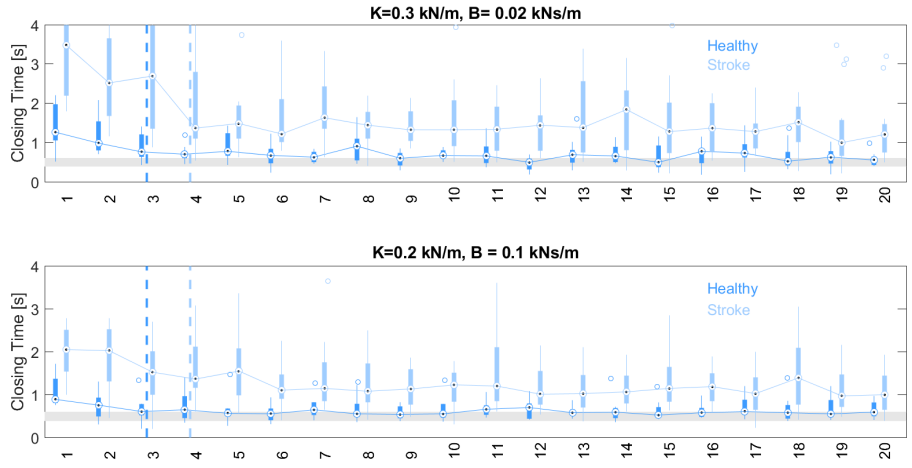


Figure 6.5: Adaptation time and performance plateau calculation for the closing time metric. Raw closing time data (blue) are filtered (light blue) using a 3-trials moving average window. Adaptation time (dotted grey) is defined as the number of trials for the filtered closing time to go below the average of the unfiltered closing time (over all the trials, red dotted). The average of the closing times achieved after adaptation represents the performance plateau (red).

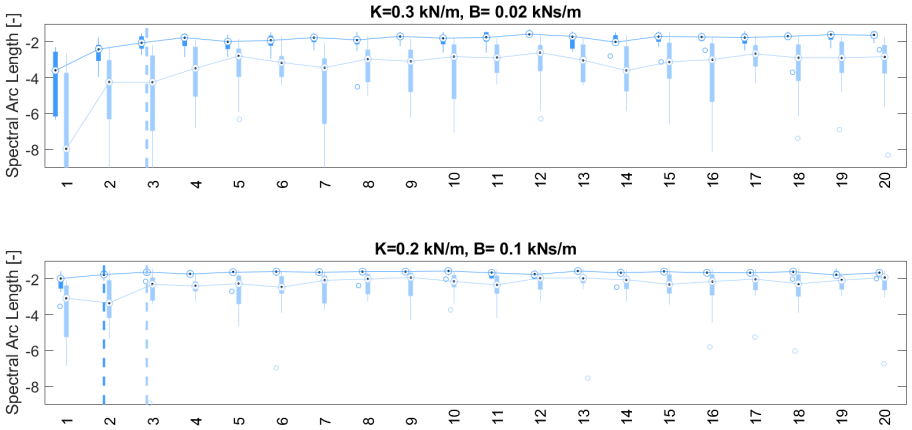
6.3.4 Clinical artificial intelligence

The monitoring strategies mentioned so far, as well as any other autonomous algorithm guaranteeing safety and appropriate patient-tailoring of the therapy plan, could be grouped under the name "clinical artificial intelligence". We define clinical artificial intelligence any combination of technical or clinical knowledge (e.g., medical, psychological) that can be embedded, in the form of algorithms, in artificial devices [Lambercy et al., 2021]. These algorithms can be used to analyze or process online the data generated by the device, and generate clinical decisions, therapy adaptation strategies (e.g., online adaptation of therapy exercises), reactions in case of emergencies, and monitoring of the subject progress through assessment scores. Such smart supervising strategies are essential to implement robot-assisted therapy protocols and platforms when external supervision is lacking [Kanzler et al., 2020].

Thanks to the successful collaboration with Giada Devittori, who started her PhD in the last year and a half, additional monitoring algorithms were recently added to our minimally-supervised therapy platform to increase its high-level intelligence, and solve remaining challenges that could compromise the feasibility of our therapy approach. The exercises and user interfaces developed within this thesis allow to substitute an important part of the "therapist intelligence" for what concerns the execution, control and adaptation of the therapy exercises. However, they rely on the patient to be manually executed from a graphical list in the GUI. Through fuzzy logic algorithms, the clinical artificial intelligence allows to generate a therapy



(a)



(b)

Figure 6.6: Box plots of the closing time (a) and spectral arc length (b) for all the stroke (light blue) and unimpaired (blue) subjects over 20 trials during the baseline session. In (a) and (b), the top plot represents the stiffness-dominated viscoelasticity and the bottom one the damping-dominated viscoelasticity. The connected circles in the boxes represent the median values among the subjects. The vertical dashed lines represent the median adaptation times among all the subjects. The horizontal gray area is the time target for a successful trial completion ($500 \pm 100 ms$).

plan based on therapist inputs (e.g., exercises to train, exercise frequency), and to automatically propose/stop the exercises following the plan. Furthermore, it corrects the exercise difficulty in case it reaches an upper or lower saturation (e.g., via an intelligent factor described in Figures 6.2 to 6.4), and produces longitudinal patient statistics (e.g., on exercise dose or performance) that the therapist can access offline for remote monitoring. Finally, the clinical artificial intelligence allows to react in safety conditions. For instance, in case the muscle tone monitoring detects an abnormal tone increases in two or three consecutive exercise blocks, the clinical artificial intelligence can stops the exercise and starts another exercise with less motor training, or terminate the therapy session if this kind of exercise is not available.

Apart from assessment-driven adaptation algorithms of therapy intensity and difficulty, which have been often investigated in literature [Giang et al., 2020, Grimm et al., 2016, Metzger et al., 2014b], the use of clinical artificial intelligence in technology-assisted neurorehabilitation is still largely unexplored. In a pilot study with 18 chronic stroke patients, artificial clinical intelligence's decisions regarding exercise selection were proposed during supervised robot-assisted rehabilitation to the supervising therapists, showing a high level of agreement [Panarese et al., 2012]. Increasing interest is attracted by the use of machine learning techniques or, similarly to our approach, fuzzy logic algorithms to observe the patient behavior and recommend appropriate therapy exercises, or to adapt existing therapy exercises according to the patient needs. However, their use has been so far mostly theorized or simulated [Gmez-Portes et al., 2021, Philipp et al., 2019]. Monitoring strategies have been proposed to detect compensatory movements or pain [Wittmann et al., 2016, Cai et al., 2020, Bouteraa et al., 2021].

In the future, novel online monitoring (and reaction) strategies could be explored, and could allow to assess continuously different aspects of sensorimotor control. For instance, patient voluntary muscle force and ability to move could be investigated through the force sensors during exercise calibration, motor control could be assessed by evaluating force profiles (e.g., symmetry) and movement SAL during active exercises. The detection of muscle fatigue could be useful for exercise difficulty adaptation [Thacham Poyil et al., 2020], but cannot be easily performed in minimally-supervised settings, as it would require an electromyographical sensor (e.g., bracelet or patch). A relation between end-effector forces and EMG signals could be identified to get rid of the EMG [Dorgham et al., 2019], but this would be highly inaccurate (e.g., depending on the grasping strategy) and subject specific. The influence of cognitive deterioration on sensorimotor function should be assessed. This could be inspired by the Hand Active Sensation Test [Williams et al., 2006] and the Tactile working memory scale [Nicholas et al., 2019], which are among the very few cognitive scales that assess cognitive abilities within ADL or rehabilitation sensorimotor tasks. Compared to pure visual observation or pure motion tracking, all these monitoring strategies could be best achieved (without supervision) via physical human-robot interaction. Additional assessments of, for instance, pain, motivation or inattention could be automatically implemented via cameras, virtual reality or a posteriori exercise data analysis [Rinderknecht et al., 2018].

6.4 Towards a continuum of care with our portable devices with high usability

To make the step into the home environment of neurological subjects, robotic devices should be rethought to guarantee simplicity of use, adaptability to different users and ergonomics, affordability and scalability, safety and portability. We proved the efficacy in terms of motor impairment reduction of the neurocognitive robot-assisted therapy concept in supervised clinical settings [Ranzani et al., 2020], and showed that the ReHapticKnob can offer this therapy approach with minimal supervision in controlled settings through our new minimally-supervised therapy platform. However, the ReHapticKnob cannot make the step out of the clinic due to its size, cost and technology complexity. To make our minimally-supervised therapy platform usable in different environments (e.g., clinic, home), we developed Handybot, a novel portable haptic device training hand and wrist function. HandyBot respects the most recent safety norms for medical devices and resulted to be usable by subjects after chronic stroke with minimal supervision in controlled settings. Excluding exoskeletons, only few portable powered devices exist for the hand [Tong et al., 2015, Khor et al., 2014, Hesse et al., 2008] and none of them offers the possibility to train haptic/sensorimotor tasks. Our usability evaluation suggested that two DOF would be sufficient to train hand and wrist with an end-effector approach, while increasing the device compactness, and design and use simplicity. In fact, simultaneously training grasping, forearm pronosupination and wrist flexion-extension is a challenge for stroke patients, particularly when using an end-effector device. Furthermore, the cost of the device is lower than other powered devices that are comparable in terms of functionality [Huang et al., 2018, Metzger et al., 2011, Lambercy et al., 2007], but could still be reduced to become more scalable for the home market.

Based on this evidence and usability insights, before the end of the PhD we started the development of a new portable device, ReHandyBot (Figure 6.7), which combines the best design elements of ReHapticKnob and HandyBot. The device includes the state of the art electrical and safety components of HandyBot, which guarantee good functionality and medical safety compliance with a low price and compact size. A new custom-made PCB (Figure 6.8) allows to further reduce the device size by embedding together the motors servocontrollers (Escon 50/8, Maxon Motors), power converters, encoder line driver boards, and relays for brakes and safety. The device mechanics matches the 2-DOF actuation of ReHapticKnob to guarantee good control performance and, compared to the mechanics of HandyBot, a more compact design, which is simpler to manufacture and assemble. More details on the mechanics design and specifications can be found in Metzger et al. [2011]. The 6-DOF load cells used to measure forces and torques in ReHapticKnob (mini40, ATI Industrial Automation) are replaced with two single DOF load cells (LCL-040, Omega), which showed good performance in HandyBot. Given the symmetrical nature of the robot kinematics, one sensor is used to estimate the grasping force (i.e., $2 * F_x$), while the other is used to estimate the rotational torque (i.e., $2 * F_y * x_{GR}$), as shown in Figure 6.9. By default, ReHandyBot could be used to train grasping and pronosupination but, rotating the device vertically, it could also train grasping and wrist flexion-extension

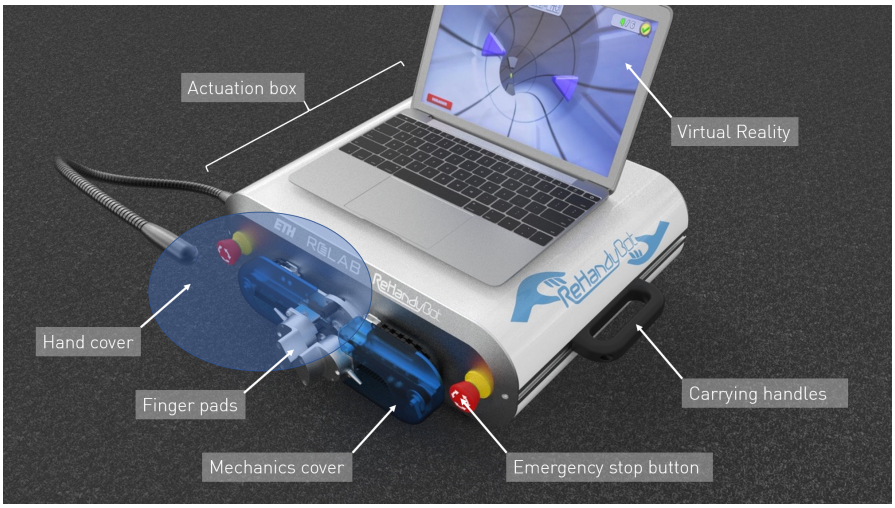


Figure 6.7: ReHandyBot, a portable table-top end-effector robot for the assessment and therapy of grasping and forearm pronosupination tasks. Virtual tasks are haptically reproduced through two pads that get in contact with the fingers of the user, and visually rendered in a virtual reality environment presented on a computer screen. Two easily reachable emergency stop buttons are embedded in the actuation box, which includes the actuators as well as electronics and safety components. A flexible hand cover (transparent for illustration purposes) can be moved to cover the hand during the exercises, while plastic mechanics' covers protect the hand of the patient from snag hazards.

(through the same rotational DOF). The device was recently manufactured and assembled (Figure 6.10) showing encouraging preliminary control performance results in the grasping DOF compared to HandyBot and ReHapticKnob (Figure 6.11) with a size and weight of only 400x450x130 mm and approximately 10 kg, respectively. In particular, the range of renderable impedances is larger than HandyBot but smaller than ReHapticKnob, since the device has the same geared mechanics of ReHapticKnob, which increases the impedance range compared to HandyBot (see Sec. 5.4.2), but few differences that could compromise stability. The low-cost force sensor allows less accurate force measurements compared to the mini40, and myRIO allows lower accuracies in sensor measurements and in the current control of the motors due to the different voltage resolution and ranges (e.g., acquisition/generation ranges) used in AI and AO channels compared to the PCIs of the ReHapticKnob. Moreover, myRIO can reach smaller sampling frequencies and the host-target communication implemented via USB is slightly slower than the Ethernet communication of the ReHapticKnob. Furthermore, the encoders have smaller resolution (i.e., number of windows per rotation) and the motors are controlled by different servocontrollers (i.e., Escon 50/8 instead of ADS 50/10 4-Q-DC, Maxon Motors) that allow lower motor current peaks.

Added to our minimally-supervised therapy platform, both HandyBot and ReHandyBot will allow to develop a continuum of care that starts in the clinic and continues at home after discharge. In the clinic, the patient could learn how to use the platform together with the therapist and progressively decrease the amount of supervision until almost full independence

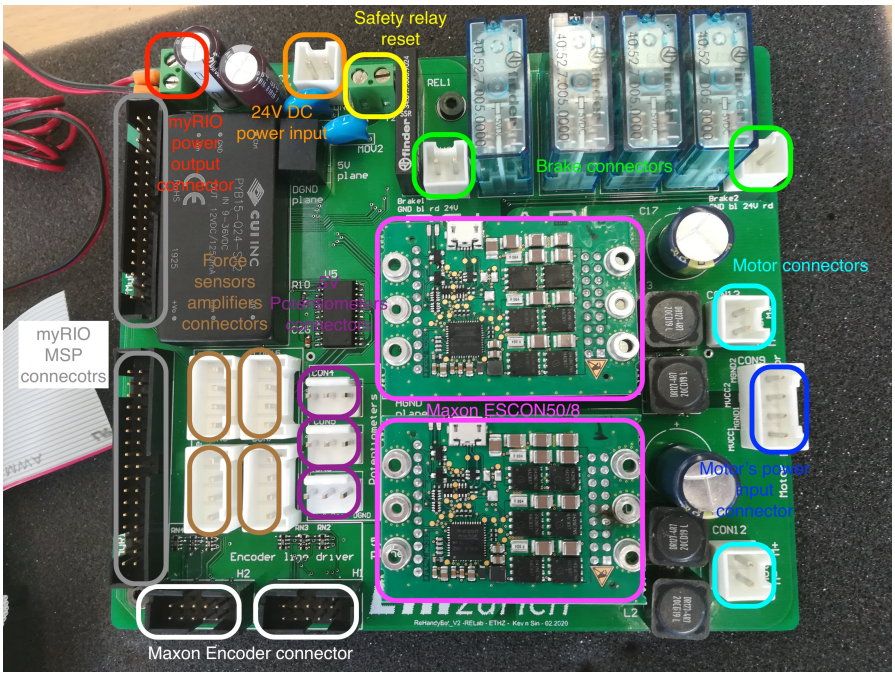


Figure 6.8: New PCB of ReHandyBot, including electrical connectors, motor servocontrollers (Escon 50/8, Maxon), brake relays, power converters, and other components not shown such as safety relay and encoder line drive circuit.

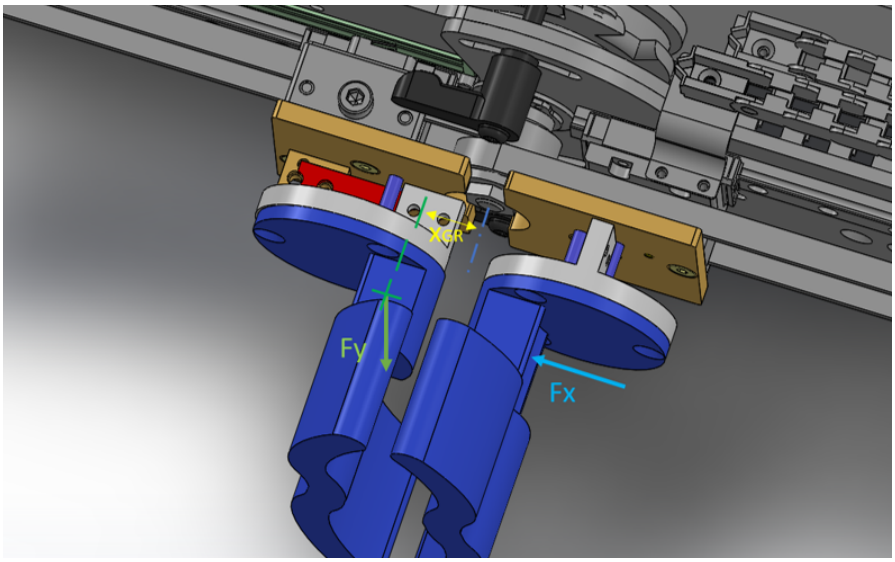


Figure 6.9: New force sensors of ReHandyBot. Two 1-DOF load cells measure the grasping force (F_x) and the forearm pronosupination torque as function of the grasping position ($F_y * x_{GR}$).

