THE ROLE OF SOUND IN ROBOT-ASSISTED HAND FUNCTION TRAINING POST-STROKE

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an der Kultur-, Sozial- und Bildungswissenschaftlichen Fakultät/
Institut für Rehabilitationswissenschaften/Rehabilitationstechnik & Neue Medien
der Humboldt-Universität zu Berlin

Der Präsident der Humboldt-Universität zu Berlin
Prof. Dr. Sabine Kunst

Die Dekanin der Kultur-, Sozial- und Bildungswissenschaftlichen Fakultät
Prof. Dr. Julia von Blumenthal

Gutachter

Erstgutachter: Prof. Dr. Michael Arnold-Wahl

Zweitgutachter: Prof. Dr. med. Dr. phil. Stefan Evers

I certify that this thesis, and the research to which it refers, are the product of my own work, and that any ideas or quotations from the work of other people, published or otherwise, are fully acknowledged in accordance with the standard referencing practices of the discipline. I acknowledge the helpful guidance and support of my supervisor, Prof. Dr. Michael Wahl.

TABLE OF CONTENT	3-6

ABSTRACT (deutsche Version)

In Folge eines Schlaganfalls leiden 90% aller Patienten an einer Handparese, die sich in 30-40% als chronisch manifestiert. Derzeit wächst seitens der Neurologie und Technologie das Forschungsinteresse an der Effektivität robotergestützter Therapieansätze, welche für schwer betroffene Patienten als besonders vielversprechend eingestuft werden. Die hierfür verwendeten Therapieroboter setzen sich aus einem mechanischen Teil und einer softwaregestützten virtuellen Umgebung zusammen, welche neben dem graphischen Interface, audio-visuelles Feedback sowie Musik beinhaltet. Bisher wurden Effekte der klanglichen Anteile dieses Szenarios noch nicht hinsichtlich möglicher Einflüsse auf Motivation, Bewegungsdurchführung, motorisches Lernen und den gesamten Rehabilitationsprozess untersucht. Die vorliegende Arbeit untersucht die Rolle von Sound in robotergestütztem Handfunktionstraining. Die Hauptziele im Rahmen dessen sind es, 1) Potentiale von Sound/ Musik für den Kontext robotergestützten Handfunktionstrainings zu explorieren, 2) spezifizierte klangliche Umgebungen zu entwickeln, 3) zu untersuchen, ob Schlaganfallpatienten von diesen spezifizierten Soundanwendungen profitieren, 4) ein besseres Verständnis über Wirkmechanismen von Sound und Musik mit Potential für robotergestützte Therapie darzulegen, und 5) Folgetechnologien über eine effektive Applikation von Sound/ Musik in robotergestützter Therapie zu informieren.

Schlagwörter: robotergestützte Therapie; Handparese; Schlaganfallrehabilitation; Rhythmisch akustische Stimulation; Musiktherapie

ABSTRACT (english version)

90% of all stroke survivors suffer from a hand paresis which remains chronic in 30-40% of all cases. Currently, there is an increasing research interest in neurology and technology on the effectiveness of robot-assisted therapies. Robotic training is considered as especially promising for patients suffering from severe limitations. Commonly, rehabilitation robots consist of a mechanical part and a virtual training environment with a graphical user interface, audio-visual feedback, sound, and music. So far, the effects of sound and music that are embedded within these scenarios have never been evaluated in particular while taking into account that it might influence motivation, motor execution, motor learning and the whole recovery process. This thesis investigates the role of sound in robot-assisted hand function training post-stroke. The main goals of this work are 1) to explore potentials of sound/ music for robotic hand function training post-stroke, 2) to develop specified sound-/ music-applications for this context, 3) to examine whether stroke patients benefit from these specified sound/ music-application, 4) to gain a better understanding of sound-/ music-induced mechanisms with therapeutic potentials for

robotic therapy, and 5) to inform further arising treatment approaches about effective applications of sound or music in robotic post-stroke motor training.

keywords: *robotic therapy; hand paresis; post-stroke motor rehabilitation; Rhythmic auditory stimulation; music therapy*

THESIS STATEMENT

Commonly robotic rehabilitation devices are combined with virtual reality scenarios including sound. So far, the role of sound has never been specified for the context of robot-assisted hand rehabilitation, nor evaluated particularly by observing its effectiveness in rehabilitation. Following, there is a need to investigate whether sound is effective for robotic motor training post-stroke, and which kind of music, sound or parameter of sound is effective or not. The first step of this thesis reviews research on effectiveness of sound applications for post-stroke motor training. Next, specified sound designs for the application in technology-assisted therapy are suggested and in a third step finally promising sound designs are evaluated empirically. The main hypothesis is that specified sound such as polymetric music and game-related sound feedback applied to robotic hand function training post-stroke leads to significant effects on recovery, whereby effects are expected to be ambivalent dependent upon the grade of severity of a hand paresis syndrome.

INTRODUCTION

1. THE ROLE OF SOUND AND MUSIC FOR ROBOTIC HAND FUNCTION TRAINING POST-STROKE

INTRODUCTION

1. THE ROLE OF SOUND AND MUSIC FOR ROBOTIC HAND FUNCTION TRAINING POST-STROKE

1.1 Music as a therapeutic tool

Music took a key phylogenetic role in human evolution by co-shaping cognitive, motor and social systems linked to auditory perception, vocalization, coordinated movements, fine motor skills, the expression and encoding of emotional content and intentions of others, and the ability to feel social cohesion within groups (Patel 2014; Kirschner, Tomasello 2010; Balasubramanian et al.). Music appears in every culture and influences societies and beliefs strongly (Cross 2003; Patel 2014; Schulkin, Raglan 2014; Phillips-Silver et al. 2010; Altenmüller, Schlaug 2015). Cross-culturally, today and dating back even to antiquity, music was and is used in a variety of contexts ranging from rituals and sports to therapy (Altenmüller, Schlaug 2015; Thaut 2015). The intention behind the application of music to these different contexts is most often to exploit music as tool to increase perceptual, motoric, emotional and social aspects (Thaut et al. 2015). Studies on the effectiveness of music utilized in therapeutic settings indicate that music can improve recovery outcomes, health and well-being (Gebauer, Vuust 2014; MacDonald 2013). This might be due to several reasons: Music has the power to cause an urge to move, it can influence mood levels, levels of arousal, relaxation and attention, and it can play a role in structuring and organizing collective behavior in social groups (Burger et al. 2013; Särkämö, Soto 2012; Sammler et al. 2007; Kirschner, Tomasello 2010). Musical activities such as music-listening, playing an instrument, singing or dancing, activate brain areas specialized in auditory perception, emotional evaluation, cognitive and motor domains. Musical training which is performed regularly was shown to promote sensorimotor and cognitive domains (Koelsch 2011; Blood, Zatorre 2001; Wan, Schlaug 2010). Next to training effects resulting from regular practice that can shape long-lasting neural pathways, music can impact mood, cognition and motor performance temporarily (Särkämö et al. 2008; Särkämö, Soto 2012; Sammler et al. 2007; Jacobsen et al. 2015; Altenmüller, Schlaug 2015). The "tool-like" impact of music on all these aspects might explain why music has served as "therapeutic tool" for centuries (Altenmüller, Schlaug 2015; Koelsch et al. 2011; Chanda, Levitin 2013; Burger et al. 2013). In the role of a "therapeutic tool", music can be used to retrain lost skills, to sustain a specific state of ability in degenerative diseases, and to overcome pathology-related deficits ranging from motor and cognitive to psychological problems. Furthermore, it can support motivation during psychologically-demanding phases and it can promote social interaction in a rehabilitative context (Vuilleumier, Trost 2015). In summary, music enables to bridge, to link or to compensate malfunctioning mental, motoric, emotional or social processes

(Merker et al. 2009; Phillips-Silver et al. 2010; Koelsch 2011; Ross, Balasubramaniam 2014; Patel 2014).

In music therapeutic interventions, musical activities such as listening, playing an instrument, singing or moving to music are used as therapeutic drivers to induce mental, motoric, emotional or social changes. Despite a huge body of research demonstrated that music applied to sports or therapy has positive effects, explanations on how music causes these beneficial effects are still insufficient. Music is a highly complex construct containing rhythm, timbre, melody, contour which all changes dynamically over time. It transports socio-cultural, musical, kinesthetic and aesthetic information. Music is most often perceived rather as a whole formation that unfolds over time than a construct of several components that are perceived as independent parameters. The formation of meaning of a musical piece depends upon the perceiving subject situated within a specific context. Musical meaning depends upon autobiographical experiences of music including listening and active practice, personal tendencies for musical memory formation, the level of skill to interpret a piece, the cultural background, the current situation in which the piece is heart, the current mood and mental state and many more aspects (Jäncke 2008; Koelsch 2011; Margulis 2014). According, the formation of musical meaning can be considered as highly subjective. Because of that, it is demanding to determine which aspect of a musical stimulus causes what. So far, it is still unclear which parameter or which combination of parameters of sound and music are responsible for certain reactions of specifically situated individuals. Especially in the case of music for clinical usage, there are many open questions which need to be answered before confirming evidence-based effectiveness of music as an overall therapeutic tool. So far, the possibility that the powerful tool music could as well cause negative aspects in some patient populations has not been studied nor reported, yet. To gain a better understanding on how music and sound affect human behavior, future research needs to investigate systemically the effects of music for different populations, applications and contexts (Gebauer, Vuust 2014). In summary, music can be considered a therapeutic tool with capabilities that can shape mental states and motor behavior as well as balance relations between individuals in groups by inducing feelings of cohesion which can mediate cultural values. It can influence motor and cognitive performance temporarily while inducing long-lasting neural plastic changes when musical training is performed regularly. Because of that, music can be considered a rich tool influencing cognition and emotion as well as social and motor domains in populations ranging from healthy subjects to patient populations.

As summarized above, music might impact many domains such as cognition, motor control and learning, next to motivation. Music can not only cause powerful effects but also risky side-effects as well as no effects or beneficial effects. Currently, new technologies such as the internet, computers, mobile phones, virtual realities as well as devices such as robots and wearable technologies are becoming a part of everyday life. Also, in the context of rehabilitation, these new technologies, especially virtual reality concepts and robots, are more and more widely used to extend conventional training. The common idea behind the application of sound and music is to motivate patients (Rosati et al. 2011; Gebauer, Vuust 2014; Taheri et al. 2012; Friedman et al. 2014). Music and sound could furthermore influence motor performance and motor learning as well as psychological and social aspects that could impact functional outcomes. In order to provide information for future therapies, music and sound need to be investigated within the interplay of therapeutic usage and modern environments. Research on the effectiveness of sound and music in this context could update and optimize usage of current technology-driven therapies as well as prospective devices. Therefore clinical investigations need to be carried out that observe whether music and sound are effective for specific rehabilitation contexts which combine new technologies with sound and music.

In this thesis the role of music and sound as an extension of technology-assisted rehabilitation is discussed. The aim of this work is to outline that music and sound can be considered a rich tool box for therapeutic usage, either generating strong positive effects, or none, or even negative effects. To gain beneficial effects, sound and music need to be carefully specified for patient populations with different pathological characteristics as well as applied sensitively to its context of use and effect-intention.

1.2 Clinical relevance of music and sound for neurorehabilitation

Especially within the last decade, the body of research on music as a therapeutic tool has grown considerably. Very recent literature research on studies including the word "*music intervention*" was carried out by Gebauer and Vuust in the year 2014, underlining an increasing number of publications from 5 publications in the year 1990 to 225 in the year 2014 (see Fig.1). This increase of publications indicates a growing interest in research which originates from disciplines ranging from rehabilitation science, music therapy, as an autonomous research domain, to musicology, neurology, medicine and technology. All these disciplines seem to consider music interventions as highly relevant to study. This might be based on a variety of reasons: A recent literature research with the keywords "*music + adverse effects*", "*music intervention + adverse effects*", "*music intervention + or therapy + or adverse effects / side effects*" showed that music does not cause side effects or adverse effects. All reports about music applied to therapy either present no effects or positive effects. The only studies noting problems of music as a therapy-driver are related to special pathologies such as musicogenic epilepisa, amusia or hearing deficits (Kamioka et al. 2014). In contrast, positive effects are being widely discussed, thereby outlining logical reasons for its usage: Compared to medication, music does not cause intoxication. Instead, it is known to induce neurochemical changes that cause pleasurable and rewarding feelings. Music can be used non-invasively and shows minimal or no side effects and is low-cost (Chanda, Levitin 2013). For example, the application of relaxation music in operative settings serves as a replacement to painkillers. Here, music is cheaper and does not cause any side effects (Gebauer, Vuust 2014; van der Hejden et al. 2015).

Moreover, nearly all the patient population seems to benefit from music as it involves so many domains at once. The spectrum of studies on music interventions covers personality problems and cognitive, motor, social and/or emotional deficits as well as settings in which music serves as a relaxation tool during operations and as a tool to increase levels of attention, focus and memory. This is based on the fact, that even the very simple activity of music-listening activates a widespread brain network involving cognitive, motor and emotional domains (Zatorre et al. 2007; Särkämö et al. 2008): Throughout musical activities, a distributed brain network is active that encodes a stream of acoustic signals as music with meaning, that allows humming a well-known melody and tapping along the beat without effort while associating the current point of time with previous experiences in which the musical piece was heard before (Koelsch 2011; Altenmüller, Schlaug 2015; Zatorre et al. 2007; Sammler et al. 2007). This can cause feelings ranging from sadness to melancholy, happiness and enjoyment. At the same time, the composer's intention of emotional expression can be interpreted (Juslin 2013a, 2013b; Nieminen et al. 2011). In summary, these aspects illustrate that memory, emotional evaluation, motoric and imagined motoric processes are involved during exposure to music which all can be exploited as a therapeutic driver.