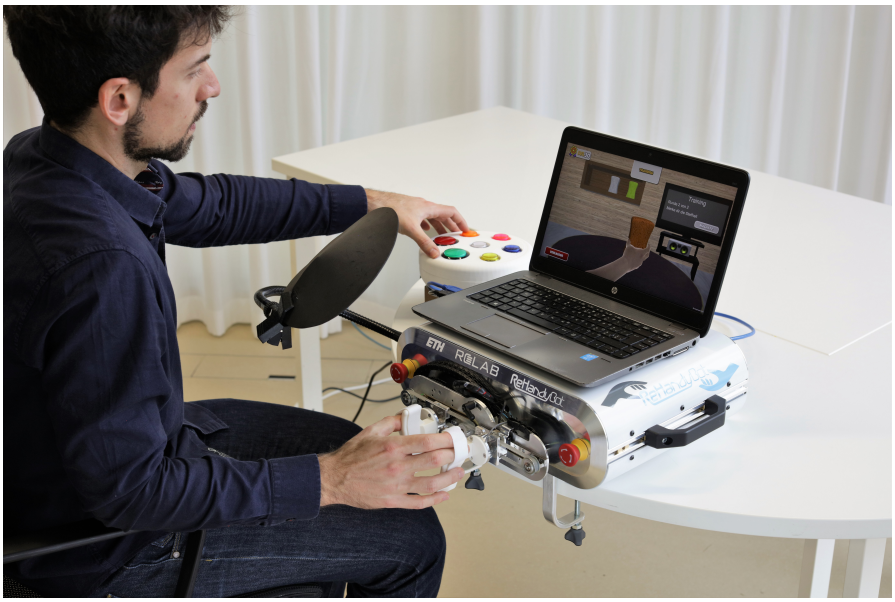


Figure 6.10: Preliminary tests of the first prototype of ReHandyBot using the sponge exercise (i.e., stiffness-based identification of different sponges). The user cannot see his/her hand thanks to a movable hand cover (black).

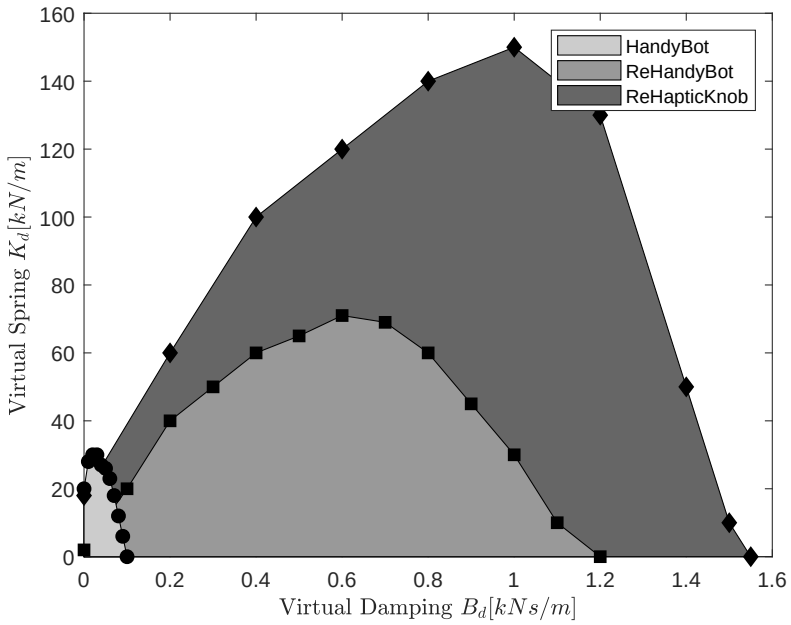


Figure 6.11: KB plots of ReHandyBot compared with HandyBot and ReHapticKnob for the grasping DOF: Stable desired spring-damper combinations renderable as rigid contact via impedance control with force feedback.

is ensured. Then, the patient could start training independently with the platform in parallel to conventional therapy sessions. After discharge, the patient could continue the training at home with minimal help of family members or friends. This therapy framework would allow to increase the therapy dose, reduce the therapy costs (e.g., by reducing the therapist time), avoid limb non-use and progressively promote patient autonomy and independence.

6.5 Contributions

Returning to our thesis goals, this thesis allowed to show that:

- an assessment-driven neurocognitive therapy program performed with a haptic device allows to achieve non-inferior therapy outcomes compared to conventional neurocognitive therapy;
- after appropriate usability-driven design modifications, a robot-assisted therapy platform can be safely and intuitively used upon first exposure with minimal supervision;
- to guarantee patient safety and appropriate tailoring of the therapy, the platform can automatically detect changes in patient conditions and continuously monitor/investigate their evolution over time;
- the therapy platform can be used with a portable therapy device, with the potential of increasing therapy dose in different environments.

Three are the main contributions of this work. First, through a resource demanding clinical trial, it was demonstrated that a robotic device can be used to offer sensorimotor therapy of hand function after neurological injury, achieving non-inferior therapy outcomes compared to conventional care. Sensorimotor and cognitive robot-assisted therapy has been rarely seen in literature and allows favorable increases in FMA-UE and other secondary outcomes. This established the necessary ground to support the second contribution of the thesis, which is the development of a user-friendly robot-assisted platform for minimally-supervised therapy, which can be used with multiple devices to start the therapy in the clinic and continue it seamlessly at home. The platform is usable with minimal supervision at first exposure and allows basic monitoring of the patient ability, physical conditions and safety. The third contribution of the thesis is the development of two portable therapy devices that are compatible with the therapy platform. HandyBot is the only portable powered device training simultaneously grasping, pronosupination and wrist flexion-extension. The therapy platform has been designed through close exchange with patients and the medical staff of the Clinica Hildebrand Centro Riabilitazione Brissago, while HandyBot was developed in close collaboration with an industrial partner within the European Project SoftPro (Horizon 2020). Based on its advanced development status, HandyBot was selected as one of the four final demonstrators of SoftPro. ReHandyBot is essentially a portable version of the ReHapticKnob, with higher portability and scalability, and is currently undergoing preliminary successful experiments to characterize

its control performance. HandyBot and ReHandyBot are the only portable powered devices allowing to haptically train hand function with minimal supervision.

This project will continue divided in two follow-up PhD projects within the Future Health Technology (FHT) programme of the Singapore-ETH Centre. One PhD project will focus on the portable devices and their use in the home environment, thus ReHandyBot will soon fly to Singapore to continue its path towards the patients' home. Moreover, we are currently in touch with an industrial partner that could be interested in the technology of ReHandyBot. The other PhD project, which already started, is currently focusing on the usability and feasibility of minimally-supervised therapy concept in clinical settings. A clinical trial about the use of the developed ReHapticKnob platform is currently undergoing at the Clinica Hildebrand Centro Riabilitazione Brissago, where patients undertake a 4-weeks program including a week of supervised therapy (i.e., the therapist fully guides the therapy with the platform), a week of semi-supervised therapy (i.e., the therapist is present and intervenes in case the patient needs help), and two weeks of minimally-supervised use (i.e., the patient is assigned with time slots of recommended autonomous use of the platform). The trial showed promising preliminary results with six subacute patients. These subjects could easily learn how to use the platform and five of them could use it independently respecting recommended time slots and maintaining therapy dose per session comparable with the supervised sessions. Within the scope of this thesis, we could not test our minimally-supervised portable therapy platform in different environments (e.g., at home) over time, nor the achievable therapy doses using this approach. However, our results set the fundamental elements that allow to start testing the feasibility of minimally-supervised robot-assisted therapy in real-world settings, as a continuum that starts in the clinic and continues at home. Moreover, such longitudinal investigations will allow to verify if our approach increases the therapy dose and/or the amount of functional recovery at the level of the hand compared to currently available therapies.

6.5.1 Dissemination

The research carried out in the scope of this thesis led to the preparation or publication of one book chapter, one conference paper, and four journal papers.

- Ranzani, R., Albrecht, M., Haarman C., Koh E., Devittori G., Held, J. P. O., Tönis F., Lambercy O., and Gassert R (in preparation). Design, characterization and preliminary usability testing of a portable robot for minimally-supervised therapy of hand function.
- Ranzani, R., Eicher, L., Viggiano F., Engelbrecht B., Held, J. P. O., Lambercy O., and Gassert R. (2021). Towards a platform for robot-assisted minimally-supervised therapy of hand function: design and pilot usability evaluation. Front Bioeng Biotechnol, 9.
- Ranzani*, R., Lambercy*, O., Metzger, JC. et al. (2020). Neurocognitive robot-assisted rehabilitation of hand function: a randomized control trial on motor recovery in subacute stroke. J NeuroEngineering Rehabil 17, 115.

- Ranzani, R., Viggiano, F., Engelbrecht, B., Held, J. P. O., Lambercy, O., and Gassert, R. (2019). Method for muscle tone monitoring during robot-assisted therapy of hand function: a proof of concept. In 2019 IEEE 16th International Conference on Rehabilitation Robotics (ICORR) (pp. 957-962).
- Rinderknecht, M. D., Ranzani, R., Popp, W. L., Lambercy, O., and Gassert, R. (2018). Algorithm for improving psychophysical threshold estimates by detecting sustained inattention in experiments using PEST. Attention, Perception, and Psychophysics, 80(6), 1629-1645.
- Lambercy, O., Ranzani, R., and Gassert, R. (2018). Robot-assisted rehabilitation of hand function. In Rehabilitation Robotics (pp. 205-225). Academic Press.

Furthermore, to maximize exchange with clinical partners, patients and colleagues in the field, the PhD candidate led the organization of the summer school Translational Robotics for Clinical Rehabilitation (TRCR, 2016), was the head of the Powered Leg Prosthesis race at Cybathlon (2016), and volunteered as expert coach at Enable Makeathon in Bengaluru, India (2015).

6.6 Outlook

In the future, the following steps could be undertaken (in order of priority):

- Identify minimum protocols and guidelines to establish when it is appropriate for the patient to switch to minimally-supervised therapy in the clinic or, more importantly, at home. Within this PhD, we proposed the use of quantitative checklists and questionnaires to objectively identify when the use of minimally-supervised therapy is feasible. Assessing the patient ability to use the platform before this transition is necessary to guarantee patients' safety when supervision is lacking. Moreover, this approach allows to evaluate when the patients can autonomously execute the exercises correctly, since a misexecution of the therapy tasks could promote the learning of abnormal motor control patterns or of compensatory strategies [Perfetti and Grimaldi, 1979]. One checklist is currently in use within the RHK clinical trial. During the semi-supervised week, the therapist is supposed to observe the patient behavior and record on the checklist the items in which the patient needed help. If at the end of the week the patient presents major problems that would heavily affect the execution of minimally-supervised therapy (e.g., cannot autonomously place the hand inside the finger pads) he/she continues another week of semisupervised therapy and then repeats the therapist assessment. If the patient presents just a few minor issues (e.g., cannot grasp objects in one exercise), he/she can start training with minimal supervision and the exercises with issues are discarded from the initial minimally-supervised therapy plan. Finally, it will be important to define best practices to instruct therapist and/or family members on how to perform minimally-supervised therapy and assist the patient when needed.

- Verify the effective therapy dose and compliance of stroke patients when using the therapy platform either in the clinic or at home, since a motivation drop could come into place over time.

- Investigate whether adding the training of wrist flexion-extension (e.g., in HandyBot) can lead to an increased functional recovery at the level of the hand. This could be hypothesized based on the intrinsic anatomical and physiological coupling between fingers and wrist, which are controlled by several identical muscles (e.g., extensor digitorum communis, extensor pollicis longus, flexor digitorum superficialis, flexor pollicis longus) and nerves (e.g., radial, median, ulnar). The positioning of wrist and forearm has a direct effect on the control capability of hand-grip strength [Liao, 2014], and the electromyographic activity associated with digit movement is linked to the movements of the wrist [Beringer et al., 2020]. Furthermore, intact wrist function is essential to guarantee hand mobility in space and wrist-hand synergies are important for the execution of daily life tasks [Jarque-Bou et al., 2019].

- Develop a mobile virtual app that would allow to supervise or operate multiple therapy platforms. The app could serve as "virtual therapist" that recommends the most appropriate therapy for the day and follows the patient progress across different devices. For instance, the virtual therapist would guide the patient in early rehabilitation phases while using complex and expensive robotic devices in the clinic, or at home (e.g., rented out by the clinic), and would gradually propose simpler and cheaper devices that the patient could afford privately and that would be better integrated in ADL (e.g., sensors [Wang et al., 2017], tablets [Albiol-Pérez et al., 2014], smart watches [Chae et al., 2020], low-cost gloves or exoskeletons [Bützer et al., 2020]).

- Establish telemonitoring solutions that will be useful for the therapist to supervise multiple (remote) therapy platforms, collect patient data or intervene (e.g., through teleoperation) when therapist's support or physical assistance are needed. Moreover, the extensive amount of data collected online through minimally-supervised therapy platforms could help identifying evidence-based best practices (e.g., upper and lower therapy dose thresholds, therapy type) to promote or predict recovery.

- Perform systematic cost-utility analyses to evaluate the cost effectiveness of robot-assisted therapy [Lloréns et al., 2015, Hesse et al., 2014, Lo et al., 2019b]. These analyses should consider available guidelines to select the most appropriate metrics [Whitehead and Ali, 2010]. In particular, it would be important to consider metrics such as therapy dose, percentage of unsupervised use, possibility to perform group therapies, number of clinicians involved to operate the device [Aprile et al., 2019].

Bibliography

Esam H Abdelhameed, Keita Kamada, Noritaka Sato, and Yoshifumi Morita. Post-stroke robotic-assisted therapy: Time-variant damping coefficient based control algorithm for isotonic exercise through circular motion. In *2015 IEEE International Conference on Mechatronics (ICM)*, pages 437–441. IEEE, 2015.

Sergei V Adamovich, Gerard G Fluet, Alma S Merians, Abraham Mathai, and Qinyin Qiu. Incorporating haptic effects into three-dimensional virtual environments to train the hemiparetic upper extremity. *IEEE Transactions on Neural Systems and Engineering, Rehabilitation*, 17 (5):512–520, 2009. ISSN 1534-4320.

Joy Adamson, Andy Beswick, and Shah Ebrahim. Is stroke the most common cause of disability? *Journal of stroke cerebrovascular diseases*, 13(4):171–177, 2004. ISSN 1052-3057.

Félicie Affolter. *Wahrnehmung, Wirklichkeit und Sprache*. Neckar, 1987.

Francesco Aggogeri, Tadeusz Mikolajczyk, and James O'Kane. Robotics for rehabilitation of hand movement in stroke survivors. *Advances in Mechanical Engineering*, 11(4): 1687814019841921, 2019.

Mindy Lipson Aisen, H Igo Krebs, Neville Hogan, Fletcher McDowell, and Bruce T Volpe. The effect of robot-assisted therapy and rehabilitative training on motor recovery following stroke. *Archives of neurology*, 54(4):443–446, 1997. ISSN 0003-9942.

Martin L Albert. A simple test of visual neglect. *Neurology*, 1973. ISSN 1526-632X.

Sergio Albiol-Pérez, Guillermo Palacios-Navarro, Nancy Guerrón-Paredes, José-Antonio Gil-Gómez, José-Antonio Lozano Quilis, Hermenegildo Gil-Gómez, and Pilar Manzano. The perfetti method, a novel virtual fine motor rehabilitation system for chronic acquired brain injury. In *Proceedings of the 8th International Conference on Pervasive Computing Technologies for Healthcare*, pages 451–454. ICST (Institute for Computer Sciences, Social-Informatics and Telecommunications Engineering), 2014. ISBN 1631900110.

Laura Allen, Ava John-Baptiste, Matthew Meyer, Marina Richardson, Mark Speechley, David Ure, Maureen Markle-Reid, and Robert Teasell. Assessing the impact of a home-based stroke rehabilitation programme: a cost-effectiveness study. *Disability and rehabilitation*, 41(17): 2060–2065, 2019.

Khader A Almhdawi, Virgil G Mathiowetz, Matthew White, and Robert C delMas. Efficacy of occupational therapy task-oriented approach in upper extremity post-stroke rehabilitation. *Occupational therapy international*, 23(4):444–456, 2016.

Anna Aminov, Jeffrey M Rogers, Sandy Middleton, Karen Caeyenberghs, and Peter H Wilson. What do randomized controlled trials say about virtual rehabilitation in stroke? a systematic literature review and meta-analysis of upper-limb and cognitive outcomes. *Journal of neuroengineering and rehabilitation*, 15(1):29, 2018. ISSN 1743-0003.

Farshid Amirabdollahian, Serdar Ates, Angelo Basteris, Alfredo Cesario, Jaap Buurke, H Hermens, Dennis Hofs, Ellinor Johansson, Gail Mountain, and Nasrin Nasr. Design, development and deployment of a hand/wrist exoskeleton for home-based rehabilitation after stroke-script project. *Robotica*, 32(8):1331–1346, 2014. ISSN 0263-5747.

Irene Aprile, Arianna Cruciani, Marco Germanotta, Valerio Gower, Cristiano Pecchioli, Davide Cattaneo, Federica Vannetti, Luca Padua, and Furio Gramatica. Upper limb robotics in rehabilitation: an approach to select the devices, based on rehabilitation aims, and their evaluation in a feasibility study. *Applied Sciences*, 9(18):3920, 2019.

Irene Aprile, Giulia Guardati, Valeria Cipollini, Dionysia Papadopoulou, Alessia Mastrorosa, Letizia Castelli, Serena Monteleone, Alessandra Redolfi, Silvia Galeri, and Marco Germanotta. Robotic rehabilitation: an opportunity to improve cognitive functions in subjects with stroke. an explorative study. *Frontiers in Neurology*, 11:1498, 2020.

Serdar Ates, Claudia JW Haarman, and Arno HA Stienen. Script passive orthosis: design of interactive hand and wrist exoskeleton for rehabilitation at home after stroke. *Autonomous Robots*, 41(3):711–723, 2017. ISSN 0929-5593.

Sivakumar Balasubramanian, Alejandro Melendez-Calderon, Agnes Roby-Brami, and Etienne Burdet. On the analysis of movement smoothness. *Journal of neuroengineering and rehabilitation*, 12(1):1–11, 2015.

Aaron Bangor, Philip Kortum, and James Miller. Determining what individual sus scores mean: Adding an adjective rating scale. *Journal of usability studies*, 4(3):114–123, 2009. ISSN 1931-3357.

Nino Basaglia et al. *Progettare la riabilitazione. Il lavoro in team interprofessionale*. Edi Ermes, 2002.

Nestor A Bayona, Jamie Bitensky, Katherine Salter, and Robert Teasell. The role of task-specific training in rehabilitation therapies. *Topics in stroke rehabilitation*, 12(3):58–65, 2005.

Ricardo Beira, Ali Sengül, Masayuki Hara, Patrick Schoeneich, and Hannes Bleuler. Tendon-based transmission for surgical robotics: Systematic experimental friction modeling. In *International Conference on Applied Bionics and Biomechanics (ICABB-2010)*, 2010.

Ricardo Beira, Reymond Clavel, and Hannes Bleuler. Mechanical manipulator for surgical instruments, October 9 2018. US Patent 10,092,359.

Jared A Bell, Malerie L Wolke, Ryan C Ortez, Theresa A Jones, and Abigail L Kerr. Training intensity affects motor rehabilitation efficacy following unilateral ischemic insult of the sensorimotor cortex in c57bl/6 mice. *Neurorehabilitation and neural repair*, 29(6):590–598, 2015.

Carl R Beringer, Misagh Mansouri, Lee E Fisher, Jennifer L Collinger, Michael C Munin, Michael L Boninger, and Robert A Gaunt. The effect of wrist posture on extrinsic finger muscle activity during single joint movements. *Scientific reports*, 10(1):1–11, 2020.

Julie Bernhardt, Karen Borschmann, Lara Boyd, S Thomas Carmichael, Dale Corbett, Steven C Cramer, Tammy Hoffmann, Gert Kwakkel, Sean I Savitz, Gustavo Saposnik, et al. Moving rehabilitation research forward: developing consensus statements for rehabilitation and recovery research. *International journal of stroke*, 11(4):454–458, 2016.

Julie Bernhardt, Kathryn S Hayward, Numa Dancause, Natasha A Lannin, Nick S Ward, Randolph J Nudo, Amanda Farrin, Leonid Churilov, Lara A Boyd, and Theresa A Jones. A stroke recovery trial development framework: Consensus-based core recommendations from the second stroke recovery and rehabilitation roundtable. *International Journal of Stroke*, 14(8): 792–802, 2019. ISSN 1747-4930.

Rachele Bertani, Corrado Melegari, C Maria, Alessia Bramanti, Placido Bramanti, and Rocco Salvatore Calabrò. Effects of robot-assisted upper limb rehabilitation in stroke patients: a systematic review with meta-analysis. *Neurological Sciences*, 38(9):1561–1569, 2017.

Rebecca L Birkenmeier, Eliza M Prager, and Catherine E Lang. Translating animal doses of task-specific training to people with chronic stroke in 1-hour therapy sessions: a proof-of-concept study. *Neurorehabilitation and neural repair*, 24(7):620–635, 2010.

Teresa Blanco, Alfredo Berbegal, Rubén Blasco, and Roberto Casas. Xassess: crossdisciplinary framework in user-centred design of assistive products. *Journal of Engineering Design*, 27 (9):636–664, 2016. ISSN 0954-4828.

Yannick Bleyenheuft and Andrew M Gordon. Precision grip in congenital and acquired hemiparesis: similarities in impairments and implications for neurorehabilitation. *Frontiers in human neuroscience*, 8:459, 2014.

Berta. Bobath. *Adult hemiplegia : evaluation and treatment / Berta Bobath*. Heinemann Medical London, 2nd ed. edition, 1978. ISBN 0433033347.

Karel Bobath and Berta Bobath. Spastic paralysis treatment of by the use of reflex inhibition. *The British journal of physical medicine: including its application to industry*, 13(6):121, 1950.

Krista M Bond and Jordan A Taylor. Flexible explicit but rigid implicit learning in a visuomotor adaptation task. *Journal of neurophysiology*, 113(10):3836–3849, 2015.

Jackie Bosch, Martin J O'Donnell, Susan Barreca, Lehana Thabane, and Laurie Wishart. Does task-oriented practice improve upper extremity motor recovery after stroke? a systematic review. *International Scholarly Research Notices*, 2014, 2014.

Matteo Bottin, Silvio Cocuzza, Nicola Comand, and Alberto Doria. Modeling and identification of an industrial robot with a selective modal approach. *Applied Sciences*, 10(13):4619, 2020.

Mohamed Bouri, Charles Baur, Reymond Clavel, CJ Newman, and M Zedka. Handreha": a new hand and wrist haptic device for hemiplegic children. In *ACHI 2013, The Sixth International Conference on Advances in Computer-Human Interactions*, pages 286–292, 2013.

Yassine Bouteraa, Ismail Ben Abdallah, Khaled Alnowaiser, and Atef Ibrahim. Smart solution for pain detection in remote rehabilitation. *Alexandria Engineering Journal*, 60(4):3485–3500, 2021.

Mark G Bowden, Michelle L Woodbury, and Pamela W Duncan. Promoting neuroplasticity and recovery after stroke: future directions for rehabilitation clinical trials. *Current opinion in neurology*, 26(1):37–42, 2013.

Michelle Broderick, Leeza Almedom, Etienne Burdet, Jane Burridge, and Paul Bentley. Self-directed exergaming for stroke upper limb impairment increases exercise dose compared to standard care. *Neurorehabilitation and Neural Repair*, pages 1–12, 2021.

JG Broeks, GJ Lankhorst, K Rumping, and AJH Prevo. The long-term outcome of arm function after stroke: results of a follow-up study. *Disability and rehabilitation*, 21(8):357–364, 1999. ISSN 0963-8288.

John Brooke. Sus-a quick and dirty usability scale. *Usability evaluation in industry*, 189(194): 4–7, 1996.

Thomas Brott, Harold P Adams, Charles P Olinger, John R Marler, William G Barsan, Jose Biller, Judith Spilker, Renee Holleran, Robert Eberle, and Vicki Hertzberg. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke*, 20(7):864–870, 1989. ISSN 0039-2499.

S Brunnström. Movement therapy in hemiplegia: A neurophysiological approach/1st edn hagerstown. *MD-Harper & Row*, 1970.

Ethan Buch, Cornelia Weber, Leonardo G Cohen, Christoph Braun, Michael A Dimyan, Tyler Ard, Jurgen Mellinger, Andrea Caria, Surjo Soekadar, Alissa Fourkas, et al. Think to move: a neuromagnetic brain-computer interface (bci) system for chronic stroke. *Stroke*, 39(3): 910–917, 2008.

Charles G Burgar, Susan L Garber, HF Machiel Van der Loos PhD, and OTR Deborah Kenney MS. Robot-assisted upper-limb therapy in acute rehabilitation setting following stroke: Department of veterans affairs multisite clinical trial. *Journal of rehabilitation research and development*, 48(4):445, 2011. ISSN 0748-7711.

Alexander Buryanov and Viktor Kotiuk. Proportions of hand segments. *Int. J. Morphol*, pages 755–758, 2010.

Imke Büsching, Aida Sehle, Jana Stürner, and Joachim Liepert. Using an upper extremity exoskeleton for semi-autonomous exercise during inpatient neurological rehabilitation-a pilot study. *Journal of neuroengineering and rehabilitation*, 15(1):72, 2018.

Cathrin Bütefisch, Horst Hummelsheim, Petra Denzler, and Karl-Heinz Mauritz. Repetitive training of isolated movements improves the outcome of motor rehabilitation of the centrally paretic hand. *Journal of the neurological sciences*, 130(1):59–68, 1995.

Andrew J Butler, Gereon R Fink, Christian Dohle, Gilbert Wunderlich, Lutz Tellmann, Rudiger J Seitz, Karl Zilles, and Hans-Joachim Freund. Neural mechanisms underlying reaching for remembered targets cued kinesthetically or visually in left or right hemispace. *Human brain mapping*, 21(3):165–177, 2004.

Tobias Bützer, Olivier Lambercy, Jumpei Arata, and Roger Gassert. Fully wearable actuated soft exoskeleton for grasping assistance in everyday activities. *Soft Robotics*, 2020.

Persson Hanna C, Parziali Marina, Danielsson Anna, and Sunnerhagen Katharina S. Outcome and upper extremity function within 72 hours after first occasion of stroke in an unselected population at a stroke unit. a part of the salgot study. *BMC Neurology*, 12(1):162, 12 2012. ISSN 1471-2377.

Siqi Cai, Guofeng Li, Enze Su, Xuyang Wei, Shuangyuan Huang, Ke Ma, Haiqing Zheng, and Longhan Xie. Real-time detection of compensatory patterns in patients with stroke to reduce compensation during robotic rehabilitation therapy. *IEEE journal of biomedical and health informatics*, 24(9):2630–2638, 2020.

Mónica S Cameirão, Sergi Bermúdez i Badia, Esther Duarte Oller, and Paul FMJ Verschure. Neurorehabilitation using the virtual reality based rehabilitation gaming system: methodology, design, psychometrics, usability and validation. *Journal of neuroengineering and rehabilitation*, 7(1):48, 2010.

Ivan Camponogara and Robert Volcic. Grasping movements toward seen and handheld objects. *Scientific reports*, 9(1):1–8, 2019.

Fioravante Capone, Sandra Miccinilli, Giovanni Pellegrino, Loredana Zollo, Davide Simonetti, Federica Bressi, Lucia Florio, Federico Ranieri, Emma Falato, Alessandro Di Santo, et al. Transcutaneous vagus nerve stimulation combined with robotic rehabilitation improves upper limb function after stroke. *Neural plasticity*, 2017, 2017.

James R Carey, William K Durfee, Ela Bhatt, Ashima Nagpal, Samantha A Weinstein, Kathleen M Anderson, and Scott M Lewis. Comparison of finger tracking versus simple movement training via telerehabilitation to alter hand function and cortical reorganization after stroke. *Neurorehabilitation and neural repair*, 21(3):216–232, 2007.

Leeanne Carey, Richard Macdonell, and Thomas A Matyas. Sense: Study of the effectiveness of neurorehabilitation on sensation: a randomized controlled trial. *Neurorehabilitation and neural repair*, 25(4):304–313, 2011. ISSN 1545-9683.

Håkan Carlsson, Gunvor Gard, and Christina Brogårdh. Upper-limb sensory impairments after stroke: self-reported experiences of daily life and rehabilitation. *Journal of Rehabilitation Medicine*, 50(1):45–51, 2018.

Maura Casadio, Pietro Morasso, Vittorio Sanguineti, and Psiche Giannoni. Minimally assistive robot training for proprioception enhancement. *Experimental brain research*, 194(2):219–231, 2009.

José M Catalan, JV Garcia, D Lopez, J Diez, Andrea Blanco, Luis Daniel Lledo, Francisco J Badesa, A Ugartemendia, Iñaki Díaz, and R Neco. Patient evaluation of an upper-limb rehabilitation robotic device for home use. In *2018 7th IEEE International Conference on Biomedical Robotics and Biomechatronics (Biorob)*, pages 450–455. IEEE, 2018. ISBN 1538681838.

Sang Hoon Chae, Yushin Kim, Kyoung-Soub Lee, and Hyung-Soon Park. Development and clinical evaluation of a web-based upper limb home rehabilitation system using a smartwatch and machine learning model for chronic stroke survivors: Prospective comparative study. *JMIR mHealth and uHealth*, 8(7):e17216, 2020.

Dora YL Chan, Chetwyn CH Chan, and Derrick KS Au. Motor relearning programme for stroke patients: a randomized controlled trial. *Clinical rehabilitation*, 20(3):191–200, 2006.

Ratanapat Chanubol, Parit Wongphaet, Napapit Chavanich, Cordula Werner, Stefan Hesse, Anita Bardeleben, and Jan Merholz. A randomized controlled trial of cognitive sensory motor training therapy on the recovery of arm function in acute stroke patients. *Clinical rehabilitation*, 26(12):1096–1104, 2012. ISSN 0269-2155.

Charalambos P Charalambous. *Interrater reliability of a modified Ashworth scale of muscle spasticity*, pages 415–417. Springer, 2014.

Subhasis Chaudhuri and Amit Bhardwaj. *Kinesthetic Perception*. Singapore: Springer, 2018.

Hui-Mei Chen, Christine C Chen, I-Ping Hsueh, Sheau-Ling Huang, and Ching-Lin Hsieh. Test-retest reproducibility and smallest real difference of 5 hand function tests in patients with stroke. *Neurorehabilitation and neural repair*, 23(5):435–440, 2009. ISSN 1545-9683.

Mei-Hsiang Chen, Lan-Ling Huang, and Chao-Hua Wang. Developing a digital game for stroke patients' upper extremity rehabilitation–design, usability and effectiveness assessment. *Procedia Manufacturing*, 3:6–12, 2015. ISSN 2351-9789.

Xiaowei Chen, Fuqian Liu, Zhaohong Yan, Shihuan Cheng, Xunchan Liu, He Li, and Zhenlan Li. Therapeutic effects of sensory input training on motor function rehabilitation after stroke. *Medicine*, 97(48), 2018.

Yu Chen, Kingsley Travis Abel, John T Janecek, Yunan Chen, Kai Zheng, and Steven C Cramer. Home-based technologies for stroke rehabilitation: a systematic review. *International journal of medical informatics*, 123:11–22, 2019. ISSN 1386-5056.

N. Chengalur, Somadeepti, H. Rodgers, Suzanne, and E. Bernard, Thomas. *Kodak's ergonomic design for people at work*. John Wiley & Sons, 2004.

Nai-Fang Chi, Yi-Chieh Huang, Hsiao-Yean Chiu, Hsiu-Ju Chang, and Hui-Chuan Huang. Systematic review and meta-analysis of home-based rehabilitation on improving physical function among home-dwelling patients with a stroke. *Archives of physical medicine and rehabilitation*, 101(2):359–373, 2020. ISSN 0003-9993.

Younggeun Choi, James Gordon, Hyeshin Park, and Nicolas Schweighofer. Feasibility of the adaptive and automatic presentation of tasks (adapt) system for rehabilitation of upper extremity function post-stroke. *Journal of neuroengineering and rehabilitation*, 8(1):1–12, 2011.

Jared Clarke, Kristopher D Langdon, and Dale Corbett. Early poststroke experience differentially alters periinfarct layer ii and iii cortex. *Journal of Cerebral Blood Flow & Metabolism*, 34(4):630–637, 2014.

J Edward Colgate and J Michael Brown. Factors affecting the z-width of a haptic display. In *Proceedings of the 1994 IEEE International Conference on Robotics and Automation*, pages 3205–3210. IEEE, 1994. ISBN 0818653302.

International Electrotechnical Commission et al. Medical electrical equipment-part 1: General requirements for basic safety and essential performance. *IEC 60601-1: 2005*, 2005.

Louise Ann Connell, NB Lincoln, and KA Radford. Somatosensory impairment after stroke: frequency of different deficits and their recovery. *Clinical rehabilitation*, 22(8):758–767, 2008.

Lauri Connelly, Yicheng Jia, Maria L Toro, Mary Ellen Stoykov, Robert V Kenyon, and Derek G Kamper. A pneumatic glove and immersive virtual reality environment for hand rehabilitative training after stroke. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 18(5):551–559, 2010. ISSN 1534-4320.

Susan S Conroy, Jill Whitall, Laura Dipietro, Lauren M Jones-Lush, Min Zhan, Margaret A Finley, George F Wittenberg, Hermano I Krebs, and Christopher T Bever. Effect of gravity on robot-assisted motor training after chronic stroke: a randomized trial. *Archives of physical medicine and rehabilitation*, 92(11):1754–1761, 2011. ISSN 0003-9993.

Dale Corbett, Matthew Jeffers, Carine Nguemeni, Mariana Gomez-Smith, and Jessica Livingston-Thomas. Lost in translation: rethinking approaches to stroke recovery. In *Progress in brain research*, volume 218, pages 413–434. Elsevier, 2015.

Paul Cordo, Helmi Lutsep, Linda Cordo, W Geoffrey Wright, Timothy Cacciatore, and Rachel Skoss. Assisted movement with enhanced sensation (ames): coupling motor and sensory to remediate motor deficits in chronic stroke patients. *Neurorehabilitation & neural repair*, 23 (1):67–77, 2009. ISSN 1545-9683.

Martina Coscia, Maximilian J Wessel, Ujwal Chaudary, José del R Millán, Silvestro Micera, Adrian Guggisberg, Philippe Vuadens, John Donoghue, Niels Birbaumer, and Friedhelm C Hummel. Neurotechnology-aided interventions for upper limb motor rehabilitation in severe chronic stroke. *Brain*, 142(8):2182–2197, 2019.

Steven C. Cramer. Drugs to enhance motor recovery after stroke. *Stroke*, 46(10):2998–3005, 2015.

Steven C Cramer, Lucy Dodakian, Vu Le, Jill See, Renee Augsburger, Alison McKenzie, Robert J Zhou, Nina L Chiu, Jutta Heckhausen, and Jessica M Cassidy. Efficacy of home-based telerehabilitation vs in-clinic therapy for adults after stroke: A randomized clinical trial. *JAMA neurology*, 76(9):1079–1087, 2019. ISSN 2168-6149.