Furthermore, musical interventions contain a variety of musical aspects: Music can be used actively in manners of listening as an activity, of dancing moving to music, and it can be performed with instruments in motor training (Särkämö, Soto 2012; Shanahan et al. 2015; Schneider et al. 2007).

In addition, a growing number of therapeutic technologies utilize virtual reality scenarios in which sound and music increase physical realism of surreal environments (Rosati et al. 2011). Sound and music are commonly applied to this context with the intention to increase motivation and to enrich the training environment. Yet this field still lacks further risk analysis whether sound and music are beneficial for all patient populations and within the specified context. The reason for sound-applications in the field of new technologies might be based on outcomes of current research which were summarized above. These outcomes present music as an influencing factor that can either be proven ineffective or therapeutic enhancive only. In order to prevent negative side effects and increase treatment effects, there is a need for clinical evaluations that can provide information for this field about adequate application of sound or music that might have the power to influence motivation and function positively.

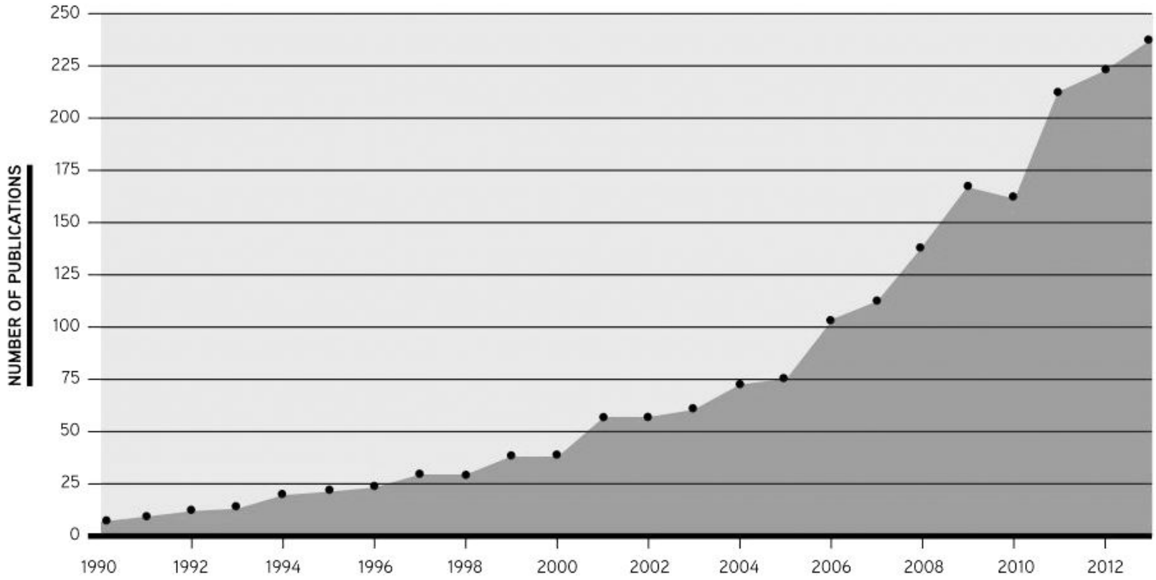


Fig. 1: This graph shows the number of scientific publications per year in the time span 1990-2013 containing the term "music intervention" (Gebauer, Vuust 2014).

1.3 Motivation for studying the role of sound in robotic hand rehabilitation training post-stroke

From the perspective of music therapy and neurorehabilitation, the linkage of movement and music offers promising opportunities to drive therapeutic interventions that promote post-stroke recovery in motor, cognitive, emotional and social domains (Koeneman et al. 2004; Thaut et al. 2015; Amengual et al. 2013). So far, music therapeutic interventions for a specific population of stroke patients vary from music listening, dance, singing and playing musical instruments in single- and group-settings (Gebauer, Vuust 2014; Bradt et al. 2010). In the field of motor rehabilitation, treatment of the hemiparesis is a very important focus as nearly 90% of all patients suffer from this problem (Oujamaa et al. 2009; Prange et al. 2006; Krakauer 2005). Hemiparesis also involves the arm and the hand. The paretic hand affects nine out of ten stroke patients (Krakauer 2005; Hesse et al. 2014). As a hand paresis limits management of independent daily living fundamentally, effective therapies are needed that increase functional outcome, thereby leading to a decrease of the high number of cases that suffer from severe grades of a paresis which often persist chronically. Up to date, treatment of the paretic hand post-stroke is known to gain best outcomes when therapies are applied as early as possible after the insult with high-frequency and intensity, containing goal-directed task training which is executed in a repetitive manner (Langhorne et al. 2009). Still, three out of four patients suffer from chronic and severe syndromes. Consequently, more research is needed to increase functional recovery outcome by involving evidence-based knowledge and by extending conventional approaches, to reach a better outcome. Therefore it is important to determine factors that limit advances in recovery or which result in chronic symptoms. These factors might be linkages between patient characteristics and treatment-related aspects. It is a big challenge for the field of post-stroke motor rehabilitation to create therapeutic environments that are beneficial for all grades of severity of a hemiparesis, including the high number of patients suffering from severe grades. Krakauer 2005 showed that also chronic patients can achieve advances when training is executed more prolonged and with a higher intensity than in mild or moderate cases. According to Krakauer 2005, the treatment possibilities for severe grades of a hand paresis are very limited (Krakauer 2005). Therefore, future research should also develop therapeutic techniques that enable to achieve small advances for chronic cases or which prevent the worsening of a given chronic state.

In the specific case of the paretic arm, music therapeutic interventions have already been investigated. In total, four different studies were carried out using music as a main therapeutic driver to achieve recovery improvements of the paretic upper extremity including the hand:

1) Schneider at al. 2008 carried out a comparative study in which functional effects of musical training with electronic drum pads or a midi-piano were compared to effects of conventional training only. The results showed that compared to the control-group receiving conventional training only, the music group gained significant better outcomes in movement qualities such as movement speed, precision and smoothness, and in clinical motor tests such as the Action Research Arm Test, the Box and Block Test, the Nine Hole Peg Test, and in activities of daily life (Schneider et al. 2007).

2) Friedman et al. 2014 explored a sensorized glove interface called "Music-Glove" for hand function training post-stroke. They performed a study in which effects of Music-Glove training were compared to isometric task training and strength training (Friedman et al. 2014). In the Music-glove training the game "Frets on Fire" was played. In this musical video game a popular music piece is played back. The task is to hit notes which are displayed graphically to play along the piece (Taheri et al. 2012; Friedman et al. 2014). The main findings of this study were that musical training resulted in better functional outcome in the Box and Block Test, and higher motivation ratings compared to other training groups (Friedman et al. 2014). Taheri et al. 2012 furthermore evaluated a robot-assisted hand trainer called "FINGER" (Finger Individuating Grasp Exercise Robot) with this kind of game. The studies of Taheri et al. 2012 and 2014 focused on technical control aspects of the robotic interface but as well report that robotic hand training with

this musical video game provides a motivating training environment (Taheri et al. 2012; Taheri et al. 2014).

3) Whitall et al. 2000 studied the effect of bilaterally executed arm training along a metronome-cue. This study showed that such training could gain positive outcomes. But the study lacked a control group training without sound (Whitall et al. 2000). Therefore, no general conclusions can be drawn from this result.

4) Thaut et al. 2002 studied the effects of the application of a rhythmic cue compared to using no cue at all in reaching task training (Thaut et al. 2002). This study involved 21 stroke subjects suffering from an arm paresis. The metronome tempo was self-selected. Test subjects were advised to select a tempo that would allow them to be in sync with the cyclic movement of the arm in a natural way. The results showed that during the rhythmic stimulation, significant improvements of spatiotemporal control of the arm, a reduction of variability of movement timing and the reaching trajectories as well as an immediate reduction in the variability of arm kinematics within the first two to three repetitions of each trial were achieved. Furthermore, the rhythmic stimulation led to a significant increase of the range of motion of the elbow while the total movement smoothness of wrist movements were significantly enhanced. This study did not observe whether such training can lead to positive carry-over effects, but instead focused on the influence of the rhythmic stimulation during movement performance. Therefore, the visible effects cannot be directly translated to therapeutic effectiveness.

In summary, the above outlined studies explored effects of music and sound in upper limb motor therapy post-stroke including the hand. In all the studies, music or sound was used as a main therapeutic driver by extending conventional movement training with either audio-feedback, a rhythmic structure and/or motivational aspects of music as a rewarding experience. These studies indicate that patients suffering from a moderate to mild arm paresis can benefit from active music therapeutic interventions or an auditory rhythmic cue applied to movement training. However, these studies excluded patients suffering from severe grades of paresis. Presently, music or sound-based arm therapy post-stroke lacks training opportunities for patients who are not able to execute more than minimal active movements with the hand or the arm.

Modern robotic therapies are considered to be a very promising therapeutic approach complementing conventional treatment for severely affected cases (Hesse et al. 2014). Robots allow to assist movement initiation of active movement, the completion of minimal movements up to a full range of the intended motion, to counteract an increasing muscle tone by enabling passive movement training while assessing the whole therapy process and providing preset-assessments that enable refinement of therapeutic foci (Sale et al. 2014). Usually, these devices provide a virtual training scenario which contains sound and music. So far the role of music and sound in this context might have been underestimated. Music is commonly displayed in the background of training games.

Interactive game sounds are applied in the same style as in commercial computer games.

The central questions in this thesis are whether music and sound are beneficial and whether, both music in the background and sound in games, need to be specified. The motivation to study specifically the topic of sound in robotic hand function training post-stroke, which is presented in this work, is based on several reasons.

First of all, there is an enormous increase of robotic technologies used in the field of rehabilitation (Poli et al. 2013). Nearly all robotic tools are combined with virtual scenarios including sound and music which are used without any further scientific base. Further knowledge on the interplay of machine-assisted rehabilitation and sound is needed, on the one hand, to provide effective training in which sound serves as a beneficial extension, and on the other hand, to prevent sound-induced negative effects. The application of music or sound involves the risk of it being perceived as stressful and overstimulating, thereby leading to patients becoming distracted. Furthermore, the audio-component could cause distraction in patients during training or superimpose patient-therapist interaction. At the same time, music and sound have potentials to promote motor relearning, motor control and motor performance. Music and sound might increase motivation, perceived involvement, and attention.

Second, in the very special case of hand training post-stroke, which involves muscle tone problems, sound and music could take influence on the muscle tone. This could result in either an increase of muscle tone, which is counterproductive in cases of patients suffering from post-stroke spasticity or in assisting other groups of patients to lower muscle tension allowing them to regain active control on extensor muscles or increase muscle tone in a beneficial manner during movement initiation. The auditory environment applied to robotic hand function training should facilitate the learning process of reacquiring force-dosage skills for single finger movements while increasing force production skills in finger extension. There is a need to study whether music and sound have the power to cause either clinically-relevant, ambivalent or beneficial effects or not any effects at all.

Third, from the perspective of a music therapy, music and sound might offer rich opportunities to stimulate motor, cognitive, emotional and social aspects during robotic training, and thereby increase recovery outcome. As described above, currently, there is no music therapeutic technique or musical tool available that is specified for usage with patients suffering from severe grades of a hand paresis. Therefore, the observation of music and sound applied to a technical tool that allows including all grades of severity of a paresis might answer relevant questions whether music and sound is beneficial or not for different patient characteristics.

Fourth, these technical tools might allow exploring new mappings of movement to sound which could promote motor learning while extending pre- and post-treatment assessments with data on the over-all performance during training. This could include data which reflects the effects of specific parameters, not just on carry-over effects, but also on direct effects on performance. As Thaut et al. 2002 showed, a rhythmic structure changes the motor performance, not just the functional outcome. This might be relevant to understand how sound affects the performance during robotic training.

Fifth, up to this point, no music therapeutic tool is existent which is accessible for patients suffering from severe grades of a hand paresis. If music and sound are explored in manners of effectiveness for post-stroke hand training, the usage of robotic technologies will enable the inclusion of stroke patients suffering from all grades of severity. As it is so far unclear whether music and sound can change the recovery outcome when applied to robotic training, it might be relevant to investigate robotically-guided passive movement in combination with music or sound as well. Under these circumstances, the effects on muscle tension might be interesting to observe in order to provide information for research on post-stroke spasticity.

In summary, it is presently critical to contribute information for further arising technologies on the effectiveness as well as on the potentials and dangers of sound applications in this field. Many open questions need to be answered to provide specified sound that is effective and safe for this context. Consequently, this work aims to introduce research on the role of sound in robot-assisted hand function training to the research community of technically-assisted neurorehabilitation.

1.4 Thesis structure

This thesis explores the role of sound and music in rehabilitation robotics for post-stroke motor training of the paretic upper extremity with a special focus on the paretic hand. This topic involves the perspective of rehabilitation science, music therapy, musicology, neurology, neurorehabilitation and rehabilitation engineering. The main goal of this work is to generate knowledge on the effects of sound or music applied to robotic rehabilitation training of the paretic hand post-stroke and to inform the field of neurorehabilitation about the effective usage of sound and music applied to technology-assisted movement training. As mentioned before, currently the number of rehabilitation robotics is increasing rapidly. As these systems commonly use sound in virtual training scenarios, there is a need to provide information for further arising technologies on the impact of sound and music. So far, no evaluation of sound and music in this complex training system has been carried out to detect whether it leads to positive or adverse effects. Due to a huge research body on music interventions post-stroke indicating that music does cause effects within the recovering brain, it is highly relevant to investigate its effects on function and motivation. The strength of the effects indicates that they can also occur in ambivalent manners. Furthermore, new interface options that might enable advances in recovery should be explored.