Toby B Cumming, Karen Tyedin, Leonid Churilov, Meg E Morris, and Julie Bernhardt. The effect of physical activity on cognitive function after stroke: a systematic review. *Int Psychogeriatr*, 24(4):557–67, 2012.

Erika Shirley Moreira da Silva, Gabriela Nagai Ocamoto, Gabriela Lopes dos Santos-Maia, Roberta de Fátima Carreira Moreira Padovez, Claudia Trevisan, Marcos Amaral de Noronha, Natalia Duarte Pereira, Alexandra Borstad, and Thiago Luiz Russo. The effect of priming on outcomes of task-oriented training for the upper extremity in chronic stroke: A systematic review and meta-analysis. *Neurorehabilitation and Neural Repair*, page 1545968320912760, 2020.

Ralph B D'Agostino, Lisa M Sullivan, and Alexa S Beiser. *Introductory applied biostatistics*. Thomson Brooks/Cole, 2006. ISBN 053442399X.

Emily J Dalton, Leonid Churilov, Natasha A Lannin, Dale Corbett, and Kathryn S Hayward. Dose articulation in preclinical and clinical stroke recovery: Refining a discovery research pipeline and presenting a scoping review protocol. *Frontiers in neurology*, 10:1148, 2019.

Janis J Daly, Jessica P McCabe, John Holcomb, Michelle Monkiewicz, Jennifer Gansen, and Svetlana Pundik. Long-dose intensive therapy is necessary for strong, clinically significant, upper limb functional gains and retained gains in severe/moderate chronic stroke. *Neurorehabilitation and neural repair*, 33(7):523–537, 2019. ISSN 1545-9683.

Numa Dancause, Alain Ptito, and Mindy F Levin. Error correction strategies for motor behavior after unilateral brain damage: short-term motor learning processes. *Neuropsychologia*, 40 (8):1313–1323, 2002.

Robert A Davidoff. Skeletal muscle tone and the misunderstood stretch reflex. *Neurology*, 42 (5):951–951, 1992. ISSN 0028-3878.

Fred D Davis. *A technology acceptance model for empirically testing new end-user information systems: Theory and results*. Thesis, MIT, 1985.

Gabriel John L de Leon, Joana Patrice M Gratuito, and Ronaldo V Polancos. The impact of command buttons, entry fields, and graphics on single usability metric (sum). *Proceedings of the International Conference on Industrial Engineering and Operations Management Dubai*, 2020.

Matthias Decker and Yeongmi Kim. A hand exoskeleton device for robot assisted sensory-motor training after stroke. In *2017 IEEE World Haptics Conference (WHC)*, pages 436–441. IEEE, 2017.

Catherine Donaldson, Raymond Tallis, Simon Miller, Alan Sunderland, Roger Lemon, and Valerie Pomeroy. Effects of conventional physical therapy and functional strength training on upper limb motor recovery after stroke: a randomized phase ii study. *Neurorehabilitation and neural repair*, 23(4):389–397, 2009.

Osama Dorgham, Ibrahim Al-Mherat, Jawdat Al-Shaer, Sulieman Bani-Ahmad, and Stephen Laycock. Smart system for prediction of accurate surface electromyography signals using an artificial neural network. *Future Internet*, 11(1):25, 2019.

Susan Doyle, Sally Bennett, Susan E Fasoli, and Kryss T McKenna. Interventions for sensory impairment in the upper limb after stroke. *Cochrane Database of Systematic Reviews*, (6), 2010.

B Dubois, A Slachevsky, I Litvan, and BFAB Pillon. The fab a frontal assessment battery at bedside. *Neurology*, 55(11):1621–1626, 2000. ISSN 0028-3878.

Pamela W Duncan, Larry B Goldstein, David Matchar, George W Divine, and John Feussner. Measurement of motor recovery after stroke. outcome assessment and sample size requirements. *Stroke*, 23(8):1084–1089, 1992.

Christophe Duret, Emilie Hutin, Laurent Lehenaff, and Jean-Michel Gracies. Do all sub acute stroke patients benefit from robot-assisted therapy? a retrospective study. *Restorative neurology and neuroscience*, 33(1):57–65, 2015.

Christophe Duret, Anne-Gaëlle Grosmaire, and Hermano Igo Krebs. Robot-assisted therapy in upper extremity hemiparesis: overview of an evidence-based approach. *Frontiers in Neurology*, 10:412, 2019.

Jeremy L Emken, Raul Benitez, and David J Reinkensmeyer. Human-robot cooperative movement training: learning a novel sensory motor transformation during walking with robotic assistance-as-needed. *Journal of neuroengineering and rehabilitation*, 4(1):1–16, 2007.

Susan E Fasoli and Catherine P Adans-Dester. A paradigm shift: Rehabilitation robotics, cognitive skills training and function after stroke. *Frontiers in neurology*, 10:1088, 2019.

Joanne Feeney, George M Savva, Claire O'Regan, Bellinda King-Kallimanis, Hilary Cronin, and Rose Anne Kenny. Measurement error, reliability, and minimum detectable change in the mini-mental state examination, montreal cognitive assessment, and color trails test among community living middle-aged and older adults. *Journal of Alzheimer's Disease*, 53 (3):1107–1114, 2016. ISSN 1387-2877.

Thomas Feix, Javier Romero, Heinz-Bodo Schmiedmayer, Aaron M Dollar, and Danica Kragic. The grasp taxonomy of human grasp types. *IEEE Transactions on human-machine systems*, 46(1):66–77, 2015.

Heidi C Fischer, Kathy Stubblefield, Tiffany Kline, Xun Luo, Robert V Kenyon, and Derek G Kamper. Hand rehabilitation following stroke: a pilot study of assisted finger extension training in a virtual environment. *Topics in stroke rehabilitation*, 14(1):1–12, 2007. ISSN 1074-9357.

Marshal F Folstein, Susan E Folstein, and Paul R McHugh. "mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *Journal of psychiatric research*, 12(3):189–198, 1975. ISSN 0022-3956.

Food, Drug Administration, et al. Design considerations for devices intended for home use, 2012.

International Organization for Standardization. *Ergonomics of Human-system Interaction: Part 210: Human-centred Design for Interactive Systems*. ISO, 2019.

Rita Formisano, Patrizia Pantano, M Gabriella Buzzi, Vincenzo Vinicola, Francesca Penta, Piero Barbanti, and Gian Luigi Lenzi. Late motor recovery is influenced by muscle tone changes after stroke. *Archives of physical medicine and rehabilitation*, 86(2):308–311, 2005.

M Franceschini, F Porta La, M Agosti, and M Massucci. Is health-related-quality of life of stroke patients influenced by neurological impairments at one year after stroke? *European journal of physical and rehabilitation medicine*, 46(3):389–399, 2010.

Beverley French, Lois H Thomas, Jacqueline Coupe, Naoimh E McMahon, Louise Connell, Joanna Harrison, Christopher J Sutton, Svetlana Tishkovskaya, and Caroline L Watkins. Repetitive task training for improving functional ability after stroke. *Cochrane database of systematic reviews*, (11), 2016. ISSN 1465-1858.

Axel R Fugl-Meyer, L Jääskö, Ingegerd Leyman, Sigyn Olsson, and Solveig Steglind. The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. *Scandinavian journal of rehabilitation medicine*, 7(1):13–31, 1975. ISSN 0036-5505.

Johan Gäverth, Ann-Christin Eliasson, Kjell Kullander, Jörgen Borg, Påvel G Lindberg, and Hans Forssberg. Sensitivity of the neuroflexor method to measure change in spasticity after treatment with bot ulinum toxin a in wrist and finger muscles. *Journal of rehabilitation medicine*, 46(7):629–634, 2014.

Marco Germanotta, Valerio Gower, Dionysia Papadopoulou, Arianna Cruciani, Cristiano Pecchioli, Rita Mosca, Gabriele Speranza, Catuscia Falsini, Francesca Cecchi, Federica Vannetti, et al. Reliability, validity and discriminant ability of a robotic device for finger training in patients with subacute stroke. *Journal of NeuroEngineering and Rehabilitation*, 17(1):1–10, 2020.

Christian Giang, Elvira Pirondini, Nawal Kinany, Camilla Pierella, Alessandro Panarese, Martina Coscia, Jenifer Miehlbradt, Cécile Magnin, Pierre Nicolo, Adrian Guggisberg, et al. Motor improvement estimation and task adaptation for personalized robot-aided therapy: a feasibility study. *Biomedical engineering online*, 19:1–25, 2020.

Oonagh M Giggins, Ulrik McCarthy Persson, and Brian Caulfield. Biofeedback in rehabilitation. *Journal of neuroengineering and rehabilitation*, 10(1):60, 2013.

Glen Gillen. *Stroke rehabilitation: a function-based approach*. Elsevier Health Sciences, 2015.

Cristian Gmez-Portes, José Jesús Castro-Schez, Javier Albusac, Dorothy N Monekosso, and David Vallejo. A fuzzy recommendation system for the automatic personalization of physical rehabilitation exercises in stroke patients. *Mathematics*, 9(12):1427, 2021.

MM Gomez, AF Tomas, C Torregrosa, and TC Kabrador. The family as a therapeutic collaborator in modified constraint-induced movement therapy. *WFOT Bull*, 70:54–61, 2014.

Donald Greg Pitts and Shirley Peganoff O'Brien. Splinting the hand to enhance motor control and brain plasticity. *Topics in stroke rehabilitation*, 15(5):456–467, 2008.

Florian Grimm, Georgios Naros, and Alireza Gharabaghi. Closed-loop task difficulty adaptation during virtual reality reach-to-grasp training assisted with an exoskeleton for stroke rehabilitation. *Frontiers in neuroscience*, 10:518, 2016.

Anne-Gaëlle Grosmaire, Christophe Duret, and Hermano Igo Krebs. Robot-assisted therapy in upper extremity hemiparesis: overview of an evidence-based approach. *Frontiers in Neurology*, 10:412, 2019. ISSN 1664-2295.

Osman Hakan Gündüz and Canan Şanal Toprak. Hand function in stroke. In *Hand Function*, pages 125–135. Springer, 2019.

Arzu Guneysu Ozgur, Maximilian Jonas Wessel, Wafa Johal, Kshitij Sharma, Ayberk Özgür, Philippe Vuadens, Francesco Mondada, Friedhelm Christoph Hummel, and Pierre Dillenbourg. Iterative design of an upper limb rehabilitation game with tangible robots. In *Proceedings of the 2018 ACM/IEEE International Conference on Human-Robot Interaction*, pages 241–250, 2018.

Abhishek Gupta, Marcia K O'Malley, Volkan Patoglu, and Charles Burgar. Design, control and performance of ricewrist: a force feedback wrist exoskeleton for rehabilitation and training. *The International Journal of Robotics Research*, 27(2):233–251, 2008.

C Hagen. Rancho-los amigos levels of cognitive functioning-revised. *TBI Rehabilitation Managed Care Environment: An Interdisciplinary Approach to Rehabilitation. Continuing Education Programs of America, San Antonio, TX*, 2000.

PH Hammond, PA Merton, and G Gr Sutton. Nervous gradation of muscular contraction. *British medical bulletin*, 12(3):214–218, 1956.

Chao Han, Qiang Wang, Ping-ping Meng, and Ming-zhu Qi. Effects of intensity of arm training on hemiplegic upper extremity motor recovery in stroke patients: a randomized controlled trial. *Clinical rehabilitation*, 27(1):75–81, 2013. ISSN 0269-2155.

Lu Han, Diane Law-Gibson, and Michael Reding. Key neurological impairments influence function-related group outcomes after stroke. *Stroke*, 33(7):1920–1924, 2002.

Sandra G Hart. Nasa-task load index (nasa-tlx); 20 years later. In *Proceedings of the human factors and ergonomics society annual meeting*, volume 50, pages 904–908. Sage Publications Sage CA: Los Angeles, CA, 2006. ISBN 1541-9312.

Samar M Hatem, Geoffroy Saussez, Margaux della Faille, Vincent Prist, Xue Zhang, Delphine Dispa, and Yannick Bleyenheuft. Rehabilitation of motor function after stroke: a multiple systematic review focused on techniques to stimulate upper extremity recovery. *Frontiers in human neuroscience*, 10:442, 2016.

Nicholas G Hatsopoulos and Aaron J Suminski. Sensing with the motor cortex. *Neuron*, 72(3): 477–487, 2011.

Kathryn S Hayward, Bridee A Neibling, and Ruth N Barker. Self-administered, home-based smart (sensorimotor active rehabilitation training) arm training: a single-case report. *American Journal of Occupational Therapy*, 69(4):6904210020p1–6904210020p8, 2015. ISSN 0272-9490.

Vincent Hayward and Oliver R Astley. *Performance measures for haptic interfaces*, pages 195–206. Springer, 1996.

Stefan Hesse, H Kuhlmann, J Wilk, C Tomelleri, and Stephen GB Kirker. A new electromechanical trainer for sensorimotor rehabilitation of paralysed fingers: a case series in chronic and acute stroke patients. *Journal of Neuroengineering and rehabilitation*, 5(1):21, 2008. ISSN 1743-0003.

Stefan Hesse, Anke Heß, Cordula Werner C, Nadine Kabbert, and Rüdiger Buschfort. Effect on arm function and cost of robot-assisted group therapy in subacute patients with stroke and a moderately to severely affected arm: a randomized controlled trial. *Clinical rehabilitation*, 28(7):637–647, 2014.

Nadia Hocine, Abdelkader Gouaïch, Stefano A Cerri, Denis Mottet, Jérome Froger, and Isabelle Laffont. Adaptation in serious games for upper-limb rehabilitation: an approach to improve training outcomes. *User Modeling & User-Adapted Interaction*, 25(1):65–98, 2015. ISSN 0924-1868.

Neville Hogan and Stephen P Buerger. Impedance and interaction control. *Robotics and automation handbook*, 1, 2005.

Hannes Höppner, Maximilian Große-Dunker, Georg Stillfried, Justin Bayer, and Patrick Van Der Smagt. Key insights into hand biomechanics: human grip stiffness can be decoupled from force by cocontraction and predicted from electromyography. *Frontiers in neurorobotics*, 11:17, 2017.

Yu-wei Hsieh, Ching-yi Wu, Keh-chung Lin, Grace Yao, Kuen-yuh Wu, and Ya-ju Chang. Dose–response relationship of robot-assisted stroke motor rehabilitation: the impact of initial motor status. *Stroke*, 43(10):2729–2734, 2012.

Yu-wei Hsieh, Keh-chung Lin, Ching-yi Wu, Tsai-yu Shih, Ming-wei Li, and Chia-ling Chen. Comparison of proximal versus distal upper-limb robotic rehabilitation on motor performance after stroke: a cluster controlled trial. *Scientific reports*, 8(1):1–11, 2018.

Xianwei Huang, Fazel Naghdy, Golshah Naghdy, and Haiping Du. Clinical effectiveness of combined virtual reality and robot assisted fine hand motion rehabilitation in subacute stroke patients. In *2017 International Conference on Rehabilitation Robotics (ICORR)*, pages 511–515. IEEE, 2017.

Xianwei Huang, Fazel Naghdy, Golshah Naghdy, Haiping Du, and Catherine Todd. The combined effects of adaptive control and virtual reality on robot-assisted fine hand motion rehabilitation in chronic stroke patients: a case study. *Journal of Stroke and Cerebrovascular Diseases*, 27(1):221–228, 2018.

Isobel J Hubbard, Mark W Parsons, Cheryl Neilson, and Leeanne M Carey. Task-specific training: evidence for and translation to clinical practice. *Occupational therapy international*, 16 (3-4):175–189, 2009.

Walter Huber, Gudrun Klingenberg, Klaus Poeck, and Klaus Willmes. Die supplemente zum aachener aphasie test, aufbau und resultate der validierung. *Neurolinguistik*, 7(1):43–66, 1993.

Friedhelm C Hummel, Pablo Celnik, Alvero Pascual-Leone, Felipe Fregni, Winston D Byblow, Cathrin M Buetefisch, John Rothwell, Leonardo G Cohen, and Christian Gerloff. Controversy: noninvasive and invasive cortical stimulation show efficacy in treating stroke patients. *Brain stimulation*, 1(4):370–382, 2008.

Yu-Hsiu Hung, Pin-Ju Chen, and Wan-Zi Lin. Design factors and opportunities of rehabilitation robots in upper-limb training after stroke. In *14th International Conference on Ubiquitous Robots and Ambient Intelligence (URAI)*, pages 650–654. IEEE, 2017. ISBN 1509030565.

Chang Ho Hwang, Jin Wan Seong, and Dae-Sik Son. Individual finger synchronized robot-assisted hand rehabilitation in subacute to chronic stroke: a prospective randomized clinical trial of efficacy. *Clinical Rehabilitation*, 26(8):696–704, 2012. ISSN 0269-2155.

Koichi Hyakutake, Takashi Morishita, Kazuya Saita, Hiroyuki Fukuda, Etsuji Shiota, Yasuki Higaki, Tooru Inoue, and Yoshinari Uehara. Effects of home-based robotic therapy involving the single-joint hybrid assistive limb robotic suit in the chronic phase of stroke: A pilot study. *Journal of international biomedical research*, 2019. ISSN 2314-6133.

James N Ingram and Daniel M Wolpert. Naturalistic approaches to sensorimotor control. *Progress in Brain Research*, 191:3–29, 2011.

M Kamrul Islam and Iris Brunner. Cost-analysis of virtual reality training based on the virtual reality for upper extremity in subacute stroke (virtues) trial. *International Journal of Technology Assessment in Health Care*, 35(5):373–378, 2019.

Philip L Jackson, Martin F Lafleur, Francine Malouin, Carol Richards, and Julien Doyon. Potential role of mental practice using motor imagery in neurologic rehabilitation. *Archives of physical medicine and rehabilitation*, 82(8):1133–1141, 2001.

Néstor J Jarque-Bou, Alessandro Scano, Manfredo Atzori, and Henning Müller. Kinematic synergies of hand grasps: a comprehensive study on a large publicly available dataset. *Journal of neuroengineering and rehabilitation*, 16(1):1–14, 2019.

Shanie Amanda Liyanagamage Jayasinghe. The role of sensory stimulation on motor learning via action observation: a mini review. *Journal of neurophysiology*, 121(3):729–731, 2019.

Matthew Strider Jeffers, Sudhir Karthikeyan, Mariana Gomez-Smith, Sarah Gasinzigwa, Jannis Achenbach, Astrid Feiten, and Dale Corbett. Does stroke rehabilitation really matter? part b: an algorithm for prescribing an effective intensity of rehabilitation. *Neurorehabilitation and neural repair*, 32(1):73–83, 2018.

Roland S Johansson and J Randall Flanagan. Coding and use of tactile signals from the fingertips in object manipulation tasks. *Nature Reviews Neuroscience*, 10(5):345–359, 2009.

Roland S Johansson and AB Vallbo. Tactile sensibility in the human hand: relative and absolute densities of four types of mechanoreceptive units in glabrous skin. *The Journal of physiology*, 286(1):283–300, 1979.

Liam Johnson, Marie-Louise Bird, Makii Muthalib, and Wei-Peng Teo. An innovative stroke interactive virtual therapy (strive) online platform for community-dwelling stroke survivors: a randomised controlled trial. *Archives of Physical Medicine and Rehabilitation*, 2020. ISSN 0003-9993.

Theresa A Jones. Motor compensation and its effects on neural reorganization after stroke. *Nature Reviews Neuroscience*, 18(5):267–280, 2017.

Fabian Just, Daniel Gunz, Jaime Duarte, Davide Simonetti, Robert Riener, and Georg Rauter. Improving usability of rehabilitation robots: Hand module evaluation of the armin exoskeleton. In *International Symposium on Wearable Robotics*, pages 80–84. Springer, 2018.

Herman Kabat and Margaret Knott. Proprioceptive facilitation technics for treatment of paralysis. *Physical Therapy*, 33(2):53–64, 1953.

Anna M Kamelska-Sadowska, Joanna Wojtkiewicz, and Ireneusz M Kowalski. Review of the current knowledge on the role of stem cell transplantation in neurorehabilitation. *BioMed research international*, 2019, 2019.

Derek G Kamper. Restoration of hand function in stroke and spinal cord injury. In *Neurorehabilitation technology*, pages 311–331. Springer, 2016.

DG Kamper, BD Schmit, and WZ Rymer. Effect of muscle biomechanics on the quantification of spasticity. *Annals of biomedical engineering*, 29(12):1122–1134, 2001.

Christoph M Kanzler, Mike D Rinderknecht, Anne Schwarz, Ilse Lamers, Cynthia Gagnon, Jeremia PO Held, Peter Feys, Andreas R Luft, Roger Gassert, and Olivier Lambercy. A data-driven framework for selecting and validating digital health metrics: use-case in neurological sensorimotor impairments. *NPJ digital medicine*, 3(1):1–17, 2020.

Akim Kapsalyamov, Shahid Hussain, Askhat Sharipov, and Prashant Jamwal. Brain–computer interface and assist-as-needed model for upper limb robotic arm. *Advances in Mechanical Engineering*, 11(9):1687814019875537, 2019.

T. L. Katner and E. J. Kasarskis. *Muscle Tone*, pages 194–196. Academic Press, Oxford, 2014. ISBN 978-0-12-385158-1.

Hiroyuki Kato and Masahiro Izumiyama. Impaired motor control due to proprioceptive sensory loss in a patient with cerebral infarction localized to the postcentral gyrus. *Journal of rehabilitation medicine*, 47(2):187–190, 2015.

Richard T Katz and W Zev Rymer. Spastic hypertonia: mechanisms and measurement. *Archives of physical medicine and rehabilitation*, 70(2):144–155, 1989.

Peter J Kelly, Karen L Furie, Saad Shafqat, Nikoletta Rallis, Yuchiao Chang, and Joel Stein. Functional recovery following rehabilitation after hemorrhagic and ischemic stroke. *Archives of physical medicine and rehabilitation*, 84(7):968–972, 2003. ISSN 0003-9993.

Margaret Kelly-Hayes, Alexa Beiser, Carlos S Kase, Amy Scaramucci, Ralph B D'Agostino, and Philip A Wolf. The influence of gender and age on disability following ischemic stroke: the framingham study. *Journal of Stroke and Cerebrovascular Diseases*, 12(3):119–126, 2003. ISSN 1052-3057.

Jeffrey M Kenzie, Jennifer A Semrau, Michael D Hill, Stephen H Scott, and Sean P Dukelow. A composite robotic-based measure of upper limb proprioception. *Journal of neuroengineering and rehabilitation*, 14(1):1–12, 2017.

Simon S Kessner, Ulrike Bingel, and Götz Thomalla. Somatosensory deficits after stroke: a scoping review. *Topics in Stroke Rehabilitation*, 23(2):136–146, 2016.

KX Khor, PJH Chin, AR Hisyam, CF Yeong, ALT Narayanan, and ELM Su. Development of cr2-haptic: A compact and portable rehabilitation robot for wrist and forearm training. In *2014 IEEE Conference on Biomedical Engineering and Sciences (IECBES)*, pages 424–429. IEEE, 2014. ISBN 1479940844.

Sharon L Kilbreath and Robert C Heard. Frequency of hand use in healthy older persons. *Australian Journal of Physiotherapy*, 51(2):119–122, 2005.

Verena Klamroth-Marganska, Javier Blanco, Katrin Campen, Armin Curt, Volker Dietz, Thierry Ettlin, Morena Felder, Bernd Fellinghauer, Marco Guidali, and Anja Kollmar. Three-dimensional, task-specific robot therapy of the arm after stroke: a multicentre, parallel-group randomised trial. *The Lancet Neurology*, 13(2):159–166, 2014. ISSN 1474-4422.

Jeffrey A Kleim and Theresa A Jones. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. *Journal of speech, language, and hearing research*, 2008.

Jeffrey A Kleim, Scott Barbay, and Randolph J Nudo. Functional reorganization of the rat motor cortex following motor skill learning. *Journal of neurophysiology*, 80(6):3321–3325, 1998.

Jeffrey A Kleim, Scott Barbay, Natalie R Cooper, Theresa M Hogg, Chelsea N Reidel, Michael S Remple, and Randolph J Nudo. Motor learning-dependent synaptogenesis is localized to functionally reorganized motor cortex. *Neurobiology of learning and memory*, 77(1):63–77, 2002.

W Klomjai, A Lackmy-Vallée, N Roche, P Pradat-Diehl, V Marchand-Pauvert, and R Katz. Repetitive transcranial magnetic stimulation and transcranial direct current stimulation in motor rehabilitation after stroke: an update. *Annals of physical and rehabilitation medicine*, 58(4):220–224, 2015.

Keng H Kong, Jeanette Lee, and Karen S Chua. Occurrence and temporal evolution of upper limb spasticity in stroke patients admitted to a rehabilitation unit. *Archives of physical medicine and rehabilitation*, 93(1):143–148, 2012.

John W Krakauer, Alkis M Hadjiosif, Jing Xu, Aaron L Wong, and Adrian M Haith. Motor learning. *Comprehensive Physiology*, 9(2):613–663, 2011.

Nancy G Kutner, Rebecca Zhang, Andrew J Butler, Steven L Wolf, and Jay L Alberts. Quality-of-life change associated with robotic-assisted therapy to improve hand motor function in patients with subacute stroke: a randomized clinical trial. *Physical therapy*, 90(4):493–504, 2010. ISSN 0031-9023.

Gert Kwakkel, Boudewijn J Kollen, Jeroen van der Grond, and Arie JH Prevo. Probability of regaining dexterity in the flaccid upper limb: impact of severity of paresis and time since onset in acute stroke. *Stroke*, 34(9):2181–2186, 2003.

Gert Kwakkel, Janne M Veerbeek, Erwin EH van Wegen, and Steven L Wolf. Constraint-induced movement therapy after stroke. *The Lancet Neurology*, 14(2):224–234, 2015.

Mona Laible, Steven Grieshammer, Gundula Seidel, Michel Rijntjes, Cornelius Weiller, and Farsin Hamzei. Association of activity changes in the primary sensory cortex with successful motor rehabilitation of the hand following stroke. *Neurorehabilitation and neural repair*, 26 (7):881–888, 2012.

Olivier Lambercy, Ludovic Dovat, Roger Gassert, Etienne Burdet, Chee Leong Teo, and Theodore Milner. A haptic knob for rehabilitation of hand function. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 15(3):356–366, 2007. ISSN 1534-4320.

Olivier Lambercy, Ludovic Dovat, Hong Yun, Seng Kwee Wee, Christopher WK Kuah, Karen SG Chua, Roger Gassert, Theodore E Milner, Chee Leong Teo, and Etienne Burdet. Effects of a robot-assisted training of grasp and pronation/supination in chronic stroke: a pilot study. *Journal of neuroengineering and rehabilitation*, 8(1):63, 2011. ISSN 1743-0003.

Olivier Lambercy, Jean-Claude Metzger, Marco Santello, and Roger Gassert. A method to study precision grip control in viscoelastic force fields using a robotic gripper. *IEEE Transactions on Biomedical Engineering*, 62(1):39–48, 2014. ISSN 0018-9294.

Olivier Lambercy, Raffaele Ranzani, and Roger Gassert. *Robot-assisted rehabilitation of hand function*, pages 205–225. Elsevier, 2018.

Olivier Lambercy, Rea Lehner, Karen SuiGeok Chua, Seng Kwee Wee, Deshan Kumar Rajeswaran, Christopher Wee Keong Kuah, Wei Tech Ang, Phyllis Liang, Domenico Campolo, Asif Hussain, et al. Neurorehabilitation from a distance: can intelligent technology support decentralized access to quality therapy? *Frontiers in Robotics and AI*, 8:126, 2021.

James W Lance. Pathophysiology of spasticity and clinical experience with baclofen. *Spasticity: disordered motor control*, pages 185–204, 1980.

Catherine E Lang, Jillian R MacDonald, Darcy S Reisman, Lara Boyd, Teresa Jacobson Kimberley, Sheila M Schindler-Ivens, T George Hornby, Sandy A Ross, and Patricia L Scheets. Observation of amounts of movement practice provided during stroke rehabilitation. *Archives of physical medicine and rehabilitation*, 90(10):1692–1698, 2009.

Catherine E Lang, Keith R Lohse, and Rebecca L Birkenmeier. Dose and timing in neurorehabilitation: prescribing motor therapy after stroke. *Current opinion in neurology*, 28(6):549, 2015.

Catherine E Lang, Michael J Strube, Marghuretta D Bland, Kimberly J Waddell, Kendra M Cherry-Allen, Randolph J Nudo, Alexander W Dromerick, and Rebecca L Birkenmeier. Dose response of task-specific upper limb training in people at least 6 months poststroke: A phase ii, single-blind, randomized, controlled trial. *Annals of neurology*, 80(3):342–354, 2016.

Natasha A Lannin and RD Herbert. Is hand splinting effective for adults following stroke? a systematic review and methodological critique of published research. *Clinical rehabilitation*, 17(8):807–816, 2003.

Jeffrey Laut, Francesco Cappa, Oded Nov, and Maurizio Porfiri. Increasing patient engagement in rehabilitation exercises using computer-based citizen science. *PloS one*, 10(3), 2015.

K Laver, S George, S Thomas, JE Deutsch, and M Crotty. Virtual reality for stroke rehabilitation: an abridged version of a cochrane review. *European Journal of Physical and Rehabilitation Medicine*, 51(4):497–506, 2015.

Kate E Laver, Zoe Adey-Wakeling, Maria Crotty, Natasha A Lannin, Stacey George, and Catherine Sherrington. Telerehabilitation services for stroke. *Cochrane Database of Systematic Reviews*, (1), 2020. ISSN 1465-1858.

Enas S. Lawrence, Catherine Coshall, Ruth Dundas, Judy Stewart, Anthony G. Rudd, Robin Howard, and Charles D. A. Wolfe. Estimates of the prevalence of acute stroke impairments and disability in a multiethnic population. *Stroke*, 32:1279–1284, 2001. ISSN 0039-2499.

Moonhee Lee, Matheson Rittenhouse, and Hussein A Abdullah. Design issues for therapeutic robot systems: results from a survey of physiotherapists. *Journal of Intelligent and robotic systems*, 42(3):239–252, 2005.

Shi-Uk Lee, Dae-Yul Kim, Sung-Hye Park, Deok-Hyung Choi, Hee-Won Park, and Tai Ryoon Han. Mild to moderate early exercise promotes recovery from cerebral ischemia in rats. *Canadian journal of neurological sciences*, 36(4):443–449, 2009.

Sunghee Lee, Seahyun Bae, Daejung Jeon, and Kyung Yoon Kim. The effects of cognitive exercise therapy on chronic stroke patients' upper limb functions, activities of daily living and quality of life. *Journal of physical therapy science*, 27(9):2787–2791, 2015a.

Ya-yun Lee, Keh-chung Lin, Hsiao-ju Cheng, Ching-yi Wu, Yu-wei Hsieh, and Chih-kuang Chen. Effects of combining robot-assisted therapy with neuromuscular electrical stimulation on motor impairment, motor and daily function, and quality of life in patients with chronic stroke: a double-blinded randomized controlled trial. *Journal of neuroengineering and rehabilitation*, 12(1):96, 2015b.

Ryanne JM Lemmens, Annick AA Timmermans, Yvonne JM Janssen-Potten, Sanne ANTD Pulles, Richard PJ Geers, Wilbert GM Bakx, Rob JEM Smeets, and Henk AM Seelen. Accelerometry measuring the outcome of robot-supported upper limb training in chronic stroke: a randomized controlled trial. *PloS one*, 9(5), 2014.

Mindy F Levin, Jeffrey A Kleim, and Steven L Wolf. What do motor "recovery" and "compensation" mean in patients following stroke? *Neurorehabilitation and neural repair*, 23(4): 313–319, 2009.

Robert M Levy, Richard L Harvey, Brett M Kissela, Carolee J Winstein, Helmi L Lutsep, Todd B Parrish, Steven C Cramer, and Lalit Venkatesan. Epidural electrical stimulation for stroke rehabilitation: results of the prospective, multicenter, randomized, single-blinded everest trial. *Neurorehabilitation and neural repair*, 30(2):107–119, 2016.

James R Lewis and Jeff Sauro. The factor structure of the system usability scale. In *International conference on human centered design*, pages 94–103. Springer, 2009.

Muriel Deutsch Lezak, Diane B Howieson, David W Loring, Jill S Fischer, et al. *Neuropsychological assessment*. Oxford University Press, USA, 2004.

Kun-Hsi Liao. The effect of wrist posture and forearm position on the control capability of hand-grip strength. *International Journal of Industrial Engineering*, 21(6):295–303, 2014.

Eline CC van Lieshout, Ingrid G van de Port, Rick M Dijkhuizen, and Johanna MA Visser-Meily. Does upper limb strength play a prominent role in health-related quality of life in stroke patients discharged from inpatient rehabilitation? *Topics in Stroke Rehabilitation*, pages 1–9, 2020.

M Patrice Lindsay, Bo Norrving, Ralph L Sacco, Michael Brainin, Werner Hacke, Sheila Martins, Jeyaraj Pandian, and Valery Feigin. World stroke organization (wso): global stroke fact sheet 2019, 2019.

Xi-hua Liu, Juan Huai, Jie Gao, Yang Zhang, and Shou-wei Yue. Constraint-induced movement therapy in treatment of acute and sub-acute stroke: a meta-analysis of 16 randomized controlled trials. *Neural regeneration research*, 12(9):1443, 2017.

Jessica Livingston-Thomas, Paul Nelson, Sudhir Karthikeyan, Sabina Antonescu, Matthew Strider Jeffers, Susan Marzolini, and Dale Corbett. Exercise and environmental enrichment as enablers of task-specific neuroplasticity and stroke recovery. *Neurotherapeutics*, 13(2):395–402, 2016.

Roberto Lloréns, Enrique Noé, Carolina Colomer, and Mariano Alcañiz. Effectiveness, usability, and cost-benefit of a virtual reality–based telerehabilitation program for balance recovery after stroke: A randomized controlled trial. *Archives of physical medicine and rehabilitation*, 96(3):418–425, 2015.

Albert C Lo, Peter D Guarino, Lorie G Richards, Jodie K Haselkorn, George F Wittenberg, Daniel G Federman, Robert J Ringer, Todd H Wagner, Hermano I Krebs, and Bruce T Volpe. Robot-assisted therapy for long-term upper-limb impairment after stroke. *New England Journal of Medicine*, 362(19):1772–1783, 2010. ISSN 0028-4793.

Jessica W Lo, John D Crawford, David W Desmond, Olivier Godefroy, Hanna Jokinen, Simin Mahinrad, Hee-Joon Bae, Jae-Sung Lim, Sebastian Köhler, Elles Douven, et al. Profile of and risk factors for poststroke cognitive impairment in diverse ethnoregional groups. *Neurology*, 93(24):e2257–e2271, 2019a.

Kenneth Lo, Matthew Stephenson, and Craig Lockwood. The economic cost of robotic rehabilitation for adult stroke patients: a systematic review. *JBI Evidence Synthesis*, 17(4):520–547, 2019b.

Keith R Lohse, Catherine E Lang, and Lara A Boyd. Is more better? using metadata to explore dose–response relationships in stroke rehabilitation. *Stroke*, 45(7):2053–2058, 2014. ISSN 0039-2499.