In the first part of this thesis, the problem of stroke, post-stroke syndromes, the paretic hand post-stroke and its treatment is presented. A special focus is put on technology-assisted hand training. In the second part, therapeutic approaches including sound and music for post-stroke motor rehabilitation are reviewed. In the third part, these sections are linked together, outlining the importance of connecting technology, music and sound and evidence-based treatment approaches to provide information for further arising technologies about their effectiveness. In the third and the fourth part of this work, empirical studies are reported. This part contains an experiment series with 20 healthy subjects and 8 stroke patients, a two-armed clinical study with 34 stroke patients and a series of three single-case studies.

In the experiments with healthy subjects and stroke patients, the effects on performance and mood of four different rhythmic stimulation designs applied during a fine motor task were compared with a condition without any additional stimulation. The results of these experiments were used to provide information for an optimized sound design for a practical test phase in which promising sound-designs were applied to robotic hand function training. This phase served as a test bed to determine the final sound-design which was chosen for the clinical study.

The main part of this thesis is the presentation of an explorative not-blinded, two-armed clinical study with 34 stroke patients suffering from severe to mild hand paresis. The study participants were assigned to either a control-group receiving robot-assisted hand function training without sound or a sound-group performing robotic training extended with specified musical stimulation. All subjects received this training additionally to conventional treatment over a period of 3-4 weeks with a total of nine therapy sessions. The musical stimulus that was applied to the training of the intervention-group was polymetric music and short game-related sound feedback. To detect whether the specified music influences functional or motivational aspects compared to training without sound, assessments were performed pre-, inter-, post- and follow-up. The gained results reveal that the specified music applied to robot-assisted hand function training alters therapeutic effects achieved with robotic hand function training: In patients who were severely affected, the training effects were decreased by sound significantly. In contrast, moderate and mild cases benefited from musical stimulation distinctively. Motivation was rated substantially higher in the sound-group than in the control-group, independent of the level of severity. These findings indicate that specified music applied to technology-assisted hand function training post-stroke can either boost therapeutic effects of robot-assisted hand function training as it can also deteriorate valuable recovery advances potentially depending on the stage of recovery. This is the first time negative effects of music in rehabilitation training are reported. To explain this effect, a methodological approach is discussed. This approach suggests considering music as a potential arousal factor causing a high muscle tone. An experimental procedure to investigate muscle reactions during robotically-guided movement under different sound conditions is therefore introduced in the discussion section of chapter 4.

Furthermore, three single-case studies are presented. The single-case studies were performed along the clinical study protocol with 9 sessions of robotic hand function training spread over three weeks with three different sound-conditions. The sound conditions were different than in the clinical study: They consisted of no sound, polymetric music and self-selected favorite music. Participants underwent three training cycles under these three different conditions. Between each training condition at least a two-week washout period was applied. The goal here was to examine effects on function of an additional sound-environment with self-selected music in a within-subject design and to deepen the perspective on single finger force profiles.

BACKGROUND

2. POST-STROKE REHABILITATION, MUSIC AND SOUND, ROBOTS

2.1 The paretic hand post-stroke

2.1.1 Stroke and post-stroke consequences

2.1.2 Recovery processes post-stroke

2.1.3 The paretic hand syndrome post-stroke

2.1.4 Treatment approaches for the paretic arm and hand

2.1.5 Open questions in treating the paretic hand post-stroke

2.1.1 Stroke and post-stroke recovery

With 6,7 million cases per year, stroke is the second leading cause of death worldwide and third-leading cause of death in Germany (Langhorne et al. 2009; Heuschmann et al. 2010). With 5 million persons per year in total, the larger number of stroke victims survive the insult. Three months after the stroke, most of them still suffer from severe syndromes limiting independent management and participation in everyday life (Heuschmann et al. 2010). The most common consequences following a stroke are deficits in motor function and motor control which affects 80% of all cases (Langhorne et al. 2009). Following Langhorne et al. 2009, eight out of ten patients suffer from a hemiparesis involving the arm which resides chronically in three out of four cases (Hesse et al. 2014). This high number of chronic cases explains why stroke is one of the most significant causes of life-long disabilities in Western high-income countries (Langhorne et al. 2009; Knecht et al. 2011; Heuschmann et al. 2010; Krakauer 2005). Following to calculations of the "World Health Organization" (WHO), the number of strokes will increase up to 1,5 million cases per year till 2025 (Heuschmann et al. 2010). In the United States the predicted number of stroke survivors suffering from post-stroke disabilities in the year 2030 is higher than 10 million (Blank et al. 2014). To counteract this increasing number and to supply therapeutic demands effectively, there is a need to enhance stroke prevention, acute stroke treatment and rehabilitation post-stroke.

A stroke, also named cerebrovascular insult, occurs due to a disruption of the bloodstream within vessels supplying the brain with its metabolic demands. A low supply of essential nutrition directly leads to irreversible brain cell damage resulting in a lesion (Norouzi-Gheidari et al. 2012). A stroke can cause death or in case of surviving the stroke, a variety of other syndromes. Two different types of stroke occur most often: 80% of all stroke cases are ischemic strokes, 20% are hemorrhagic strokes (Knecht et al. 2011). An ischemic insult is caused by embolism, thrombosis, systemic hypoperfusion or venous thrombosis. In this case the blood stream supplying the brain is either reduced or totally blocked by a blood clot, fat globule, gas bubble or foreign material within a vessel. Hemorrhagic strokes result from damages in the vessel membrane which bursts as soon as there is high blood pressure. This leads to sudden bleedings into the brain which in turn damage tissue. The main risk factor for stroke is age: In Western Countries half of all stroke cases occur with an age above 73 (Heuschmann et al. 2010). Other risk factors are genetic tendencies, high blood pressure, atrial fibrillation, high blood cholesterol levels, diabetes mellitus, smoking, alcohol, drugs, lack of physical activity, obesity, processed red meat consumption and unhealthy diets (Sacco et al. 1997).

Depending on size and location of the lesion, a variety of symptoms and syndromes can occur: 90% of all stroke survivors suffer from a hemiparesis, a one-sided weakness, resulting in deficits of motor strength, motor control and body perception of one body side, contra-lateral to the side where the lesion is (Krakauer 2006; Street et al. 2015). A hemiparesis can affect the leg, arm and one side of the face. It can lead to gait- and balance-problems, deficits in control of the arm, hand and face, and is often combined with proprioceptive deficits, muscle weakness, muscle fatigue, dystonia or post-stroke spasticity (Langhorne et al. 2009). Furthermore, common post-stroke syndromes are aphasia, apraxia, ataxia, hemineglect, hemiapnosia, post-stroke depression, cognitive deficits, and fatigue (Teasell et al. 2014a, 2014b). All these post-stroke syndromes can lead to impairments with different grades of severity (Street et al. 2015; Goldstein et al. 1989).

Regarding grades of severity, a scale was developed by the "National Institute of Health Stroke Scale" (NIHSS), which subdivides the overall stroke population into very severe, severe, moderate and mild cases of stroke (Goldstein et al. 1989). Following Hesse et al. 2003, the overall stroke population is distributed in manners of severity over three parts, whereby one third of all cases shows severe symptoms, and the other two thirds suffer from mild to moderate symptoms (Hesse et al. 2003). Most of the time, patients suffering from mild to moderate symptoms can regain skills needed to manage day life again: 78-85% regain the ability to walk and 48-58% are able to manage an independent day life including self-care skills (Gresham et al. 1996). Cases with more severe symptoms are dependent on life-assistance: 15-22% cannot regain walking skills and 42-52% are not able to manage self-care tasks anymore (Gresham et al. 1996). Following Verbeek et al. 2014 who carried out a meta-analysis on stroke recovery interventions, four phases post-stroke in manners of time-span and recovery can be subdivided into: the hyper acute or acute phase (0–24 hours), the early rehabilitation phase (24 hours until 3 months), the late rehabilitation phase (3–6 months), and the chronic phase (> 6 months) (Veerbeek et al. 2014). Nordin et al. 2014 uses different grouping systems along the time-span after the insult (Nordin et al. 2014). Following Nordin et al 2014, the first time-window post-stroke, specifically between the insult and the seventh day after the insult can be labeled as "acute", while the time-span after the seventh day up until six months after later can be described as "subacute". More than six months after the insult the term "chronic" can be used (Nordin et al. 2014). Just in the term "chronic" Nordin et al. 2014 and Verbeek et al. 2014 use the same terminology. Birenbaum et al. 2010 use the term "hyperacute" for the time-span that is less than 24 hours after the insult, for "subacute" 24 hours to 5 days after the insult and "chronic" for weeks after the stroke (Birenbaum et al. 2010). In this thesis the concrete time-span after the insult will be used to prevent from confusion with the terminologies. A detailed overview on usage of the terms "hyper-acute", "acute", "subacute" and "chronic" of different authors listed above and the specification used in this thesis is shown in Table 1.

Acute/ hyper-acute	Sub-acute	chronic
www.strokecenter.org/professionals/stroke-diagnosis/neuropathology-image-library/acute-infarction/:		
1 day – 1 week	1 week – 1 month	After 1 month
Birenbaum et al. 2010:		
less than 24 hours	24 hours to 5 days	After weeks
Nordin et al. 2014:		
1 day- 1 week	1 week- 6 months	After six months
In this thesis the concrete time-span post-stroke is used.		

Table 1: Grading systems for acute, hyper acute, sub-acute and chronic states following different literature sources and terminology used in this thesis (www.strokecenter.org; Birenbaum et al. 2010; Nordin et al. 2014)

Studies evaluating the overall-effectiveness of post-stroke treatments indicate that there is a need to increase recovery outcomes (Teasell et al. 2014a): Although 70% of all stroke survivors are able to live at home without assistance three months post-stroke, still 25% depend upon home-assistance of family members or health professionals, 6% have to live in special-care homes, and 7% in other institutional homes (Heuschmann et al. 2010). The level of dependency and the grade of severity of post-stroke consequences are strongly influenced by treatment onset, treatment quality, intensity, duration of therapies as well as individual patient characteristics. Regarding the aspect of treatment onset, best outcomes are achieved when life- stabilizing interventions are applied as early as possible to stop tissue damage. Ideally the treatment takes place in stroke-units specialized in acute stroke treatment (Knecht et al. 2011). The treatment quality is known to be highest, when the acute treatment is carried out in specialized stroke-units, and following when evidence-based strategies containing high-intensity, high-frequent activating therapies that focus on repeated practice of goal directed tasks are applied (Langhorne et al. 2011). Furthermore, the overall-outcome and time-course of recovery depends upon multiple factors related to the patient characteristics like size and location of the lesion, the initial grade of severity of impairment, age, pre-existing damage of white matter, intrinsic motivation, social environment, the general ability to learn and the quality of treatment (Duncan et al. 2005; Knecht et al. 2011; Maclean, Pound 2000). The initial state after the insult and the development and time-course of specific symptoms allows to predict recovery outcomes and to adjust therapeutic goals. For example, the initial state of motoric function shortly after the insult can predict a patient`s autonomy in later life with a variance of 50%. Following Platz and Roschka 2011, the initial grade of severity of a hemiparesis allows to predict whether life-long disabilities limiting walking, grasping and management of activities in daily living will remain (Platz, Roschka 2011). Furthermore, the severity of an arm paresis syndrome some weeks after the insult is strongly related to the outcome of arm function six months later (Hankey et al. 2002). Another early predictor on the outcome of arm function is the hand: Specifically the ability of active finger extension enables to predict the outcome of arm function post-stroke (Smania et al. 2007).

In Germany, the stroke treatment is divided into different phases with phase-specific treatment goals related to the patient's needs in manners of grade of severity and not of time-span after the insult (www.kompetenznetz-schlaganfall.de/reha-neuro): In phase A, also named “acute phase”, and in phase B, the overall goal is the achievement of biological autonomy from machine-dependency and continuous care. This phase is usually carried out in the acute clinic within the first days to weeks after the insult. The main focus in the acute phase is the stabilization of vital functions or, if needed, the application of a thrombolysis. Furthermore, in this phase it is central to prevent the patient from further complications to minimize impairment and to increase functional advances. If possible, already in this very early phase, activating therapies are applied. Depending on a patient`s profile and needs, movement training, speech training and psychological therapies are performed. This is important because it is highly evident that especially within the first three months an early-onset of therapeutic interventions with high intensity training and exposure to an enriched environment stimulates recovery processes best (Knecht et al. 2011; Nudo 2013; Särkämö et al. 2008). Therefore it is recommended to transfer patients from acute treatment to a setting that focuses on rehabilitation as fast as possible. To reach this next phase, rehabilitation phase B, which is carried out in rehabilitation centers, a certain level of stability and independence is needed. The main goal in phase B is to provide therapies that rehabilitate the patient up to a level that enables management of independent living (www.stroke.org 2015). Therefore a multi-professional team provides therapies that aim to retrain lost skills and to develop compensation strategies if deficits reside chronically. In phases C and D the goal is to achieve independence of continuous care in manners of functional autonomy. In phase D a special focus is given on regaining social autonomy in manners of life without assistance. In phase E the focus lies on the maintenance of an achieved rehabilitated state (Knecht et al. 2011). The underlying mechanisms which drive advance and recovery up from the acute state to these different rehabilitation stages will be discussed in the next chapter.