Rui CV Loureiro and William S Harwin. Reach & grasp therapy: design and control of a 9-dof robotic neuro-rehabilitation system. In *IEEE 10th International Conference on Rehabilitation Robotics*, pages 757–763. IEEE, 2007. ISBN 1424413192.

Rui CV Loureiro, Bob Lamperd, Christine Collin, and William S Harwin. Reach & grasp therapy: Effects of the gentle/g system assessing sub-acute stroke whole-arm rehabilitation. In *Rehabilitation Robotics, 2009. ICORR 2009. IEEE International Conference on*, pages 755–760. IEEE, 2009. ISBN 1424437881.

Elaine C Lu, Rosalie H Wang, Debbie Hebert, Jennifer Boger, Mary P Galea, and Alex Mihailidis. The development of an upper limb stroke rehabilitation robot: identification of clinical practices and design requirements through a survey of therapists. *Disability and Rehabilitation: Assistive Technology*, 6(5):420–431, 2011. ISSN 1748-3107.

Yafei Lu and Dapeng Fan. Transmission backlash of precise cable drive system. *Proceedings of the Institution of Mechanical Engineers, Part C: Journal of Mechanical Engineering Science*, 227(10):2256–2267, 2013. ISSN 0954-4062.

Peter S Lum, Charles G Burgar, Machiel Van der Loos, and Peggy C Shor. Mime robotic device for upper-limb neurorehabilitation in subacute stroke subjects: A follow-up study. *Journal of rehabilitation research and development*, 43(5):631, 2006. ISSN 0748-7711.

Peter S Lum, Sasha B Godfrey, Elizabeth B Brokaw, Rahsaan J Holley, and Diane Nichols. Robotic approaches for rehabilitation of hand function after stroke. *American journal of physical medicine & rehabilitation*, 91(11):S242–S254, 2012. ISSN 0894-9115.

Erik Lundström, Anja Smits, Andreas Terént, and Jörgen Borg. Time-course and determinants of spasticity during the first six months following first-ever stroke. *Journal of rehabilitation medicine*, 42(4):296–301, 2010.

Paweł Maciejasz, Jörg Eschweiler, Kurt Gerlach-Hahn, Arne Jansen-Troy, and Steffen Leonhardt. A survey on robotic devices for upper limb rehabilitation. *Journal of neuroengineering and rehabilitation*, 11(1):3, 2014. ISSN 1743-0003.

Crystal L MacLellan, Michael B Keough, Shirley Granter-Button, Garry A Chernenko, Stephanie Butt, and Dale Corbett. A critical threshold of rehabilitation involving brain-derived neurotrophic factor is required for poststroke recovery. *Neurorehabilitation and neural repair*, 25(8):740–748, 2011.

Monica A Maldonado, Rachel P Allred, Erik L Felthauser, and Theresa A Jones. Motor skill training, but not voluntary exercise, improves skilled reaching after unilateral ischemic lesions of the sensorimotor cortex in rats. *Neurorehabilitation and neural repair*, 22(3): 250–261, 2008.

Stefano Masiero and Mario Armani. Upper-limb robot-assisted therapy in rehabilitation of acute stroke patients: focused review and results of new randomized controlled trial. *Journal of rehabilitation research and development*, 48(4):355, 2011. ISSN 0748-7711.

Thomas H Massie and J Kenneth Salisbury. The phantom haptic interface: A device for probing virtual objects. In *Proceedings of the ASME winter annual meeting, symposium on haptic interfaces for virtual environment and teleoperator systems*, volume 55, pages 295–300. Chicago, IL, 1994.

Virgil Mathiowetz, Gloria Volland, Nancy Kashman, and Karen Weber. Adult norms for the box and block test of manual dexterity. *American Journal of Occupational Therapy*, 39(6): 386–391, 1985. ISSN 0272-9490.

Stefano Mazzoleni, Christophe Duret, Anne Gaëlle Grosmaire, and Elena Battini. Combining upper limb robotic rehabilitation with other therapeutic approaches after stroke: Current status, rationale, and challenges. *BioMed Research International*, 2017:8905637, 2017. ISSN 2314-6133.

Jessica McCabe, Michelle Monkiewicz, John Holcomb, Svetlana Pundik, and Janis J Daly. Comparison of robotics, functional electrical stimulation, and motor learning methods for treatment of persistent upper extremity dysfunction after stroke: a randomized controlled trial. *Archives of physical medicine and rehabilitation*, 96(6):981–990, 2015. ISSN 0003-9993.

Jessica P McCabe, Dennyse Henniger, Jessica Perkins, Margaret Skelly, Curtis Tatsuoka, and Svetlana Pundik. Feasibility and clinical experience of implementing a myoelectric upper limb orthosis in the rehabilitation of chronic stroke patients: A clinical case series report. *PloS one*, 14(4), 2019.

Annabel McDermott et al. Task-oriented training–upper extremity. *Stroke Engine*, 2014.

Sara McEwen, Helene Polatajko, Carolyn Baum, Jorge Rios, Dianne Cirone, Meghan Doherty, and Timothy Wolf. Combined cognitive-strategy and task-specific training improve transfer to untrained activities in subacute stroke: an exploratory randomized controlled trial. *Neurorehabilitation and neural repair*, 29(6):526–536, 2015.

Sara E McEwen, Maria PJ Huijbregts, Jennifer D Ryan, and Helene J Polatajko. Cognitive strategy use to enhance motor skill acquisition post-stroke: a critical review. *Brain Injury*, 23(4):263–277, 2009. ISSN 0269-9052.

Jan Mehrholz, Marcus Pohl, Thomas Platz, Joachim Kugler, and Bernhard Elsner. Electromechanical and robot-assisted arm training for improving activities of daily living, arm function, and arm muscle strength after stroke. *Cochrane Database of Systematic Reviews*, (9), 2018.

Alejandro Melendez-Calderon, Davide Piovesan, and Ferdinando A Mussa-Ivaldi. Therapist recognition of impaired muscle groups in simulated multi-joint hypertonia. In *2013 IEEE 13th International Conference on Rehabilitation Robotics (ICORR)*, pages 1–6. IEEE, 2013.

Jean-Claude Metzger, Olivier Lambercy, Dominique Chapuis, and Roger Gassert. Design and characterization of the rehapticknob, a robot for assessment and therapy of hand function. In *Intelligent Robots and Systems (IROS), 2011 IEEE/RSJ International Conference on*, pages 3074–3080. IEEE, 2011. ISBN 1612844561.

Jean-Claude Metzger, Olivier Lambercy, and Roger Gassert. High-fidelity rendering of virtual objects with the rehapticknob-novel avenues in robot-assisted rehabilitation of hand function. In *Haptics Symposium (HAPTICS), 2012 IEEE*, pages 51–56. IEEE, 2012. ISBN 1467308099.

Jean-Claude Metzger, Olivier Lambercy, Antonella Califfi, Fabio M Conti, and Roger Gassert. Neurocognitive robot-assisted therapy of hand function. *IEEE transactions on haptics*, 7(2): 140–149, 2014a. ISSN 1939-1412.

Jean-Claude Metzger, Olivier Lambercy, Antonella Califfi, Daria Dinacci, Claudio Petrillo, Paolo Rossi, Fabio M Conti, and Roger Gassert. Assessment-driven selection and adaptation of exercise difficulty in robot-assisted therapy: a pilot study with a hand rehabilitation robot. *Journal of neuroengineering and rehabilitation*, 11(1):154, 2014b. ISSN 1743-0003.

Jean-Claude M Metzger. *Neurocognitive Robot-Assisted Rehabilitation of Hand Function*. Thesis, ETH Zurich, 2014.

Jan T Meyer, Stefan O Schrade, Olivier Lambercy, and Roger Gassert. User-centered design and evaluation of physical interfaces for an exoskeleton for paraplegic users. In *2019 IEEE 16th International Conference on Rehabilitation Robotics (ICORR)*, pages 1159–1166. IEEE, 2019. ISBN 1728127556.

Stella Maris Michaelsen, Ruth Dannenbaum, and Mindy F Levin. Task-specific training with trunk restraint on arm recovery in stroke: randomized control trial. *Stroke*, 37(1):186–192, 2006.

Laura C Miller and Julius PA Dewald. Involuntary paretic wrist/finger flexion forces and emg increase with shoulder abduction load in individuals with chronic stroke. *Clinical Neurophysiology*, 123(6):1216–1225, 2012.

Jasmine L Mirdamadi and Hannah J Block. Somatosensory changes associated with motor skill learning. *Journal of Neurophysiology*, 123(3):1052–1062, 2020.

George Mochizuki, Andrew Centen, Myles Resnick, Catherine Lowrey, Sean P Dukelow, and Stephen H Scott. Movement kinematics and proprioception in post-stroke spasticity: assessment using the kinarm robotic exoskeleton. *Journal of neuroengineering and rehabilitation*, 16(1):1–13, 2019.

Manuela Morreale, Pasquale Marchione, Antonio Pili, Antonella Lauta, Stefano F Castiglia, Aldo Spallone, Francesco Pierelli, and Patrizia Giacomini. Early versus delayed rehabilitation treatment in hemiplegic patients with ischemic stroke: proprioceptive or cognitive approach. *Eur J Phys Rehabil Med*, 52:81–89, 2016.

Jacqui H Morris, Frederike van Wijck, Sara Joice, Simon A Ogston, Ingrid Cole, and Ronald S MacWalter. A comparison of bilateral and unilateral upper-limb task training in early poststroke rehabilitation: a randomized controlled trial. *Archives of physical medicine and rehabilitation*, 89(7):1237–1245, 2008.

Jacqui H Morris, Frederike Van Wijck, Sara Joice, and Marie Donaghy. Predicting health related quality of life 6 months after stroke: the role of anxiety and upper limb dysfunction. *Disability and rehabilitation*, 35(4):291–299, 2013. ISSN 0963-8288.

Keith W Muir, Diederik Bulters, Mark Willmot, Nikola Sprigg, Anand Dixit, Nick Ward, Pippa Tyrrell, Arshad Majid, Laurence Dunn, Philip Bath, et al. Intracerebral implantation of human neural stem cells and motor recovery after stroke: multicentre prospective single-arm study (pisces-2). *Journal of Neurology, Neurosurgery & Psychiatry*, 91(4):396–401, 2020.

Aditi A Mullick, Sandeep K Subramanian, and Mindy F Levin. Emerging evidence of the association between cognitive deficits and arm motor recovery after stroke: a meta-analysis. *Restorative neurology and neuroscience*, 33(3):389–403, 2015.

Jörn Munzert, Britta Lorey, and Karen Zentgraf. Cognitive motor processes: the role of motor imagery in the study of motor representations. *Brain research reviews*, 60(2):306–326, 2009.

Hirofumi Nakayama, Henrik Stig Jørgensen, Hans Otto Raaschou, and Tom Skyhøj Olsen. Recovery of upper extremity function in stroke patients: The copenhagen stroke study. *Archives of physical medicine and rehabilitation*, 75:394–398, 1994. ISSN 0003-9993.

Hyung Seok Nam, Nhayoung Hong, Minwoo Cho, Chiwon Lee, Han Gil Seo, and Sungwan Kim. Vision-assisted interactive human-in-the-loop distal upper limb rehabilitation robot and its clinical usability test. *Applied Sciences*, 9(15):3106, 2019.

Tobias Nef, Matjaz Mihelj, and Robert Riener. Armin: a robot for patient-cooperative arm therapy. *Medical & Biological Engineering & Computing*, 45(9):887–900, 2007. ISSN 0140-0118.

David L Nelson, Margaret A Mitchell, Paul G Groszewski, Stephen L Pennick, and Paul R Manske. *Wrist range of motion in activities of daily living*, pages 329–334. Springer, 1994.

Victoria Nemchek, Emma M Haan, and Abigail L Kerr. Intermittent skill training results in moderate improvement in functional outcome in a mouse model of ischemic stroke. *Neurorehabilitation and Neural Repair*, 35(1):79–87, 2021.

Jude T Nicholas, Annika M Johannessen, and Trees Van Nunen. *Tactile Working Memory Scale: A Professional Manual*. Nordens välfärdscenter/Nordic Welfare Centre, 2019.

Jakob Nielsen. 10 usability heuristics for user interface design. *Nielsen Norman Group*, 1(1), 1995.

Sharon M Nijenhuis, Gerdienke B Prange-Lasonder, Arno HA Stienen, Johan S Rietman, and Jaap H Buurke. Effects of training with a passive hand orthosis and games at home in chronic stroke: a pilot randomised controlled trial. *Clinical rehabilitation*, 31(2):207–216, 2017. ISSN 0269-2155.

Cynthia C Norkin and D Joyce White. *Measurement of joint motion: a guide to goniometry*. FA Davis, 2016. ISBN 0803658478.

Don Norman. *The design of everyday things: Revised and expanded edition*. Basic books, 2013. ISBN 0465072992.

Sarah Northcott and Katerina Hilari. Why do people lose their friends after a stroke? *International Journal of Language & Communication Disorders*, 46(5):524–534, 2011.

Sarah Northcott, Becky Moss, Kirsty Harrison, and Katerina Hilari. A systematic review of the impact of stroke on social support and social networks: associated factors and patterns of change. *Clinical Rehabilitation*, 30(8):811–831, 2016.

Randoff J Nudo, Garrett W Milliken, W Merzenich Jenkins, and Michæl M Merzenich. Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. *Journal of Neuroscience*, 16(2):785–807, 1996.

Randolph J Nudo. Recovery after brain injury: mechanisms and principles. *Frontiers in human neuroscience*, 7:887, 2013.

RANDOLPH J Nudo and Garret W Milliken. Reorganization of movement representations in primary motor cortex following focal ischemic infarcts in adult squirrel monkeys. *Journal of neurophysiology*, 75(5):2144–2149, 1996. ISSN 0022-3077.

Christopher J Nycz, Tobias Bützer, Olivier Lambercy, Jumpei Arata, Gregory S Fischer, and Roger Gassert. Design and characterization of a lightweight and fully portable remote actuation system for use with a hand exoskeleton. *IEEE Robotics and Automation Letters*, 1 (2):976–983, 2016.

A O'Bryant, B Bernier, and TA Jones. Abnormalities in skilled reaching movements are improved by peripheral anesthetization of the less-affected forelimb after sensorimotor cortical infarcts in rats. *Behavioural brain research*, 177(2):298–307, 2007.

NJ O'dwyer, L Ada, and PD Neilson. Spasticity and muscle contracture following stroke. *Brain*, 119(5):1737–1749, 1996.

Felipe Orihuela-Espina, Giovana Femat Roldán, Israel Sánchez-Villavicencio, Lorena Palafox, Ronald Leder, Luis Enrique Sucar, and Jorge Hernández-Franco. Robot training for hand motor recovery in subacute stroke patients: a randomized controlled trial. *Journal of Hand Therapy*, 29(1):51–57, 2016. ISSN 0894-1130.

Fabio Oscari, Christian Finetto, Steve A Kautz, and Giulio Rosati. Changes in muscle coordination patterns induced by exposure to a viscous force field. *Journal of neuroengineering and rehabilitation*, 13(1):1–16, 2016.

Yang-Kun Ou, Yu-Lin Wang, Hua-Cheng Chang, and Chun-Chih Chen. Design and development of a wearable exoskeleton system for stroke rehabilitation. In *Healthcare*, volume 8, page 18. Multidisciplinary Digital Publishing Institute, 2020.

Sharon Oviatt. Human-centered design meets cognitive load theory: designing interfaces that help people think. In *Proceedings of the 14th ACM international conference on Multimedia*, pages 871–880, 2006.

Stephen J Page, Linda Levin, Valerie Hermann, Kari Dunning, and Peter Levine. Longer versus shorter daily durations of electrical stimulation during task-specific practice in moderately impaired stroke. *Archives of physical medicine and rehabilitation*, 93(2):200–206, 2012.

Stephen J Page, Valerie Hill, and Susan White. Portable upper extremity robotics is as efficacious as upper extremity rehabilitative therapy: a randomized controlled pilot trial. *Clinical rehabilitation*, 27(6):494–503, 2013. ISSN 0269-2155.

Alexandra Paget-Blanc, Johanna L Chang, Maira Saul, Regina Lin, Zaghloul Ahmed, and Bruce T Volpe. Non-invasive treatment of patients with upper extremity spasticity following stroke using paired trans-spinal and peripheral direct current stimulation. *Bioelectronic medicine*, 5(1):1–10, 2019.

Alessandro Panarese, Roberto Colombo, Irma Sterpi, Fabrizio Pisano, and Silvestro Micera. Tracking motor improvement at the subtask level during robot-aided neurorehabilitation of stroke patients. *Neurorehabilitation and neural repair*, 26(7):822–833, 2012.

AD Pandyan, M Cameron, J Powell, DJ Stott, and MH Granat. Contractures in the post-stroke wrist: a pilot study of its time course of development and its association with upper limb recovery. *Clinical Rehabilitation*, 17(1):88–95, 2003.

Stefano Paolucci, Gabriella Antonucci, Maria Grazia Grasso, Maura Bragoni, Paola Coiro, Domenico De Angelis, Francesca Romana Fusco, Daniela Morelli, Vincenzo Venturiero, and Elio Troisi. Functional outcome of ischemic and hemorrhagic stroke patients after inpatient rehabilitation: a matched comparison. *Stroke*, 34(12):2861–2865, 2003. ISSN 0039-2499.

Yu-Cheng Pei, Jean-Lon Chen, Alice MK Wong, and Kevin C Tseng. An evaluation of the design and usability of a novel robotic bilateral arm rehabilitation device for patients with stroke. *Frontiers in neurorobotics*, 11:36, 2017. ISSN 1662-5218.

Carlo Perfetti and Luigi Grimaldi. *Rieducazione motoria dell'emiplegico*. Ghedimedia, 1979. ISBN 8877800097.