2.1.2 Post-stroke recovery processes

Following an insult, complex recovery processes take place in which the whole brain and especially the surrounding areas of the lesion undergo neuro-plastic changes (Nudo 2013; Cramer, Riley 2008). These neuro-plastic changes are based on the brain`s capacity to rewire new neural pathways. This process is named “neural plasticity”. After a brain damage like a stroke, neural plastic processes involve on one hand spontaneous nerve sprouting, also named lesion-induced plasticity, and on the other hand training-induced plasticity. Both processes are strongest and fastest in the first three to six months post-stroke, and most of them occur in the nearest surroundings of the lesion area (Teasell et al. 2012; Krakauer 2005, 2006). The bigger the lesion is, the more widespread new plastic formations grow (Nudo 2013). Nudo 2013 reviewed studies that observed post-stroke neuroplasticity which was induced by motor training, by experience, by injury or these processes interacting with each other. Concluding to Nudo 2013, the strongest modulators of neural plastic changes post-stroke are induced by experiences and by training. In the case of training-induced effects, new formations result from exposure to external stimuli, from motor learning and from combinations of motor actions and sensorial experiences (Krakauer 2006; Cramer, Riley 2008). In contrast, lesion-induced plasticity occurs without any external stimulation. Both spontaneous nerve sprouting in the case of lesion-induced plasticity and experience- or action-based plastic changes are mechanisms that enable the acquisition of a new skill as well as the creation of new cognitive concepts needed to recover a brain from stroke (Cramer, Riley 2008).

Generally, the brain`s capacity depends upon functional connectivity between different areas and networks. The more connections between different areas are given, the faster the nerve conduction can happen. Anatomically, neural plastic processes lead to changes in functional connections between different brain areas. This takes place on different levels like within fine structures of nervous tissue and in macroscopic gross structures of the brain anatomy (Altenmüller, Schlaug 2015). After a stroke, on the level of fine structures, nerve sprouting occurs (Nudo 2013). The density of grey matter can change due to an enlargement of neurons and due to changes in synaptic density. White matter can show changes in an enlargement of myelin cells that cover axons. These axons transmit electric signals via nerve fiber tracks. When they are enlarged, nerve conduction can take place faster (Altenmüller, Schlaug 2015).

Following an insult, two spontaneous processes happen at the same which both lead to neuro-plastic changes: First of all, the process of spontaneous nerve sprouting leads to growth of new formations. At the same time a decrease of grey or white matter in the lesion surroundings can be seen. This decrease is associated with a decreasing size of the post-stroke edema. This decrease in turn allows a reperfusion of the lesion's surroundings, also named penumbra. Following, usually the diaschisis is lowered again as well. Because of this can increase again in the lesion-surrounding areas. Within days up to one month, the process of spontaneous neurogenesis slows down (Nudo 2013). Afterwards, neural changes are mainly caused by training or by exposure to enriched environments (Särkämö, Soto 2012; Nudo 2013). Plastic changes that are induced by training were shown to be caused by repeated motor activity, sensory input, mental imagery and movement observation (Blefari et al. 2015; Ronsse et al. 2011). In the case of training that focuses specifically on the acquisition of motor skills, namely motor learning, changes are mainly induced by movement repetition, error-based learning experiences and kinesthetic imagination (Nudo 2013; Israely, Carmeli 2015). Clinical neuro-imaging studies on motor training-induced neuroplasticity showed that training results in an increase of the size of task-related cortical networks (Amengual et al. 2013). Especially studies comparing brain scans before and after complex task acquisition involving the need for high temporo-spatial precision like it is needed in musical- or sport-activities, were shown to result in such an increase (Amengual et al. 2013). It was also shown that musical or sports-training can cause even more fundamental changes up to the level of brain anatomy. This can be seen especially when such training is performed regularly, and was carried out before and/or during puberty or in a professional manner (Altenmüller, Schlaug 2015; Münte et al. 2002). According to Nudo 2013, neuro-plastic changes and mechanisms that were observed in a healthy brain during normal development can show similarities to processes taking place in the recovering brain: In the case of post- stroke recovery, the more-use of one extremity or a specific muscle-group in task-specific training was shown to increase the size of the cortical representation as well (Takeuchi, Izumi 2013): The increase of size of the cortical network related to the more-use of the trained arm was shown to be use-dependent, and to be associated with functional enhancement (Sterr, Freivogel 2004). For example, studies investigating the effectiveness of Constrained-Induced-Movement Therapy (CIMT) showed that the more-use of the affected arm post-stroke which is not restricted but forced to be used in this therapeutic technique, results in increased activtiy of the neural network of the affected arm-side compared to the side which is restricted and used less (Takeuchi, Izumi 2013). It was shown that CIMT-training resulted in increased grey matter as also in bilaterally distributed sensorimotor areas compared to control-groups (Takeuchi, Izumi 2013; Corbetta et al. 2015). Many different reorganizational processes occur on cortical and subcortical levels at once and also interact with each other. As mentioned before, plastic changes interact especially in the lesion's surroundings. According to Ward et al. 2006, a reduction of nervous cells in the surrounding area of the lesion leads to increased excitability in this lesion-near part of the brain. This is known as one part of the phenomenon described as over-activation. Furthermore, it was shown that active hand movements performed in the initial phase post-stroke, lead to activation of the primary cortex and in addition to that, to an activation of other areas which are not located on the primary cortex. This over-activation was shown to resist in patients suffering from chronic syndromes. In contrast, among patients that recover well this over-activation decreases with time. Likewise, bilateral activation of the sensorimotor cortex was observed to take place: A bilateral activation of the sensorimotor cortex was shown to correlate with slower symptom decrease (Ward 2006). Moreover, it was shown that hemispheric interactions between affected and non-affected side can occur: For example, studies on recovery processes from aphasia showed that this process results in neuro-plastic changes in both hemispheres. As already mentioned before, not just spontaneous nerve sprouting, motor experience-based plasticity or hemispheric interaction plasticity take place, but furthermore sensorial stimulation can lead to neural plastic changes (Kattenstroth et al. 2012). The phenomenon of experience-dependent plasticity was already shown in studies observing animals that were exposed to either enriched environments or non-enriched environments. Animals in the enriched-environment-group showed higher numbers of synapses than animals in the control-group. This was interpreted as result of neural plasticity stimulated by the enriched environment (Salvanes et al. 2013). Therefore the exposure to an enriched environment is considered as a highly relevant aspect to stimulate plastic changes in the recovering brain (Särkämö et al. 2008; Kattenstroth et al. 2012). In summary neuro-plastic processes enable recovery. Therapeutic approaches should therefore take into account how neuroplasticity can be promoted in a beneficial manner. In the next section the paretic hand syndrome will be discussed particularly which was mentioned in this chapter as well, when discussing aspects of hemispheric interaction seen due to CIMT training.

2.1.3 The paretic hand syndrome post-stroke

One of the most common consequences following a stroke is the hemiparesis which involves the upper limb and the hand (Langhorne et al. 2009; Pollock et al. 2014). This thesis addresses the treatment of the paretic hand syndrome which will be characterized here in detail. Therefore, first limitations caused by the paretic hand syndrome are summarized. A short description of the hand anatomy is given in the following section, which informs about pathological characteristics of the hand paresis including single symptoms of the hand paresis syndrome, grades of severity, development of recovery, and predictors of outcome.

Due to a hand paresis, problems occur that limit the ability to use the hand to grasp, to manipulate objects or to cooperate with the other hand in bimanual tasks. These limitations make it very difficult to manage activities of daily living (ADL). The hand is needed to grasp and manipulate objects in activities like eating, clothing, for opening doors, holding a telephone receiver or shaking a hand. With one hand-only, some tasks can be performed already. But the cooperation of two hands enables to execute complex tasks needed in daily life as well. Examples for bimanual tasks are applying tooth paste to a tooth brush, opening a bottle, closing the zipper, cutting bread, or riding a bicycle (Dietz et al. 2013). As nine out of ten patients are affected by an arm paresis including the hand of which this syndrome remains chronic in three out of four cases, there is a need to enhance treatment strategies so that more patients can actively participate and manage their daily lives (Hesse et al. 2008).

Before presenting a detailed description of the pathological characteristics of the hand paresis, a short overview of the hand anatomy will provide an introduction to the topic. Following Schmidt and Lanz 2003, the hand consists of 27 bones whereby 14 bones are related to the proximal, intermediate and distal phalanges of the fingers (see Fig. 2: A and B). The fingers and the wrist are connected the metacarpals and eight carpal bones.

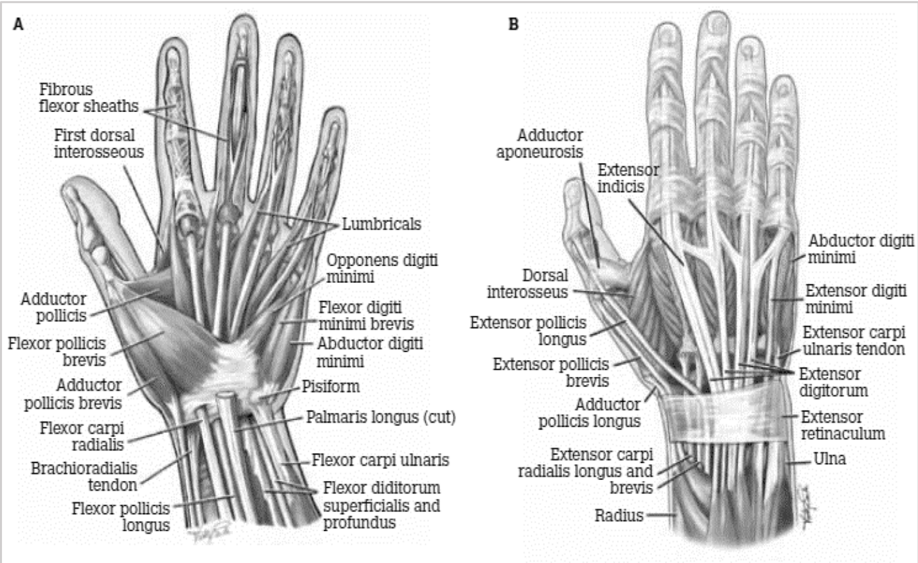


Fig. 2A: Hand anatomy of right hand flexor muscles; 2B: Hand anatomy of right hand extensor muscles (www.humananatomybody.info).

Regarding muscular control, the hand is controlled by extrinsic and intrinsic muscle groups. The extrinsic muscle groups consist of long flexors and extensors which are located in the forearm (see Fig. 2: A and B). The intrinsic muscle groups are located between the metacarpal bones and they control the thumb, the little finger, four dorsally and three volarly, as also the lumbrical muscles which originate from the deep flexor muscles and control the dorsal extension (see Fig. 2A). The fingers are controlled by two long flexor muscle groups located in the forearm. The tendons are connected to the phalanges of the fingers. A deep flexor is connected to the distal phalanx, whereby the surperficial flexor is connected to the middle phalanx. These flexors allow to flex all fingers at once. The thumb is controlled by the thenar muscle group that also controls opponents and abductor brevis. Together this muscle group allows to produce opposition of thumb to other fingers. This position is needed for grasping and manipulating objects. The extensors originate in the forearm. To shape extensor hood mechanisms the tendons unite the interosseous and lumbrical muscles. The thumb has total two extensors which are located in the forearm (see Fig. 2B: Extensor pollicis brevis, Extensor carpi radialis longus and brevis). The index finger and the little finger both have extra extensors. All these extensors are located within six distinct compartments. The nerves of the hand are either radial, median or ulnar nerves. The radial nerve innervates the extensors of the fingers as also the abductor of the thumb.

Main problems of a hand paresis are muscle weakness, over-excitability, and muscle-co activation patterns resulting in muscle synergies which counteract isolated finger movements, specifically finger-, hand- and wrist-extension (Kamper et al. 2006; Balasubramanian et al. 2010). In the initial phase following a stroke, the hand paresis is characterized by deficits in skeletal motor unit control, which can be summarized practically in limitations of voluntary movement. In this state, the muscle tone is either totally flaccid or shows a diminished muscle tone (Blank et al. 2014). During this initial phase, some muscle groups are not used at all. This non-use of affected muscles leads to a shortening of fibers. This can in turn lead to soft tissue contractures later on.

Moreover, some patients develop spastic symptoms. A key predictor of post-stroke spasticity (PSS) is occurrence of spasticity within one moth post-stroke. A special risk group for PSS is a patient initially suffering from a severe grade of the arm paresis (Lundstrom et al. 2010). Spasticity can be defined as "*a motor disorder which leads to velocity dependent increase of tonic stretch reflexes with exaggerated tendon jerks, resulting from hyper excitability of the stretch reflex, as one component of the upper motor neuron syndrome*" (Wissel et al. 2015). This definition goes back to Lance et al. 1995 and was extended by Young et al. 1995 with the idea that spasticity might result from abnormal intra-spinal processing of primary afferent inputs (Wissel et al. 2013). Practically, afferent inputs can be any sensorial stimulation from outside onto the hand. In general, spastic co-contraction patterns limit the ability to extend the fingers, the wrist or the elbow (Ivanhoe, Reistetter 2004; Sheean, McGuire 2009; Wissel et al. 2013; Wissel et al.2015). Muscle co-activation patterns are caused due to hyper excitability of spinal reflexes like the stretch reflex or flexor withadrawal reflexes. These reflexes can be induced during rest or by sensorial stimulation (Sheean, McGuire 2009). In the case of a spastic hand paresis, the most common spastic co-contraction pattern is a coupling of the flexor- extensor muscles in which the stronger flexor muscle group superimposes active movement by a blocking force against the extensors. The muscle groups that are particularly affected in the case of a spastic arm and hand are the long flexor muscles of the forearm, the flexor muscles of the wrist and the fingers including the deep flexors. These flexor-groups are over-activated while the extensor muscles are too weak to counteract. Taken together, these spastic symptoms can be characterized as pathological muscle reaction which gets induced by external stimuli like stretch movements, passive movements and potentially also other sensorial stimuli. The spastic muscle tension leads to unusual positions of the affected body part. This in turn causes soft tissue damage over longer time-spans.