Carlo Perfetti and Susanne Wopfner-Oberleit. *Der hemiplegische Patient: kognitiv therapeutische Übungen*. Pflaum, 1997.

Jérôme Perret and Pierre Vercruysse. Advantages of mechanical backdrivability for medical applications of force control. In *Workshop on Computer/Robot Assisted Surgery (CRAS)*, 2014.

Helen Petrie and Nigel Bevan. The evaluation of accessibility, usability, and user experience. *The universal access handbook*, 1:1–16, 2009.

Evan Pezent, Chad G Rose, Ashish D Deshpande, and Marcia K O'Malley. Design and characterization of the openwrist: A robotic wrist exoskeleton for coordinated hand-wrist rehabilitation. In *International Conference on Rehabilitation Robotics (ICORR)*, pages 720–725. IEEE, 2017. ISBN 1538622963.

Patrick Philipp, Nicole Merkle, Kai Gand, and Carola Gißke. Continuous support for rehabilitation using machine learning. *it-Information Technology*, 61(5-6):273–284, 2019.

Ophélie Pila, Christophe Duret, François-Xavier Laborne, Jean-Michel Gracies, Nicolas Bayle, and Emilie Hutin. Pattern of improvement in upper limb pointing task kinematics after a 3-month training program with robotic assistance in stroke. *Journal of neuroengineering and rehabilitation*, 14(1):105, 2017.

Michelle Ploughman, Shirley Granter-Button, Garry Chernenko, Zachary Attwood, Budd A Tucker, Karen M Mearow, and Dale Corbett. Exercise intensity influences the temporal profile of growth factors involved in neuronal plasticity following focal ischemia. *Brain research*, 1150:207–216, 2007.

Alex Pollock, Sybil E Farmer, Marian C Brady, Peter Langhorne, Gillian E Mead, Jan Mehrholz, and Frederike van Wijck. Interventions for improving upper limb function after stroke. *Cochrane Database of Systematic Reviews*, (11), 2014.

Michael Posa, Mark Tobenkin, and Russ Tedrake. Stability analysis and control of rigid-body systems with impacts and friction. *IEEE Transactions on Automatic Control*, 61(6):1423–1437, 2015. ISSN 0018-9286.

Valerie Power, Adam de Eyto, Bernard Hartigan, Jesús Ortiz, and Leonard W O'Sullivan. Application of a user-centered design approach to the development of xosoft–a lower body soft exoskeleton. In *International Symposium on Wearable Robotics*, pages 44–48. Springer, 2018.

Gerdienke B Prange, Michiel JA Jannink, Catharina GM Groothuis-Oudshoorn, Hermie J Hermens, and Maarten J IJzerman. Systematic review of the effect of robot-aided therapy on recovery of the hemiparetic arm after stroke. *Journal of rehabilitation research and development*, 43(2):171, 2006. ISSN 0748-7711.

SV Prokopenko, VA Rudnev, EM Arakchaa, and SN Derevtsova. Use of the principle of proprioceptive correction in the restoration of voluntary movements in the paralyzed arm in patients in the late recovery and residual post-stroke periods. *Neuroscience and behavioral physiology*, 38(6):627–631, 2008.

J Andrew Pruszynski, Isaac Kurtzer, Timothy P Lillicrap, and Stephen H Scott. Temporal evolution of "automatic gain-scaling". *Journal of neurophysiology*, 102(2):992–1003, 2009.

J Andrew Pruszynski, Roland S Johansson, and J Randall Flanagan. A rapid tactile-motor reflex automatically guides reaching toward handheld objects. *Current Biology*, 26(6):788–792, 2016.

Horst Przuntek, Peter H Kraus, Peter Klotz, and Amos D Korczyn. *Instrumental methods and scoring in extrapyramidal disorders*. Springer Science & Business Media, 2012.

Lloyd U Pumpa, Liana S Cahill, and Leeanne M Carey. Somatosensory assessment and treatment after stroke: An evidence-practice gap. *Australian occupational therapy journal*, 62(2):93–104, 2015.

QIAN Qiuyang, Chingyi Nam, Ziqi Guo, Yanhuan Huang, Xiaoling Hu, Stephanie C Ng, Yongping Zheng, and Waisang Poon. Distal versus proximal-an investigation on different supportive strategies by robots for upper limb rehabilitation after stroke: a randomized controlled trial. *Journal of neuroengineering and rehabilitation*, 16(1):64, 2019.

Fanny Quandt and Friedhelm C Hummel. The influence of functional electrical stimulation on hand motor recovery in stroke patients: a review. *Experimental & translational stroke medicine*, 6(1):1–7, 2014.

Zdravko Radman. *The hand, an organ of the mind: What the manual tells the mental*. MIT Press, 2013. ISBN 0262018845.

Preeti Raghavan. Upper limb motor impairment post stroke. *Physical medicine and rehabilitation clinics of North America*, 26(4):599, 2015.

Pretti Raghavan. The nature of hand motor impairment after stroke and its treatment. *Current treatment options in cardiovascular medicine*, 9(3):221–228, 2007. ISSN 1092-8464.

Raffaele Ranzani, Federica Viggiano, Bernadette Engelbrecht, Jeremia PO Held, Olivier Lambercy, and Roger Gassert. Method for muscle tone monitoring during robot-assisted therapy of hand function: A proof of concept. In *IEEE 16th International Conference on Rehabilitation Robotics (ICORR)*, pages 957–962. IEEE, 2019. ISBN 1728127556.

Raffaele Ranzani, Olivier Lambercy, Jean-Claude Metzger, Antonella Califfi, Stefania Regazzi, Daria Dinacci, Claudio Petrillo, Paolo Rossi, Fabio M. Conti, and Roger Gassert. Neurocognitive robot-assisted rehabilitation of hand function: a randomized control trial on motor recovery in subacute stroke. *Journal of NeuroEngineering and Rehabilitation*, 17(1):115, 2020. ISSN 1743-0003.

Raffaele Ranzani, Lucas Eicher, Federica Viggiano, Bernadette Engelbrecht, Jeremia PO Held, Olivier Lambercy, and Roger Gassert. Towards a platform for robot-assisted minimally-supervised therapy of hand function: design and pilot usability evaluation. *Frontiers in Bioengineering and Biotechnology*, 9, 2021.

Catherine L. Reed and Mounia Ziat. Haptic perception: From the skin to the brain. In *Reference Module in Neuroscience and Biobehavioral Psychology*. Elsevier, 2018. ISBN 978-0-12-809324-5.

Lisa Reissner, Gabriella Fischer, Renate List, Pietro Giovanoli, and Maurizio Calcagni. Assessment of hand function during activities of daily living using motion tracking cameras: A systematic review. *Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine*, 233(8):764–783, 2019. ISSN 0954-4119.

Ulrik Röijezon, Ragnar Faleij, Petros Karvelis, George Georgoulas, and George Nikolakopoulos. A new clinical test for sensorimotor function of the hand–development and preliminary validation. *BMC musculoskeletal disorders*, 18(1):407, 2017. ISSN 1471-2474.

Mike D Rinderknecht, Raffaele Ranzani, Werner L Popp, Olivier Lambercy, and Roger Gassert. Algorithm for improving psychophysical threshold estimates by detecting sustained inattention in experiments using pest. *Attention, Perception, & Psychophysics*, 80(6):1629–1645, 2018.

Paul Rinne, Mursyida Hassan, Cristina Fernandes, Erika Han, Emma Hennessy, Adam Waldman, Pankaj Sharma, David Soto, Robert Leech, Paresh A Malhotra, et al. Motor dexterity and strength depend upon integrity of the attention-control system. *Proceedings of the National Academy of Sciences*, 115(3):E536–E545, 2018.

Helen Rodgers, Helen Bosomworth, Hermano I Krebs, Frederike van Wijck, Denise Howel, Nina Wilson, Lydia Aird, Natasha Alvarado, Sreeman Andole, and David L Cohen. Robot assisted training for the upper limb after stroke (ratuls): a multicentre randomised controlled trial. *The Lancet*, 394(10192):51–62, 2019. ISSN 0140-6736.

Brandon Rohrer, Susan Fasoli, Hermano Igo Krebs, Richard Hughes, Bruce Volpe, Walter R Frontera, Joel Stein, and Neville Hogan. Movement smoothness changes during stroke recovery. *Journal of neuroscience*, 22(18):8297–8304, 2002.

RANULFO Romo, SALVADOR Ruiz, PATRICIA Crespo, ANTONIO Zainos, and HUGO Merchant. Representation of tactile signals in primate supplementary motor area. *Journal of neurophysiology*, 70(6):2690–2694, 1993.

Giulio Rosati, Antonio Rodà, Federico Avanzini, and Stefano Masiero. On the role of auditory feedback in robot-assisted movement training after stroke: review of the literature. *Computational intelligence and neuroscience*, 2013, 2013.

Justin B Rowe, Vicky Chan, Morgan L Ingemanson, Steven C Cramer, Eric T Wolbrecht, and David J Reinkensmeyer. Robotic assistance for training finger movement using a hebbian model: A randomized controlled trial. *Neurorehabilitation and neural repair*, 31(8):769–780, 2017. ISSN 1545-9683.

Patrizio Sale, Valentina Lombardi, and Marco Franceschini. Hand robotics rehabilitation: feasibility and preliminary results of a robotic treatment in patients with hemiparesis. *Stroke research and treatment*, 2012, 2012.

Laia Sallés, Patricia Martín-Casas, Xavier Gironès, María José Durà, José Vicente Lafuente, and Carlo Perfetti. A neurocognitive approach for recovering upper extremity movement following subacute stroke: a randomized controlled pilot study. *Journal of physical therapy science*, 29(4):665–672, 2017. ISSN 0915-5287.

Fabrice R Sarlegna and Robert L Sainburg. The roles of vision and proprioception in the planning of reaching movements. In *Progress in motor control*, pages 317–335. Springer, 2009.

W-R Schabitz, C Berger, R Kollmar, M Seitz, E Tanay, M Kiessling, S Schwab, and C Sommer. Effect of brain-derived neurotrophic factor treatment and forced arm use on functional motor recovery after small cortical ischemia. *Stroke*, 35(4):992–997, 2004.

Antje Schmidt, Jürgen Wellmann, Matthias Schilling, Jan-Kolja Strecker, Clemens Sommer, Wolf-Rüdiger Schäbitz, Kai Diederich, and Jens Minnerup. Meta-analysis of the efficacy of different training strategies in animal models of ischemic stroke. *Stroke*, 45(1):239–247, 2014.

Emma J Schneider, Natasha A Lannin, Louise Ada, and Julia Schmidt. Increasing the amount of usual rehabilitation improves activity after stroke: a systematic review. *Journal of physiotherapy*, 62(4):182–187, 2016. ISSN 1836-9553.

Othmar Schuhfried, Richard Crevenna, Veronika Fialka-Moser, and Tatjana Paternostro-Sluga. Non-invasive neuromuscular electrical stimulation in patients with central nervous system lesions: an educational review. *Journal of rehabilitation medicine*, 44(2):99–105, 2012.

Syed Ghulam Sarwar Shah and Ian Robinson. User involvement in healthcare technology development and assessment. *International Journal of Health Care Quality Assurance*, 2006.

Syed Ghulam Sarwar Shah and Ian Robinson. Benefits of and barriers to involving users in medical device technology development and evaluation. *International journal of technology assessment in health care*, 23(1):131–137, 2007. ISSN 1471-6348.

L Shaw, Helen Rodgers, C Price, Frederike van Wijck, Phil Shackley, Nick Steen, M Barnes, G Ford, and L Graham. Botuls: a multicentre randomised controlled trial to evaluate the clinical effectiveness and cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type a. *Health Technol Assess*, 14(26):1–113, 2010.

Lisa Sheehy, Anne Taillon-Hobson, Heidi Sveistrup, Martin Bilodeau, Christine Yang, Vivian Welch, Alomgir Hossain, and Hillel Finestone. Home-based virtual reality training after discharge from hospital-based stroke rehabilitation: a parallel randomized feasibility trial. *Trials*, 20(1):1–9, 2019.

Fatima de NAP Shelton, Bruce T Volpe, and Mike Reding. Motor impairment as a predictor of functional recovery and guide to rehabilitation treatment after stroke. *Neurorehabilitation and neural repair*, 15(3):229–237, 2001. ISSN 1545-9683.

Anne Shumway-Cook and Marjorie H Woollacott. *Motor control: translating research into clinical practice*. Lippincott Williams & Wilkins, 2007.

Manoj Sivan, Justin Gallagher, Sophie Makower, David Keeling, Bipin Bhakta, Rory J O'Connor, and Martin Levesley. Home-based computer assisted arm rehabilitation (hcaar) robotic device for upper limb exercise after stroke: results of a feasibility study in home setting. *Journal of neuroengineering and rehabilitation*, 11(1):163, 2014. ISSN 1743-0003.

Lisa Skedung, Martin Arvidsson, Jun Young Chung, Christopher M Stafford, Birgitta Berglund, and Mark W Rutland. Feeling small: exploring the tactile perception limits. *Scientific reports*, 3(1):1–6, 2013. ISSN 2045-2322.

T.M. Skirven, A.L. Osterman, J. Fedorczyk, P.C. Amadio, S. Felder, and E.K. Shin. *Rehabilitation of the Hand and Upper Extremity*. Elsevier Health Sciences, 2020. ISBN 9780323547154.

CL Smith et al. *Usability engineering in the design and evaluation of a functional electrical stimulation system for upper limb rehabilitation*. PhD thesis, University of Salford, 2015.

Samuel J Sober and Philip N Sabes. Multisensory integration during motor planning. *Journal of Neuroscience*, 23(18):6982–6992, 2003.

Surjo R Soekadar, Niels Birbaumer, Marc W Slutzky, and Leonardo G Cohen. Brain–machine interfaces in neurorehabilitation of stroke. *Neurobiology of disease*, 83:172–179, 2015.

Disa K Sommerfeld, Ullabritt Gripenstedt, and Anna-Karin Welmer. Spasticity after stroke: an overview of prevalence, test instruments, and treatments. *American Journal of Physical Medicine & Rehabilitation*, 91(9):814–820, 2012.

Danny Spampinato and Pablo Celnik. Multiple motor learning processes in humans: Defining their neurophysiological bases. *The Neuroscientist*, page 1073858420939552, 2020.

Michelle L Starkey, Christiane Bleul, Irin C Maier, and Martin E Schwab. Rehabilitative training following unilateral pyramidotomy in adult rats improves forelimb function in a non-task-specific way. *Experimental neurology*, 232(1):81–89, 2011.

Joel Stein, Lauri Bishop, Glen Gillen, and Raimund Helbok. Robot-assisted exercise for hand weakness after stroke: a pilot study. *American journal of physical medicine & rehabilitation*, 90(11):887–894, 2011. ISSN 0894-9115.

Kim C Stewart, James H Cauraugh, and Jeffery J Summers. Bilateral movement training and stroke rehabilitation: a systematic review and meta-analysis. *Journal of the neurological sciences*, 244(1-2):89–95, 2006.

F Stolk-Hornsveld, JL Crow, EP Hendriks, R Van Der Baan, and BC Harmeling-Van der Wel. The erasmus mc modifications to the (revised) nottingham sensory assessment: a reliable somatosensory assessment measure for patients with intracranial disorders. *Clinical rehabilitation*, 20(2):160–172, 2006. ISSN 0269-2155.

Molly Follette Story. Medical devices in home health care. In *The role of human factors in home health care: workshop summary*, pages 145–172. National Academies Press, Washington, DC, 2010.

Mary Ellen Stoykov, Gwyn N Lewis, and Daniel M Corcos. Comparison of bilateral and unilateral training for upper extremity hemiparesis in stroke. *Neurorehabilitation and neural repair*, 23(9):945–953, 2009.

Gail M Sullivan and Anthony R Artino Jr. Analyzing and interpreting data from likert-type scales. *Journal of graduate medical education*, 5(4):541, 2013.

Evan A Susanto, Raymond KY Tong, Corinna Ockenfeld, and Newmen SK Ho. Efficacy of robot-assisted fingers training in chronic stroke survivors: a pilot randomized-controlled trial. *Journal of neuroengineering and rehabilitation*, 12(1):42, 2015. ISSN 1743-0003.

Nevio Luigi Tagliamonte, Maria Scorcia, Domenico Formica, Domenico Campolo, and Eugenio Guglielmelli. Effects of impedance reduction of a robot for wrist rehabilitation on human motor strategies in healthy subjects during pointing tasks. *Advanced Robotics*, 25(5):537–562, 2011. ISSN 0169-1864.

Craig D Takahashi, Lucy Der-Yeghiaian, Vu Le, Rehan R Motiwala, and Steven C Cramer. Robot-based hand motor therapy after stroke. *Brain*, 131(2):425–437, 2007. ISSN 1460-2156.

Eugene YH Tang, Obreniokibo Amiesimaka, Stephanie L Harrison, Emma Green, Christopher Price, Louise Robinson, Mario Siervo, and Blossom CM Stephan. Longitudinal effect of stroke on cognition: a systematic review. *Journal of the American Heart Association*, 7(2): e006443, 2018.

G Tardieu. A la recherche d'une technique de mesure de la spasticite. *Rev Neurol*, 91:143–144, 1954.

Hashem Abu Tariah, Abdul-Majeed Almalty, Ziad Sbeih, and Saleh Al-Oraibi. Constraint induced movement therapy for stroke survivors in jordon: a home-based model. *International Journal of Therapy and Rehabilitation*, 17(12):638–646, 2010.

Edward Taub, Gitendra Uswatte, Rama Pidikiti, et al. Constraint-induced movement therapy: a new family of techniques with broad application to physical rehabilitation-a clinical review. *Journal of rehabilitation research and development*, 36(3):237–251, 1999.

Jordan A Taylor, John W Krakauer, and Richard B Ivry. Explicit and implicit contributions to learning in a sensorimotor adaptation task. *Journal of Neuroscience*, 34(8):3023–3032, 2014.