At later stages of recovery spastic dystonia may also occur. Dystonia is defined as an increase in muscle tone. Sanger et al. 2010 described this symptom as *"a movement disorder in which involuntary sustained or intermittent muscle contractions cause twisting and repetitive movements, abnormal postures, or both."* (Sanger et al. 2010).

Over the time course of recovery, a non-use of extensor muscles as also the over-use of over-activated flexor units, lead to changes in the tissues- either as causality from spasticity or dystonia: This can result in tissue shortenings, contractions and stiffness. In some cases, additionally to the already mentioned main problems, somatosensible deficits may occur. These problems can involve aesthesia, algesia, hemihypesthesia, loss of two-point-discrimination or deep sensitivity. Additionally, sensible misperception like a pain syndrome can arise (Lambercy et al. 2013). In summary, the hand paresis is characterized by muscle weakness, hyper excitability, spasticity or dystonia, proprioceptive deficits and can be accompanied by a pain syndrome.

The grade of severity of a hand paresis syndrome is distributed bimodally, showing either a high grade of severity or mild grades of severity (Nakayama et al. 1994). The specific characterization of severe, moderate and mild cases of a hand paresis will be described here in detail: Within the research community different terms and concepts are used to specify grades of syndrome severity of an arm or hand paresis, but no detailed descriptions are given that focus on the hand only. The development of the hand is more fine-grained than the arm and is therefore often used as predictor for the development of the whole arm (Blank et al. 2014). By using assessments on the hand the overall therapeutic strategy for the arm can be informed. This already outlines that it might be relevant to differ the whole arm from the hand as one part of the upper extremity which needs to be considered not only in a whole-arm perspective (Smania et al. 2007). For the arm paresis syndrome, a three-step grading system is commonly used, which ranges from severe, to moderate, to a mild paresis (Platz, Roschka 2011) (see Table 2). These subdivisions are defined as "severe", when patients show no or very limited voluntary movement in the upper extremity, or if they do not show minimal function in the hand or the arm which restricts from managing activities needed for daily living (Koh et al. 2015). The term "moderate paresis" describes patients showing lowered levels of strength while movement of the affected arm is already possible. A "mild paresis" covers a state in which the level of strength is reduced. Patients suffering from a mild paresis usually show a nearly full range of motion and force production ability. These patients are able to perform activities of daily life. They mainly suffer from reduced movement velocity, deficits in precision and fast adjustment during manipulation tasks. All these aspects are needed for complex manual tasks (Platz, Roschka 2011).

A different approach in subdividing the grade of severity is used by the authors Aluru et al. 2014. Aluru et al. 2014 subdivide the arm paresis into "spastic paresis", "spastic co-contraction", and "minimal paresis" (Aluru et al. 2014) (see Table 2). These authors characterize a "spastic paresis" as a weakness in the extensor muscle groups while flexor muscle groups are over activated. They describe a "spastic paresis" as product of pathological synergies in which the flexor muscles superimpose the extensor muscles resulting in spasticity. "Spastic co-contraction" is characterized by an over-activity of flexor muscle groups as stronger modulators than the extensors. The "minimal paresis" is characterized by nearly recovered extensor muscles and minimal influence of co-activation patterns.

In this thesis the grades of severity were grouped along the primary outcome measure which was the Box and Block Test (BBT) (see Fig. 3). A detailed description on the grouping approach is described in chapter 4.1. The BBT is a clinically validated assessment tool for the specification of finger dexterity with a special focus on tip pinch, pronation and supination of the wrist, and elbow elevation. In this test, subjects sit in front of a wooden box which is subdivided into two parts, separated by a wooden wall (see Fig. 3). Subjects are asked to perform a task in which they need to grasp small wooden blocks which are located in one side of the box and to transport them above the wall to the other side as fast as possible. The amount of blocks they achieve within 60 seconds reflects qualities of fine and gross motor skill, specifically grasping, lifting, and release of an object (Desrosiers et al. 1994; Mathiowetz et al. 1985).

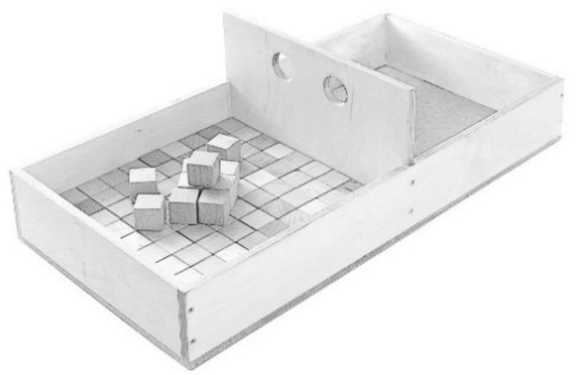


Fig. 3: Box and Block Test: wooden box, divided by a wooden wall, wooden cubes which need to be transferred from one side to the other.

Within this thesis, patients that were not able to achieve more than 15 blocks in the BBT were characterized as suffering from "severe hand paresis", whereby the group achieving 16 to 32 block as suffering from "moderate hand paresis" and the group achieving more than 33 blocks as suffering from a "mild paresis". This grading was chosen because the primary outcome measure of the clinical study could serve as homogeneous indicator and as this test reflects the ability to grasp, transport and manipulate objects, highly relevant to perform activities of daily living. More details on how patients were grouped is described in chapter 4.1.

Grading of severity (Platz, Roschka 2011; Koh et al. 2015):	
Severe	• very limited to no voluntary movement in the upper extremity, or if they do not show minimal function in the hand or the arm • restrictions in ADL (Platz, Roschka 2011).
Moderate	• lowered levels of strength • movement of the affected arm is already possible
Mild	• reduced level of strength • nearly full range of motion and force production ability • ADL can be performed • reduced velocity, deficits in precision and fast adjustment during manipulation tasks
Grading of severity (Aluru et al. 2014):	
Spastic paresis	• extensor muscle weakness • flexor muscle groups over activated • muscle synergies resulting in spasticity
Spastic co-contraction	• over activity of flexor muscle groups as stronger modulators than the extensors
Minimal paresis	• nearly recovered extensor muscles • minimal influence of co-activation patterns.
In this thesis, grading of severity is BBT-outcome related:	
Severe	• BBT: n <16
Moderate	• BBT: n >16 and n <32
mild	• BBT: n > 32

Table 2: Grading systems for severity of post-stroke upper limb paresis according to different literature sources and terminology used in this thesis (Platz, Roschka 2011; Koh et al. 2015; Aluru et al. 2014).

So far some determinants are known that allow the prediction of functional grading outcome of the hand paresis: Only 15% of all stroke patients suffering from a severe arm paresis initially are able to regain their hand function later on (Higgins et al. 2005). A special risk group for the development of a post-stroke spasticity in the hand are patients initially suffering from a severe arm paresis (Lundstrom et al. 2010). A good predictor for post-stroke spasticity is the occurrence of spasticity in the first month after the insult.

In summary, the clinical picture of the hand post-stroke is characterized by muscle weakness, over-excitability leading to changes in the muscle tone, deficits in motor control, coordination and proprioceptive skills (Kamper et al. 2006). In the early phase post-stroke, the muscle tone can turn from normal to high tone or it can turn to result flaccid. Both directions of muscle tone development results in problems of function: Patients that regain their functional ability to move voluntarily, show deficits in force production, velocity and control. To execute normal tasks with high precision, these patients need to increase attentional effort. In addition, proprioceptive problems can occur which limit movement coordination and manipulation skills. Also patients suffering from high muscle tone often cannot move the hand at all. The longer the hand or the arm is not moved, the more the flexor tone increases which superimposes antagonistic forces needed to perform tasks normally. Commonly these cases show a stereotypical hand position: flexed hand and wrist which over longer time courses can cause contractures (Lum et al. 2002). In the case of the arm and the hand, the strongest predictors of the grade of severity are the initial grade of severity of the paresis, the development within the first month, the degree of damage in cortical motor areas and in the corticospinal tract, and the ability to extend the fingers (Krakauer 2005). Regarding the treatment of the paretic hand, the best outcomes are gained within early onset of highly-intensive and high-frequent activating therapies in which goal-directed task training is performed in high repetition. Treatment approaches will be discussed in the next chapter 2.1.3 in detail. The high number of patients suffering from chronic hand paresis indicates, that there is still a need to enhance therapies. Following Krakauer et al. 2005, also chronic patients can still benefit from therapeutic treatment six months post-stroke. Chronic patients just need more time to improve (Krakauer 2005).

2.1.4 Treatment approaches for the paretic arm and hand

The effectiveness of a specific treatment depends upon several factors like the patient characteristics, onset of therapies after an insult, the intensity and duration of the training and the design of a therapeutic technique (see Fig. 4). A variety of therapeutic techniques for the treatment of the paretic upper extremity have been studied and are currently focus of ongoing research (Prange et al. 2006; Platz, Roschka 2011; Oujamaa et al. 2009; Hesse et al. 2014; Kwakkel et al. 2008; van Delden et al. 2012). These treatment approaches range from manually performed unilateral, to bilateral, to technologically-extended training in which the arm or the hand is moved by a robot in passive training or even controlled by Brain-Computer Interfaces (Pollock et al. 2014). So far, these studies showed that best outcomes are gained with interventions applied as early as possible after the insult, when carried out with high intensity and frequency, and when training contains repetitive and goal-directed tasks (Hesse et al. 2014; Pollock et al. 2014; Oujamaa et al. 2009; Teasell et al. 2012; Platz, Platz, Roschka 2011). Furthermore it was shown that the motivation of a patient influences the outcome significantly (Maclean, Pound 2000). But it is still unclear which therapeutic technique is superior to another for a specific patient profile. For some conventional therapies, studies already indicated positive effects, but these studies still lack a high level of evidence (Teasell et al. 2014a). Therapies that gained positive results were carried out in different ways, either as a stand-alone-technique, as alternative strategy to conventional treatment or as extension to standard therapies (Teasell et al. 2014a). Here three different guidelines based on reviews and one Cochrane review on evidence-based treatment for the paretic upper extremity post-stroke are summarized to present state-of-the-art knowledge with a special focus on the hand. One of these three guidelines was created by Platz and Roschka 2011. These authors carried out a systematic review in the year 2011, to inform clinical guidelines of the "Deutsche Gesellschaft für Neurologie und Rehabilitation" about evidence-based arm therapy post-stroke (Platz, Roschka 2011). The second guideline taken into account in this discussion was published by Teasell et al. 2014a, three years after Platz and Roschka 2011. Teasell et al. 2014a summarized evidence-based treatment strategies for the paretic upper extremity for the "Stroke Rehabilitation Clinician Handbook" within the community of "Evidence-based stroke rehabilitation" (Teasell et al. 2014a). The third guideline stems from Oujamaa et al. 2009 who performed a literature review on publications, studies and meta-analyses, from the year 2004 to 2008 including 66 clinical studies and meta-analyses 2004 to 2008 (Oujamaa et al. 2009). Furthermore, the Cochrane review from the year 2014 performed by Pollock et al. was included. This Cochrane review synthesizes systematic reviews focusing on the evaluation of effectiveness of different post-stroke interventions. Pollock et al. 2014 included 19 Cochrane reviews and 21 reviews by other authors, making up a total of 503 randomized controlled trials involving 18,078 stroke patients. In all these included studies effects of 18 different interventions to no-treatment were compared to conventional treatment or alternative treatments (Pollock et al. 2014). Out of 127 interventions, just one intervention showed a high level of evidence in not being beneficial in influencing outcomes related to activities of daily life: Transcranial direct current stimulation. This technique will be explained in more detail in the following section in which a variety of therapeutic techniques are summarized. Pollock et al. 2014 found furthermore a moderate level of evidence for 49/127 comparisons and low or very low levels of evidence for 77/127 comparisons. Taken together the three guidelines and the Cochrane review overlap in time-span and studies that were included to generate conclusions. Still they extend each other at some points. Regarding the factor treatment onset with therapies all authors, Platz and Roschka 2011, Teassel et al. 2014, Oujamaa et al. 2009 and Pollock et al. 2014, recommend to apply treatment onset as early as possible after the insult (see Fig.4). Teassel et al. 2014 outlines that this is important because most functional advances are achieved within the first four weeks up to twenty-four weeks after the insult and therefore training should be performed as early as possible. Following Teassel et al. 2014, treatment cycles carried out for the duration of less than twenty-four weeks were shown to gain no advances in recovery independently of therapy intensity. In manners of the treatment duration, Platz and Roschka 2011 conclude that a continuation of training should be performed if deficits remain after the first twenty-four weeks.