MiM Taylor and C Douglas Creelman. Pest: Efficient estimates on probability functions. *The Journal of the Acoustical Society of America*, 41(4A):782–787, 1967.

Manoel J Teixeira, Rubens Gisbert Cury, Ricardo Galhardoni, Victor Rossetto Barboza, André R Brunoni, Eduardo Alho, Guilherme Lepski, and Daniel Ciampi de Andrade. Deep brain stimulation of the dentate nucleus improves cerebellar ataxia after cerebellar stroke. *Neurology*, 85(23):2075–2076, 2015.

Azeemsha Thacham Poyil, Volker Steuber, and Farshid Amirabdollahian. Adaptive robot mediated upper limb training using electromyogram-based muscle fatigue indicators. *Plos one*, 15(5):e0233545, 2020.

Aye Aye Thant, Sawitri Wanpen, Nomjit Nualnetr, Rungthip Puntumetakul, Uraiwan Chatchawan, Khin Myo Hla, and Myo Thuzar Khin. Effects of task-oriented training on upper extremity functional performance in patients with sub-acute stroke: a randomized controlled trial. *Journal of physical therapy science*, 31(1):82–87, 2019.

Kelly O Thielbar, Kristen M Triandafilou, Heidi C Fischer, Jake M O'Toole, Molly L Corrigan, José M Ochoa, Mary Ellen Stoykov, and Derek G Kamper. Benefits of using a voice and emg-driven actuated glove to support occupational therapy for stroke survivors. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 25(3):297–305, 2017. ISSN 1534-4320.

KY Tong, SK Ho, PMK Pang, XL Hu, WK Tam, KL Fung, XJ Wei, PN Chen, and Mo Chen. An intention driven hand functions task training robotic system. In *2010 Annual International Conference of the IEEE Engineering in Medicine and Biology*, pages 3406–3409. IEEE, 2010.

Liu Zhu Tong, Hian Tat Ong, Jia Xuan Tan, Jeremy Lin, Etienne Burdet, SS Ge, and Chee Leong Teo. Pediatric rehabilitation with the reachman's modular handle. In *37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, pages 3933–3936. IEEE, 2015. ISBN 1424492718.

Duc A Tran, Marta Pajaro-Blazquez, Jean-Francois Daneault, Jaime G Gallegos, Jose Pons, Felipe Fregni, Paolo Bonato, and Ross Zafonte. Combining dopaminergic facilitation with robot-assisted upper limb therapy in stroke survivors: a focused review. *American Journal of Physical Medicine & Rehabilitation*, 95(6):459, 2016.

Yu-Lin Tsai, Jian-Jia Huang, Shu-Wei Pu, Hsiang-Peng Chen, Shao-Chih Hsu, Jen-Yuan Chang, and Yu-Cheng Pei. Usability assessment of a cable-driven exoskeletal robot for hand rehabilitation. *Frontiers in neurorobotics*, 13:3, 2019. ISSN 1662-5218.

Giuseppe Turchetti, Nicola Vitiello, Stefano Romiti, Elie Geisler, and Silvestro Micera. Why effectiveness of robot-mediated neurorehabilitation does not necessarily influence its adoption. *I.E.E.E. Reviews in Biomedical Engineering*, 7:143–153, 2014. ISSN 1937-3333.

Megan Turville, Leeanne M Carey, Thomas A Matyas, and Jannette Blennerhassett. Change in functional arm use is associated with somatosensory skills after sensory retraining post-stroke. *American Journal of Occupational Therapy*, 71(3):7103190070p1–7103190070p9, 2017. ISSN 0272-9490.

Thomas Evans Twitchell. Sensory factors in purposive movement. *Journal of Neurophysiology*, 17(3):239–252, 1954.

Peter P Urban, Thomas Wolf, Michael Uebele, Jürgen J Marx, Thomas Vogt, Peter Stoeter, Thomas Bauermann, Carsten Weibrich, Goran D Vucurevic, Astrid Schneider, et al. Occurence and clinical predictors of spasticity after ischemic stroke. *Stroke*, 41(9):2016–2020, 2010.

Shahabeddin Vahdat, Mohammad Darainy, and David J Ostry. Structure of plasticity in human sensory and motor networks due to perceptual learning. *Journal of Neuroscience*, 34(7): 2451–2463, 2014.

Bulmaro A Valdés, Courtney GE Hilderman, Chai-Ting Hung, Navid Shirzad, and HF Machiel Van der Loos. Usability testing of gaming and social media applications for stroke and cerebral palsy upper limb rehabilitation. In *2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, pages 3602–3605. IEEE, 2014. ISBN 1424479290.

Ann Van de Winckel, Nicole Wenderoth, Willy De Weerdt, Stefan Sunaert, Ron Peeters, Wim Van Hecke, Vincent Thijs, Stephan P Swinnen, Carlo Perfetti, and Hilde Feys. Frontoparietal involvement in passively guided shape and length discrimination: a comparison between subcortical stroke patients and healthy controls. *Experimental brain research*, 220(2):179–189, 2012. ISSN 0014-4819.

Anne L van Ommeren, Laura C Smulders, Gerdienke B Prange-Lasonder, Jaap H Buurke, Peter H Veltink, and Johan S Rietman. Assistive technology for the upper extremities after stroke: systematic review of users' needs. *JMIR rehabilitation and technologies, assistive*, 5 (2):e10510, 2018.

Fabio Vanoglio, Palmira Bernocchi, Chiara Mulè, Francesca Garofali, Chiara Mora, Giovanni Taveggia, Simonetta Scalvini, and Alberto Luisa. Feasibility and efficacy of a robotic device for hand rehabilitation in hemiplegic stroke patients: a randomized pilot controlled study. *Clinical rehabilitation*, 31(3):351–360, 2017. ISSN 0269-2155.

Janne M Veerbeek, Anneli C Langbroek-Amersfoort, Erwin EH van Wegen, Carel GM Meskers, and Gert Kwakkel. Effects of robot-assisted therapy for the upper limb after stroke: a systematic review and meta-analysis. *Neurorehabilitation and neural repair*, 31(2):107–121, 2017. ISSN 1545-9683.

Janne Marieke Veerbeek, Erwin van Wegen, Roland van Peppen, Philip Jan van der Wees, Erik Hendriks, Marc Rietberg, and Gert Kwakkel. What is the evidence for physical therapy

poststroke? a systematic review and meta-analysis. *PloS one*, 9(2):e87987, 2014. ISSN 1932-6203.

ED Vidoni, NE Acerra, E Dao, SK Meehan, and LA Boyd. Role of the primary somatosensory cortex in motor learning: An rtms study. *Neurobiology of learning and memory*, 93(4): 532–539, 2010.

Robert A Virzi. Refining the test phase of usability evaluation: How many subjects is enough? *Human factors*, 34(4):457–468, 1992. ISSN 0018-7208.

Judith DM Vloothuis, Marijn Mulder, Janne M Veerbeek, Manin Konijnenbelt, Johanna MA Visser-Meily, Johannes CF Ket, Gert Kwakkel, and Erwin EH van Wegen. Caregiver-mediated exercises for improving outcomes after stroke. *Cochrane Database of Systematic Reviews*, (12), 2016.

V. Vojta. *Die cerebrale Bewegungsstörung im Säuglingsalter*. Stuttgart: Enke, 1976.

Bruce T Volpe, Daniel Lynch, Avrielle Rykman-Berland, Mark Ferraro, Michael Galgano, Neville Hogan, and Hermano I Krebs. Intensive sensorimotor arm training mediated by therapist or robot improves hemiparesis in patients with chronic stroke. *Neurorehabilitation and neural repair*, 22(3):305–310, 2008.

Kimberly J Waddell, Rebecca L Birkenmeier, Jennifer L Moore, T George Hornby, and Catherine E Lang. Feasibility of high-repetition, task-specific training for individuals with upper-extremity paresis. *American Journal of Occupational Therapy*, 68(4):444–453, 2014.

Joanne M Wagner, Jennifer A Rhodes, and Carolynn Patten. Reproducibility and minimal detectable change of three-dimensional kinematic analysis of reaching tasks in people with hemiparesis after stroke. *Physical therapy*, 88(5):652–663, 2008. ISSN 0031-9023.

Todd H Wagner, Albert C Lo, Peter Peduzzi, Dawn M Bravata, Grant D Huang, Hermano I Krebs, Robert J Ringer, Daniel G Federman, Lorie G Richards, and Jodie K Haselkorn. An economic analysis of robot-assisted therapy for long-term upper-limb impairment after stroke. *Stroke*, 42(9):2630–2632, 2011. ISSN 0039-2499.

Esteban Walker and Amy S Nowacki. Understanding equivalence and noninferiority testing. *Journal of general internal medicine*, 26(2):192–196, 2011. ISSN 0884-8734.

Frederick R Walker, Kimberley A Jones, Madeleine J Patience, Zidan Zhao, and Michael Nilsson. Stress as necessary component of realistic recovery in animal models of experimental stroke. *Journal of Cerebral Blood Flow & Metabolism*, 34(2):208–214, 2014.

Sandy McCombe Waller and Jill Whitall. Bilateral arm training: why and who benefits? *NeuroRehabilitation*, 23(1):29–41, 2008.

Hewei Wang, Ray Arceo, Shugeng Chen, Li Ding, Jie Jia, and Jun Yao. Effectiveness of interventions to improve hand motor function in individuals with moderate to severe stroke: a systematic review protocol. *BMJ open*, 9(9):e032413, 2019.

Qi Wang, Panos Markopoulos, Bin Yu, Wei Chen, and Annick Timmermans. Interactive wearable systems for upper body rehabilitation: a systematic review. *Journal of neuroengineering and rehabilitation*, 14(1):1–21, 2017.

Nick S Ward and Leonardo G Cohen. Mechanisms underlying recovery of motor function after stroke. *Archives of neurology*, 61(12):1844–1848, 2004.

Nick S Ward, Fran Brander, and Kate Kelly. Intensive upper limb neurorehabilitation in chronic stroke: outcomes from the queen square programme. *Journal of Neurology, Neurosurgery & Psychiatry*, 90(5):498–506, 2019.

Kimberley A Wattchow, Michelle N McDonnell, and Susan L Hillier. Rehabilitation interventions for upper limb function in the first four weeks following stroke: a systematic review and meta-analysis of the evidence. *Archives of physical medicine and rehabilitation*, 99(2): 367–382, 2018.

Sarah J Whitehead and Shehzad Ali. Health outcomes in economic evaluation: the qaly and utilities. *British medical bulletin*, 96(1):5–21, 2010.

Michael E Wiklund and SB Wilcox. The rising bar-medical product design excellence. In *In: Designing Usability into Medical Products*, chapter 1, pages 3–9. Taylor & Francis Group, 2005.

Dustin James Williams, Hermano Igo Krebs, and Neville Hogan. A robot for wrist rehabilitation. In *Conference Proceedings of the 23rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, volume 2, pages 1336–1339. IEEE, 2001. ISBN 0780372115.

Petra S Williams, D Michele Basso, Jane Case-Smith, and Deborah S Nichols-Larsen. Development of the hand active sensation test: reliability and validity. *Archives of physical medicine and rehabilitation*, 87(11):1471–1477, 2006.

Carolee J Winstein, Joel Stein, Ross Arena, Barbara Bates, Leora R Cherney, Steven C Cramer, Frank Deruyter, Janice J Eng, Beth Fisher, and Richard L Harvey. Guidelines for adult stroke rehabilitation and recovery. *Stroke*, 47(6):e98–e169, 2016. ISSN 0039-2499.

Frieder Wittmann, Olivier Lambercy, Roman R Gonzenbach, Mark A van Raai, Raphael Höver, Jeremia Held, Michelle L Starkey, Armin Curt, Andreas Luft, and Roger Gassert. Assessment-driven arm therapy at home using an imu-based virtual reality system. In *2015 IEEE international conference on rehabilitation robotics (ICORR)*, pages 707–712. IEEE, 2015. ISBN 1479918083.

Frieder Wittmann, Jeremia P Held, Olivier Lambercy, Michelle L Starkey, Armin Curt, Raphael Höver, Roger Gassert, Andreas R Luft, and Roman R Gonzenbach. Self-directed arm therapy at home after stroke with a sensor-based virtual reality training system. *Journal of neuroengineering & rehabilitation*, 13(1):75, 2016. ISSN 1743-0003.

Jacob O Wobbrock, Leah Findlater, Darren Gergle, and James J Higgins. The aligned rank transform for nonparametric factorial analyses using only anova procedures. In *Proceedings of the SIGCHI conference on human factors in computing systems*, pages 143–146, 2011.

Hartwig Woldag, Katharina Stupka, and Horst Hummelsheim. Repetitive training of complex hand and arm movements with shaping is beneficial for motor improvement in patients after stroke. *Journal of rehabilitation medicine*, 42(6):582–587, 2010.

Steven L Wolf, Komal Sahu, R Curtis Bay, Sharon Buchanan, Aimee Reiss, Susan Linder, Anson Rosenfeldt, and Jay Alberts. The haapi (home arm assistance progression initiative) trial: a novel robotics delivery approach in stroke rehabilitation. *Neurorehabilitation and neural repair*, 29(10):958–968, 2015. ISSN 1545-9683.

Timothy J Wolf, Helene Polatajko, Carolyn Baum, Jorge Rios, Dianne Cirone, Meghan Doherty, and Sara McEwen. Combined cognitive-strategy and task-specific training affects cognition and upper-extremity function in subacute stroke: an exploratory randomized controlled trial. *American Journal of Occupational Therapy*, 70(2):7002290010p1–7002290010p10, 2016.

Elizabeth J Woytowicz, Jeremy C Rietschel, Ronald N Goodman, Susan S Conroy, John D Sorkin, Jill Whitall, and Sandy McCombe Waller. Determining levels of upper extremity movement impairment by applying a cluster analysis to the fugl-meyer assessment of the upper extremity in chronic stroke. *Archives of physical medicine and rehabilitation*, 98(3): 456–462, 2017. ISSN 0003-9993.

Chieh-Ling Yang, Keh-Chung Lin, Hsieh-Ching Chen, Ching-Yi Wu, and Chia-Ling Chen. Pilot comparative study of unilateral and bilateral robot-assisted training on upper-extremity performance in patients with stroke. *American Journal of Occupational Therapy*, 66(2): 198–206, 2012.

Margaret Yekutiel. *Sensory re-education of the hand after stroke*. Wiley, 2000. ISBN 1861561695.

Che Fai Yeong, Alejandro Melendez-Calderon, Roger Gassert, and Etienne Burdet. Reachman: a personal robot to train reaching and manipulation. In *2009 IEEE/RSJ International Conference on Intelligent Robots and Systems*, pages 4080–4085. IEEE, 2009. ISBN 1424438039.

Chanuk Yoo and JuHyung Park. Impact of task-oriented training on hand function and activities of daily living after stroke. *Journal of physical therapy science*, 27(8):2529–2531, 2015a.

Chanuk Yoo and JuHyung Park. Impact of task-oriented training on hand function and activities of daily living after stroke. *Journal of physical therapy science*, 27(8):2529–2531, 2015b.

Charlotte Ytterberg, Malin Dyback, Aileen Bergstrom, Susanne Guidetti, and Gunilla Eriksson. Perceived impact of stroke six years after onset, and changes in impact between one and six years. *Journal of Rehabilitation Medicine*, 49(8):637–643, 2017.

Ningbo Yu, Kui Wang, and Jingtai Liu. Dexterous haptic interaction for functional rehabilitation and assessment of the upper limb. In *Robotics and Biomimetics (ROBIO), 2014 IEEE International Conference on*, pages 1351–1355. IEEE, 2014. ISBN 1479973971.

M Zadravec, Z Matjačić, F Urh, M Šavc, J Kranjec, M Divjak, A Frančič, B Potočnik, A Holobar, et al. Robotic wrist rehabilitation with high-density electromyographic biofeedback for reducing co-activation of antagonist muscles and improved motor coordination: A feasibility study. *ResearchSquare*, 2020.

Johannes Zajc and Michael Russold. Elicitation of usability-related requirements for upper-limb rehabilitation systems. In *2019 IEEE 16th International Conference on Rehabilitation Robotics (ICORR)*, pages 477–482. IEEE, 2019. ISBN 1728127556.

BD Zeman and C Yiannikas. Functional prognosis in stroke: use of somatosensory evoked potentials. *Journal of Neurology, Neurosurgery & Psychiatry*, 52(2):242–247, 1989.

Wen Zeng, Yonghong Guo, Guofeng Wu, Xueyan Liu, and Qian Fang. Mirror therapy for motor function of the upper extremity in patients with stroke: A meta-analysis. *Journal of rehabilitation medicine*, 50(1):8–15, 2018.

Dandan Zhang, Yujiao Lu, Xudong Zhao, Quanguang Zhang, and Lei Li. Aerobic exercise attenuates neurodegeneration and promotes functional recovery–why it matters for neurorehabilitation & neural repair. *Neurochemistry International*, page 104862, 2020.

Hang Zhang, Hiroko Austin, Sharon Buchanan, Richard Herman, Jim Koeneman, and Jiping He. Feasibility studies of robot-assisted stroke rehabilitation at clinic and home settings using rupert. In *2011 IEEE International Conference on Rehabilitation Robotics*, pages 1–6. IEEE, 2011. ISBN 1424498627.

Mei-Hong Zhu, Ming Zeng, Mei-Fang Shi, Xu-Dong Gu, Fang Shen, Ye-Ping Zheng, and Ya-Ping Jia. Visual feedback therapy for restoration of upper limb function of stroke patients. *International Journal of Nursing Sciences*, 2020.

Sandra Zinn, Hayden B Bosworth, Helen M Hoenig, and H Scott Swartzwelder. Executive function deficits in acute stroke. *Archives of physical medicine and rehabilitation*, 88(2): 173–180, 2007.