Regarding the training intensity, these authors conclude that it is highly recommendable to carry out training five days a week with the duration of at least 30 minutes. This level of intensity was shown to be highly effective if therapies were performed within a time range from four to twenty weeks post-stroke (Platz, Roschka 2011; Teasell et al. 2014a). This means the intensity within the first time-span needs to be carried out with a high degree. Also Oujamaa et al. 2009 report that high therapy intensity influences outcomes significantly (Oujamaa et al. 2009). Self-guided training which is performed with an intensity of daily practice or at least with 90 minutes per week combined with intermediating therapeutic supervision is recommended by Platz and Roschka 2011.

For chronic cases it was shown that shorter and intensive treatment intervals are as effective as treatment intervals that are longer but less intensive (Teasell et al. 2014a; Pollock et al. 2014). Even when comparisons on different grades of training intensity were shown to gain better results when training was carried out with a high intensity, still the level of evidence is moderate and lacks statistical significance (Pollock et al. 2014). To come to this conclusion, studies involving mental practice, repetitive task training and virtual reality were included.

A variety of therapeutic schools, such as Bobath Therapy, Proprioceptive Neuro-Muscular Facilitation, Constrained-Induced Movement Therapy or Arm Function Training are currently considered as conventional therapies (see Fig. 4). Following Platz and Roschka 2011, so far no conventional therapeutic school like Bobath Therapy, Proprioceptive Neuro Muscular Facilitation (PNF) or other traditional therapeutic techniques was shown to achieve superior advances in recovery compared to each other or to an alternative treatment. The effectiveness of conventional therapeutic techniques were shown to be either comparable or inferior to each other (Platz, Roschka 2011; Teasell et al. 2014a). Pollock et al. 2014 list Constrained Induced Movement Therapy (CIMT), mental practice, mirror therapy, interventions for sensory impairment, virtual reality and a relatively high dose of repetitive task practice as beneficial techniques, all of them with a level of moderate evidence (Pollock et al. 2014).

In the following section each therapeutic technique will be explained shortly: Bobath Therapy, also named neurodevelopmental therapy, is a therapeutic technique which focuses on the reduction of muscle tone post-stroke. The training aims to reach this goal by stimulation of the affected side post-stroke which takes reflex inhibiting positions and training of postural control into account carefully (Hafsteinsdottir et al.

2007). Proprioceptive Neuro Muscular Facilitation (PNF) is a therapeutic technique which aims to increase the active and passive range of motion by active and passive stretch training (Sharman et al. 2006).

Constraint-Induced Movement Therapy (CIMT) is a therapeutic technique in which the non-affected arm is restricted and the affected arm is forced to be used. The affected arm is trained with the concept of massed practice (Corbetta et al. 2015). The effectiveness of CIMT, also named „forced use‟-therapy, is highly recommended for chronic patients (Platz, Roschka 2011). Teassel et al. 2014 also found a strong evidence on the effectiveness of CIMT and modified CIMT for chronic arm paresis compared to conventional therapies especially in active wrist and hand movements. Patients suffering from sensory deficits or a neglect benefitted especially. For other patient groups no recommendation can be drawn (Teasell et al. 2014a). CIMT was also reported to gain a level of moderate evidence by Pollock et al. 2014.

In contrast to CIMT, bilateral training focusses on interaction between the affected and non-affected side. Bilateral arm training and circuit training, both provided over a time course of several weeks with at least an intensity of three times a week, is recommended by Platz and Roschka 2011. So far no recommendation can be drawn for bilateral arm training with rhythmic auditory cueing (Platz, Roschka 2011). Pollock et al. 2014 report that unilateral arm training compared to bilateral arm training might be more effective. This result on unilateral training outperforming bilateral training is indicated with an evidence level of moderate quality. Delden et al. 2012 performed a systematic review on technical devices for bilateral upper limb training which indicate promising effects. Still the effectiveness of such a training is not signified yet. Therefore more randomized controlled trials need to be performed (van Delden et al. 2012).

Impairment Oriented Training (IOT) is a therapeutic technique based on neuroscientific knowledge which focuses first on the impairment to than enable specified and multisided training tasks which aim to train related activities of daily life. Therefore evidence-based strategies are taken into account. IOT contains two different protocols, the so-called "Arm-Function-Training" (AFT) intended for patients suffering from a mild paresis, and the "Arm-BASIC-Training" (ABT) intended for patients suffering from a severe paresis (Platz et al. 2009). Both training-scenarios aim to train the patient to perform goal-directed tasks with an adequate tempo, in a repetitive manner along movements that are oriented towards activities of daily living. Both scenarios are often performed in group settings. To reach advances in selective arm movements the ABT is recommended for severe cases. If AFT is applied additionally to conventional therapy for cases suffering from a mild paresis, this training increases sensorimotor skills and is recommended by Teasell et al. 2014a. Studies in which task-oriented training was compared to other therapeutic interventions that were performed less often showed, that task-oriented training resulted in enhanced arm function (Pollock et al. 2014). But

according to the Cochrane review, task-oriented training is still not significantly more effective in restoring arm or hand function than other techniques. Therefore it is considered as a therapeutic option which cannot be recommended differentially yet.
High-repetition training is based on the concept that repeated performance of a movement enhances motor recovery by promoting plasticity, muscle tone, increasing control, force and learning (Waddell et al. 2014). It can be implemented in many other techniques as a parameter on how a task is performed at a fundamental level. A Cochrane Review was performed in the year 2007 to observe whether repetitive training post-stroke is effective and promoting functional recovery (French et al. 2007). Following French et al. 2007 high-repetition training is not effective for upper-extremity training post-stroke. These authors found that rather task-specificity might influence upper-limb training more effectively than repetitive task training.

So far, research on motor learning strategies linked to perspectives of sports science or psychology showed controversial results for direct transfer and application to therapeutic interventions. These motor learning strategies involved aspects such as attention, effects of social interaction, self-guided training, different reward systems, sleep, training breaks, or concrete learning strategies like blocked- versus randomized-order sequence learning or feedback-based learning into therapeutic concepts. Following Platz and Roschka 2011, no recommendation can be drawn from this knowledge base yet. Teasell et al. 2014a recommend strength training which was shown to enhance grip strength significantly. This technique might originate from sports research. For training which is adjusted along the level of skill and which is based on repetitive tasks containing selective movements it was shown that some cases can benefit. While results are controversial, this motor learning approach is recommended by Platz and Roschka 2011 and Teasell et al. 2014a. Platz and Roschka 2011 recommend to perform trunk restraint training applied to reaching or grasping training to reduce compensatory trunk movement. Pollock and Teasell et al. 2014a do not report about this technique at all.

Mental practice is a therapeutic technique in which the patient tries to envision and feel movements of the affected arm without performing the movement at all or along guided movement which is performed manually by a therapist. This technique is performed as extension to other therapies as well as stand-alone technique (Park et al. 2015). Pollock et al. 2014 found a level of moderate evidence for mental practice: For subacute chronic patients with minimal rest function in the hand, mental training is recommended to enhance function. This training should be performed additionally to conventional therapy. In this training the mental imagination on usage of the affected arm multiple times a day for ten to thirty minutes was shown to be effective (Koh et al. 2015; Zimmermann-Schlatter et al. 2008; Teasell et al. 2014a). Currently there is conflicting evidence whether mental practice interventions enhance performance of activities of daily living post-stroke or not (Teasell et al. 2014a). Nearly related is the therapeutic technique of action observation in which the patient is advised to watch the own movement execution when it is performed with the non-affected side or guided by the therapist, on a video screen presented by an avatar or by a therapist. Training that is subdivided into action observation via video sequences over a time course of six minutes and combined with active practice is recommended as extension to conventional treatment for moderate cases.

Mirror Therapy is a technique in which the patient sits on a table, divided in two halves by a mirror. Movements of the non-affected body side are performed in front of the mirror. The patient observes this movement in the reflecting mirror and imagines that the mirrored movement is performed by the affected side which is behind the mirror. Following Platz and Roschka 2011 and Pollock et al. 2014, Mirror Therapy is recommended for subacute chronic patients extending conventional therapy to reach an increase in motor function. Teasell et al. 2014a report that studies on effectiveness of Mirror Training gathered conflicting evidence on the improvement of motor function post-stroke. Moderate evidence indicates that this training does not reduce spasticity.

Many therapeutic techniques involve technology that emphasizes and stimulates motor function-related processes or executes, assists and guides motor training. Sensory stimulation therapy summarizes techniques that stimulate the affected side by passive or active movement, vibro-tactile or extended with technologies like electric stimulation (Kattenstroth et al. 2012; Wang et al. 2013). So far EMG- also named biofeedback-therapies did not show relevant clinical effects in studies which could lead to a concluded recommendation whether they are safe and can be performed without side effects. Acupuncture or electric acupuncture were not shown to be effective yet. Both techniques did not show relevant clinical effects in studies. Sensible electric stimulation, thermic stimulation or sensible stimulation via intermitting pneumatic-compressive or thermic stimulations showed potential in treating somato-sensible deficits but so far effects were not shown to be clinically relevant (Morales et al. 2011). Therefore these approaches are not recommended yet. Two studies on effects of repetitive transcranial magnetic stimulation showed very promising results: In both studies a low-frequent stimulation was applied to the contra lateral side of the lesion on the motor cortex. For the epidural electric stimulation of the motor cortex just a very small study was carried out that explored safety of this technique. This therapeutic technique did not show relevant clinical effects in studies yet.

Virtual Reality Training summarizes therapeutic techniques which utilize virtual training scenarios to engage patients with games or to provide all kinds of feedback on movement qualities. In upper-limb or hand training it is a very widely used concept also for home training (Saposnik, Levin 2011). Therapeutic approaches that are based on virtual reality scenarios were shown to improve motor function in chronic stages with a level of moderate evidence (Pollock et al. 2014; Teasell et al. 2014a). Accroding to a very recent Cochrane Review of the year 2015, the use of virtual reality and interactive video games might enhance recovery in function and ADL if it is performed as an additional intervention or with the same dosage as conventional therapy (Laver et al. 2015). So far no conclusions can be drawn from studies evaluating effectiveness of virtual reality and interactive video games on grip strength. At this point it is still not clear which parameter within such a complex training environment like virtual gaming scenarios leads to measurable effects with a relevance to therapy. So far it was not shown whether gained recovery effects sustained after the treatment (Laver et al. 2015).

In neuromuscular, EMG-triggered or functional electro stimulation therapies muscular activity is amplified or stimulated via an external electric source. So far studies on neuromuscular, EMG-triggered and functional electro stimulation showed contradictory outcomes: Electro stimulation might enhance arm function but until this point not enough data is available to draw conclusions or recommendations yet. Neuro muscular electric stimulation (NMES) applied several hours a day on the shoulder muscles is not recommendable yet. In contrast, a recommendation can be drawn for chronic patients with application of EMG-ES for several hours a day at the wrist and finger extensor muscle groups (Meilink et al. 2008). Also EMG-triggered NMES applied to the extensor muscles of the forearm during bilateral movement execution is recommended if carried out in small groups and in some cases performed as home training. For patients with severe grades of hand paresis a multi-channel stimulation for grasping- and release-induction should be applied during active practice. In case of NMES and functional electric stimulation (FES) contraindications like pace maker, epilepsia or implants in the arm have to be taken into account carefully as well (Quandt, Hummel 2014; Teasell et al. 2014a). Teasell et al. 2014a report strong evidence for electrical somatosensory stimulation as it was shown to improve hand motor functions significantly.

In robotic therapy a robot, either an end-effector system or an exoskeleton device (see further explanations chapter 2.21.1) is used to provide training for the whole upper extremity, the wrist or the hand. Robotic training can be performed actively, assisted or passively. Arm-Robot-Therapy is considered a very effective approach, extending treatment especially for cases suffering from a very severe arm paresis (Klamroth-Marganska et al. 2014). Robotic therapies offer a movement training with high rates of movement repetition that cannot be executed actively by the patient. When robotic therapy is compared to NMES or EMG-NMES, hand- and finger extensor muscle units can be trained more effectively with robotic therapy (Teasell et al. 2014a). Robotic training is especially recommended by Mehrholz et al. 2012 as also by Teasell et al. 2014a for chronic patients to restore control of selective movements. Teasell et al. 2014a report strong evidence for Robot-Assisted Training improving sensorimotor training, outcomes of upper extremity functions and motor outcomes of the shoulder and elbow. In contrast, these authors conclude that wrist and hand motor outcomes do not improve from robotic therapy with a strong level of evidence. In both therapeutic approaches, NMES and robotic therapy only a small number of specific movements can be trained. Therefore these approaches can serve as special extensions to other therapeutic treatments.

Furthermore pharmacological therapies are investigated: L-Dopa can facilitate recovery in severe arm paresis cases. While the evidence is high, expected effects show middle quality and are not recommended by Platz and Roschka 2011. For d-amphetamine or the transplantation of human neural cells no recommendation can be drawn. Splinting, positioning, taping and passive movement are recommended for severe grades of paresis with spastic symptoms. The positioning carried out once or twice a day in maximal tolerated rotated positions can be performed to reduce the development of contractures in the shoulder. For other techniques involving technically assisted passive movement of the shoulder or wrist splints no effects were found (Teasell et al. 2014a; Platz, Roschka 2011). It was shown that hand splinting does not increase functional outcome parameters. A moderate level of evidence is given for daily stretch training which effectively prevents from development of contractures (Teasell et al. 2014a).

In addition, motivation, participation, training compliance and environmental factors are considered as critical components influencing treatment outcome (Maclean, Pound 2000; Maclean et al. 2000; Holmqvist, Koch 2001) (see Fig. 4). Following Holmqvist and Koch 2011, personal factors are age, gender, personality, educational and social background, previous experience, coping capacity, health status and general lifestyle. As environmental factors they consider the clinical and the social environment including quality of relation to family, healthcare professionals and other patients. Maclean and Pound 2000 carried out a critical literature review on the concept of patient motivation in the literature of physical rehabilitation. They report about a shared opinion of healthcare professionals that patient motivation influences functional outcome (Maclean, Pound 2000). Whether the problem that rehabilitation clinicians do not use a unified term when discussing or reporting on "motivation", Maclean and Pound 2000 come to the general conclusion that all factors including internal and social factors influence patient motivation and need to be studied more detailed.

Hesse et al. 2014 and Novak et al. 2014 showed that group interaction might increase motivation in arm training and in turn influence functional outcomes. Whether both of these interventions were not included in reviews yet, social interaction in therapy might take a more important role in the future as group settings are more cost-effective (Novak et al. 2014; Hesse et al. 2014). Dean 2012 carried out a study comparing effects on mobility of one group training with task-specific circuit training and a control-group which received therapies alone (Dean 2012). This study showed that for patients suffering from moderate symptoms the same level of functional outcome was achieved in both groups. As group training might also influence motivation and as it might be considered relevant for cost-reduction in the future, more research is needed to investigate the influence of social interaction in therapeutic settings on of function and motivation.

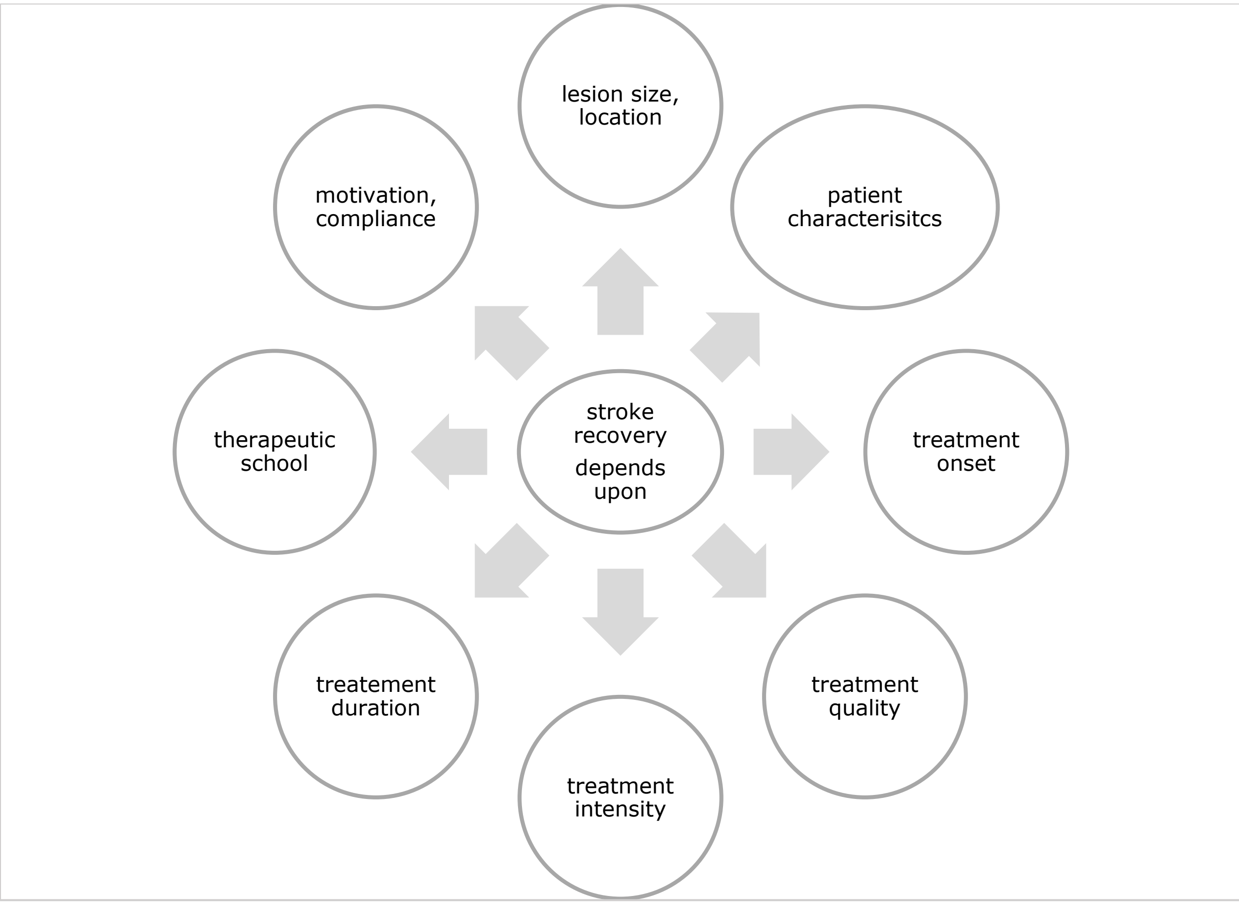


Fig. 4: Display of factors influencing post-stroke recovery

2.1.5 Open questions in treating the paretic hand post-stroke

Whether a variety of promising interventions are already implemented in clinical treatment schedules, and whether lots of new therapeutic techniques and devices are developed and investigated, all aiming to rehabilitate the paretic arm and hand post-stroke, still no high-quality evidence on the effectiveness of any intervention is given (Pollock et al. 2014). Many questions on treating a paretic arm or hand syndrome effectively remain open:

First of all, it is still unclear which of all conventional therapeutic techniques is most effective or whether one of them is more effective than another, and if so, why (Pollock et al. 2014; Teasell et al. 2014a; Platz, Roschka 2011). Therefore more randomized controlled trials (RCTs) need to be performed that involve comparisons of these different schools with control-groups. These studies need to take into account patient characteristics, training onset, duration and intensity carefully as it was shown that treatment effects also depend upon factors such as the grade of severity of the arm paresis, from the general course of recovery, the onset and intensity of a therapeutic intervention as also from a patient`s compliance with a specific technique and the therapist`s qualification in providing the therapy. When all these aspects are considered carefully in future studies this might result in more effective patient-tailored treatment.

Second, another central question is, whether bilateral arm training is more effective than unilateral training, and also here: How often, intensive and how long which training should be provided for what kind of patient, and if therapies need to be modified in manners of the time course of recovery.

Third, for future research Pollock et al. 2014 recommend to perform high quality studies on the effectiveness of CIMT, mental practice, Mirror Therapy, virtual reality and a relatively high dose of repetitive task practice, repetitive transcranial magnetic stimulation (rTMS), tDCS, hands-on therapy, music therapy, pharmacological interventions and interventions for sensory impairment with up-to-date reviews related to biofeedback, Bobath Therapy, electrical stimulation, reach-to-grasp exercise, repetitive task training, strength training and stretching and positioning. Krakauer et al. 2005 outlines that quantitative methods that specify and describe motor deficits post-stroke more precisely should be emphasized to be observed applied in motor learning strategies based on physiological rehabilitation techniques (Krakauer 2005). New technologies might contribute to better assessments that are not suffering from ceiling and floor effects, from the observer mistakes and reliability (Krakauer 2005). According to Teassel et al. 2012, there is a lack of research on interventions that focus on chronic patients (Teasell et al. 2012).

Fourth, currently, many technical devices for arm- and hand training are developed and tested to extend and enhance hand therapy. Also here it remains an open issue how to achieve functional advances that enable management of daily living best. It might be relevant to design robotic task training which focusses on ADL and to provide an additional therapy which only trains to translate new functions into real-live environments (Staubli et al. 2009).

Fifth, in clinical day-life it is very common to combine different therapies (for example Impairment Oriented Therapy (IOT) with robotic therapy). This might lead to effective or non-effective interactions. This multiple-treatment interaction might affect the recovery processes in multiple ways and needs to be studied more detailed. For the future it might be important to consider that different therapeutic approaches interact with each other in a beneficial or non-beneficial manner.

Sixth, so far none of the systematic reviews on arm rehabilitation putted a focus on the relation of motivation and function. This topic emerges more and more as highly relevant aspect especially in research on virtual reality training, robotic training and in group training. More studies need to be performed that focus on aspects like the attitude, compliance and motivation of a patient which can influence outcomes significantly (Maclean, Pound 2000; Dean 2012; Novak et al. 2014).

Seventh, beside of this, it is unclear whether training should start with hand, wrist, elbow and shoulder at once, or with a specific anatomical order. Regarding the hand, so far it is not known in which order or combinations fingers should be trained first to counteract an increase of muscle tone effectively. Usually therapies for the paretic hand focus first on treating the whole hand, or thumb and index finger, before involving the other fingers. This strategy is commonly chosen to retrain the most relevant movement for activities of daily living, grasping, as early as possible. But as mentioned in chapter 2.2., in many cases a hand paresis is accompanied with increased muscle tone, pathological muscle synergies or spasticity, counteracting isolated finger flexion and extension of thumb and index finger. Especially between these two fingers a tight muscle coupling is given which limits thumb extension needed for release after grasping. When grasping is practiced repetitively and with a high intensity this approach might be counterproductive for the development of the spasticity. Therefore it would be important to explore whether another order of fingers in hand training would promote recovery better.

Eighth, as the number of technical devices and technically-assisted therapies increases it is another important point to consider how and which feedback should be provided within these new technologies. This question involves sub-questions that range from modality-specific feedback, its design as error-, real-time- or adaptive feedback (van Vugt et al. 2016; Rosati et al. 2011).

Furthermore it might be interesting to investigate how sound and music contribute to any therapeutic technique, but also especially applied to new technologies. It is very common to use sound and music in virtual reality scenarios so that the need for investigation increases with the rising number of virtual reality training scenarios. The effectiveness of robotic technologies will be discussed in detail in the next section and as one of the main parts of this thesis, in the clinical study. This study also intends to take into account the before listed critical parameters such as patient characteristics, therapy onset, therapy structure including anatomical order, intensity and duration and the combined treatment approach. Another main goal in this thesis is to discuss the effectiveness of sound and music applied to post-stroke therapies that involve technology. Therefore this thesis aims to investigate how robotic hand function training and sound applications within the virtual training environment interact. Other central questions mentioned before as open questions are taken into account by specifying patient characteristics carefully to determine which patient group is sensitive to sound-extended robot training. Furthermore the therapy onset, duration and intensity is assessed while conventional assessment is extended by robotic technology assessment. This point was also mentioned as potential within arising possibilities that should be taken into account in future research by Pollock et al. 2014. In the next section robotic therapy for the paretic hand will be introduced in detail.

In summary, there is still a need to achieve better results in recovery as indicated by the high rate of arm and hand paresis cases that resist chronic. To gain better results in recovery, it might be important to investigate patient-tailored therapy approaches that focus on parameters which are critical for advances in research and development in the future. These parameters might be the precise observation of patient characteristics including severity, age, other diseases, therapy onset, therapy structure including anatomical order, intensity and duration as adaption to time course of recovery and their impact on outcomes and their relation to specific treatment techniques (Aluru et al. 2014; Quandt, Hummel 2014). Beside of this, combinations of different therapies should be observed to provide treatment in which different techniques complement the treatment effectively like it might be in a combination of CIMT and robotic training (Susanto et al. 2015).

2.2 Music and sound in post-stroke rehabilitation

2.2.1 Effectiveness of music and sound in post-stroke rehabilitation

2.2.2 Underlying mechanisms of music- and sound-induced effects in post-stroke motor rehabilitation

2.2.3 Open questions in music therapy for post-stroke motor training for the paretic hand

2.2.1 Effectiveness of music and sound in post-stroke rehabilitation

Music and sound were already applied to post-stroke rehabilitation in training domains ranging from motor therapies, cognitive training, speech training, to psychological training for post-stroke depression, for relaxation-, social interaction- and disease-management-training (Gebauer, Vuust 2014; Altenmüller, Schlaug 2015; Bradt et al. 2010). Whether the number of studies on music and sound interventions are currently increasing, so far the role of music and sound in neurological motor rehabilitation still needs further systematic investigation (Gebauer, Vuust 2014). In general, most significant results on the effectiveness of music and sound for post-stroke rehabilitation were shown for motor therapies, for cognitive training and for music listening interventions related to mood disorders (Bradt et al. 2010; Gebauer, Vuust 2014; Raglio et al. 2015; Särkämö, Soto 2012; Altenmüller, Schlaug 2015). Also musical intonation therapy, a speech training for aphasic patients, was shown to be beneficial. So far this technique still lacks data signifying its effectiveness (Altenmüller, Schlaug 2015). In the following section, the most important studies on music interventions that gained clinical relevant results in 1) motor training, 2) cognitive training, and 3) psychological training are summarized:

1) In the field of motor rehabilitation a variety of music interventions were developed to address post-stroke motor deficits especially in gait and arm function. Since the late nineties, a body of research on auditory entrainment and rhythmic cueing as therapeutic drivers began to grow. This research body involved baseline research on effects of rhythmic stimulation on healthy subjects and therapeutic interventions utilizing rhythmic patterns to guide motor training post-stroke (Thaut et al. 2015). Out of this, a therapeutic technique was developed which is named "Rhythmic Auditory Stimulation" (RAS). RAS was established as reproducible training protocol and as an articulated therapeutic technique for stroke patients with motor deficits. In RAS-training a metronome or strongly rhythmical music with a beat is used to engage stroke patients to synchronize movements along a beat. RAS was evaluated clinically with stroke patients suffering from hemiparesis in gait training, in unilateral arm reaching training and in bilateral arm training (Thaut et al. 2015). In both domains, upper and lower extremity training, moderate effects on motor control were gained. Bradt et al. 2010 performed a Cochrane review on music therapy for acquired brain injury including studies with total 184 participants. One of their main findings was that RAS is beneficial for gait post-stroke. This conclusion was based on two studies with low risk of bias scores evaluating RAS-gait training with total 98 stroke patients. Both of these studies showed that RAS-gait training gained significant improvements in motor qualities such as stride length, stride symmetry, cadence and gait velocity compared to standard physiotherapeutic treatment (Bradt et al. 2010). Another clinical study was carried out in which RAS applied

to arm reaching training was investigated. Results of this study showed that a significant decrease in compensatory trunk movement, an increase in shoulder flexion, and a slight increase in elbow extension was achieved. Furthermore, movement timing and velocity improved significantly (Thaut et al. 2002). This study described effects of the rhythmic cue on performance and not on carry-over effects. Moreover, Malcom et al. 2009 performed a pilot study on the effects of rhythmic auditory cueing applied to reaching task training over a 2-week treatment in five chronic stroke subjects suffering from an arm paresis. These authors also found that after the RAS-training, reaching kinematics were improved with a decrease in compensatory trunk movement, increase in shoulder flexion, and an increase in elbow extension significantly (Malcolm et al. 2009). Furthermore, movement time and velocity were significantly better than in tests before treatment. Another pilot study was carried out which evaluated effects of bilateral arm-training with rhythmic auditory cueing (BATRAC). After six weeks BATRAC-training motor performance, isometric strength and range of motion was improved (Whitall et al. 2000). All these studies lacked a control-group. Because of that, the level of evidence is weak. Paul et al. 1998 evaluated effects of active music making on elbow extension and shoulder flexion by observing 10 stroke patients. They did not find significant changes as resulting effect of this treatment (Paul, Ramsey 1998; Bradt et al. 2010).

Moreover, Schneider et al. 2007 carried out a clinical study with 20 patients suffering from a moderate arm paresis that received "Music Supported Therapy" (MST) which is active music therapy with musical instruments. In MST interventions patients learn to play easy melodies on a keyboard or to drum simple rhythms on an electronic drum-set. All study participants received 15 training sessions that were performed in addition to conventional treatment. Results of this study revealed significant improvements in speed, precision, movement smoothness and activities of daily living. Another study was carried out by Amengual et al. 2013 in which again 20 stroke patients received MST for 4 weeks. These patients underwent transcranial magnetic stimulation observations pre-and post-treatment to detect changes in the motor cortex excitability (Amengual et al. 2013). The results showed that this kind of training led to the development of new neural pathways. This newly grown network is suggested as an auditory-sensory-motor network. This network was also described by Rojo et al. 2012 who carried out a study on MST with brain imaging techniques (Altenmüller, Schlaug 2015). Concluding, MST promotes neural plasticity in auditory-sensory motor-networks.

Friedman et al. 2014 performed a study to compare effects of music-glove training with conventional therapy and isometric task training with 15 patients suffering from moderate arm paresis. Results showed that the Music-Glove training led to stronger improvements in hand function compared to the two other interventions. Beside of that, patients that trained with the Music-glove showed higher motivation ratings than the two other groups. Results sustained one month follow-up (Friedman et al. 2014). A similar effect on motivation was indicated as result of a study performed by Taheri et al. 2014 in which a robotic hand function trainer was evaluated with the same musical video game (Taheri et al. 2014).

2) In the field of cognitive training, Särkämö et al. 2008 carried out a single-blinded, randomized controlled trial with 60 stroke patients in the very early phase post-stroke to observe whether listening to either self-selected music or to audio-books or instead no additional activity at all would lead to changes within cognitive recovery, mood and perceived quality of life. Patients were randomly assigned to a music-listening-group, an audio-book-listening-group or a group that did not receive any additional activity. These patients underwent assessments three times, at baseline, after three and six months. The results revealed that the music-group showed a significant increase in verbal memory and focused attention compared to the other groups. Moreover, the music-group suffered less from post-stroke depression syndromes (negative mood and confusion). The authors concluded that music listening activates a widespread brain network including both hemispheres in regions related to attention, semantic processing, memory, motor functions and emotional evaluation, and by that music listening might encourage neural plastic changes which in turn enhance recovery and mood states (Särkämö et al. 2008). In general, mood-states can be considered as critical influence factor on motivation for rehabilitation. Health care professionals consider motivation as very important determinant for positive rehabilitation outcomes (Maclean, Pound 2000).

3) In the field of psychological training previously summarized studies of Särkämö et al. 2008 and Friedman et al. 2014, and a huge body of studies on music therapeutic interventions showed that music listening has a positive impact on mood, emotion and motivation in neurologic patients (Särkämö et al. 2008; Friedman et al. 2014; Raglio et al. 2015). This aspect is highly relevant because 40% of all stroke patients suffer from post-stroke depression. Depressive symptoms can take negative influence on functional recovery, therapy compliance and motivation, perceived quality of life and can even affect the risk of mortality (Raglio et al. 2015). Raglio et al. 2015 performed a narrative review on the effects of music listening as music therapeutic intervention for neurological patients and found that most of the studies indicated that mood related syndromes, depressive syndromes and quality of life were positively supported by music therapy.

According to the summary on studies showing effectiveness for music interventions, music can stimulate recovery processes related to cognition, emotion, motivation and motor function positively.

2.2.2 Underlying mechanisms of music- and sound-induced effects in post-stroke motor rehabilitation

In the previous section, music interventions for post-stroke rehabilitation were summarized. These interventions are applied with the intention to foster cognitive functions, motor functions, social or motivational aspects. In this section, sound- and music-induced effects and underlying mechanisms in post-stroke motor rehabilitation are described. So far the best evidence of music- and sound- induced effects in post-stroke rehabilitation was shown for RAS gait training and for music listening (Bradt et al. 2010; Särkämö, Soto 2012). First, neural plastic processes that are related to musical activities and to recovery processes are reported. Second, the effects of music listening on emotion and cognition are considered with a focus on its impact on stroke recovery. Third, the underlying mechanism of RAS is discussed.

1) Musical activities such as synchronizing movements to a beat, playing an instrument or listening to music induces long lasting plastic changes (Wan, Schlaug 2010; Amengual et al. 2013). Musical activities were shown to alter neuronal pathways especially when training is performed with a high intensity already up from childhood (Hyde et al. 2009a, 2009b). But also in adult amateur musicians plastic changes were already shown (Bangert, Altenmüller 2008). Studies comparing musicians versus non-musician brains showed that even up to levels of brain anatomy, neural plastic long lasting changes can occur (Münte et al. 2002): Amunt et al. 1997 showed that musicians have an enlarged hand area within the motor cortex compared to non-musicians. Other studies presented results that indicate an increase in grey matter density within cortical areas ranging from sensory-motor-, auditory areas, the left dorsolateral prefrontal cortex, the cerebellum, midsagittal size of the corpus callosum, in the right hemisphere arcutate fasciculus as result from music playing and in the left hemisphere arcutate fasciulus as result from vocal motor training (Bangert, Schlaug 2006; Gärtner et al. 2013; Hyde et al. 2009a, 2009b). Also on the subcortical level changes can be seen, especially on the levels of the cortico-spinal tract which will be referred to in chapter 4 again, when results gained in the clinical study are discussed. Furthermore, changes can be found in the posterior limb of the internal capsule, the cerebellar volume of grey matter which is increased. This part plays an important role for precise timing of movement and motor coordination and execution.

In summary, these studies reveal that plastic differences between musicians and a non-musician brain and the cortico-spinal tract exist. The explanation for this difference might be based on training-induced neural plastic formations (Hyde et al. 2009a, 2009b; Altenmüller, Schlaug 2015). When musical training leads to neuro plastic changes with long lasting effects, it seems obvious to utilize this phenomenon to drive recovery processes to promote learning and to stimulate growth of new neural and cortico-spinal pathways. One example for an active music intervention which is based on this concept with concrete reference is "Music Supported Therapy" (MST) in which playing a music instrument serves as motor training (Schneider et al. 2007; Amengual et al. 2013). A very recent study on effects of MST was carried out by Van Vugt et al. 2016. In this study it was tested whether auditory feedback would be the responsible component within MST (playing familiar piano pieces) that causes positive effects. Therefore two groups were compared that were either training with normal auditory feedback or jittered delayed auditory feedback (van Vugt et al. 2016). Results showed that positive effects were gained in both of the groups, while within the measure of the Nine Hole Peg Test and tests detecting tapping variability the group that had received training with jittered auditory delay feedback outperformed the other group. Because in both groups an increase in tapping speed, decrease of tapping variability, better outcomes post-treatment in the NHPT and an increase of motivation was found it was concluded that not auditory feedback was the component within MST driving positive effects on function and motivation. Van Vugt et al. 2016 suggested that rather proprioceptive and visual feedback, training-induced neural plasticity and motivation of a musical training with familiar music might be the reasons for improved function and motivation.

2) Another example in which cognitive processes drive recovery would be music-listening in the early phase post-stroke which was clinically investigated by Särkämö et al. 2008 (Särkämö et al. 2008). The study of Särkmo et al. 2008 showed that music listening improves mood levels. This indicates that music listening concretely influences the emotional state of patients. The underlying mechanisms for that might lie in neurochemical changes that are induced by music-listening which in turn causes the perception of positive mood. Chanda et al. 2013 who carried out a review on the neurochemistry of music showed that listening to pleasurable music in a healthy population can increase motivation, serves as reward or causes pleasure. Listening to relaxing music can influence arousal and stress levels, and performing music together can promote social affiliation which was in all three cases supported by studies on neurochemistry (Chanda, Levitin 2013). In addition, these authors note beneficial effects of music on immunity (Chanda, Levitin 2013).

Jäncke 2008, carried out a review on the relation of music, memory and emotion (Jäncke 2008). He lines out, that whether it was shown that music listening causes emotions and activates the limbic system, so far there is a lack of investigations that relate emotion, music and memory, all linked to processes in the limbic system. According to Jäncke 2008, music influences the emotional and cognitive system strongly, by causing awakening-mechanisms, by the impact of music on arousal, and its effect on emotional processes. Taken together, these effects attune and control a variety of cognitive domains (Jäncke 2008).

Another study performed by Eschrich et al. 2008 observed the influence of emotion on the episodic long-term memory for music (Eschrich et al. 2008). Eschrich et al. 2008 performed a study, in which effects of "emotional" music and "less emotional" musical pieces were compared by regarding the impact of structural aspects of a musical piece on memory performance. In this study, participants first had to rate 40 musical excerpts in the two domains valence and arousal. One week later, a recognition task was carried out. This study showed that pieces labeled as "positive" were remembered better than other pieces, and that the self-rated valence played an important role for the episodic long-term memory of music. Concluding to this study, strong emotions that were experienced during music listening enhanced the formation of memory and recall (Eschrich et al. 2008). When music listening is applied to a stroke therapy context, these aspects need to be considered carefully in relation to the therapeutic goals. If the focus is put on the recall of autobiographical memories, well known music might be a door to activate them. But when the training focus should instead be put on a general motivation via music, some patients could suffer from distraction when music is played back which they know well from their life before the stroke. Therefore, it is highly important to choose music in relation to defined goals and in continuous exchange with the patient. A pragmatic solution could be to assess musical preferences of the patient and to use closely related musical pieces. Another way could be to use music that is new to the patient, which the patient rates as enjoyable.

Moreover, Keller and Rieger 2009 showed that the simple activity of music listening can induce the urge to move (Keller, Rieger 2009). This phenomenon is a very important aspect when relating music and motivation: As music listening was also shown to cause motor simulations and kinesthetic simulations it might be relevant to study whether motivational levels depend upon the musical material that either allows to simulate movements in relation to its structure or not. Thinking of rhythmical music, it is likely that it is very easy to imagine a movement which is related to this structure. It might be rewarding to develop such a simulation and to map and couple it with a sounding structure: When a chain of events occurs repeatedly like rhythmic structures do, it is easy to develop expectancies. According to Huron 2006, anticipation is one of the key mechanisms preparing the body and the mind to react on predicted future events with an action selection generating a successful response which is coupled to an effective metabolic consumption (Huron 2006). The success in predicting the future and the fulfilment of an effective response might be rewarding because it enables to generate positive life consequences. In the case of RAS the prediction of the next beat is coupled with movement execution. According, when this coupling is effective and performed successfully this might be a rewarding experience.

3) Sound that is displayed rhythmically influences motor responses and by that it co-shapes movement qualities on low level and even on non-conscious response-levels (Rossignol, Jones 1976; Thaut et al. 2015; Repp, Penel 2004). The process of musical

rhythm perception involves subtasks like the encoding of basic event durations and intensities, the detection of phrases (which could also be described as mental grouping), the process of relating different durations to a pattern, and the perception of a beat which is often accompanied with a drive to move in synchrony (Iversen et al. 2009). The ability to move rhythmically to a beat usually emerges in the age of 4-5 years (Zatorre et al. 2007). This phenomenon is seen in every culture (Phillips-Silver et al. 2010; Cross 2003; Patel 2014). This process does not require high cognitive effort (Maes et al. 2014).

Beat processing engages a widely distributed network which includes motor planning regions like the premotor cortex, supplementary motor area, the basal ganglia and the cerebellum (Patel 2014; Repp und Penel 2004; van Vugt 2013). The underlying mechanism of movement-to-beat-alignment used in RAS might be explained best via the conceptual term of "entrainment": On a very abstract level, entrainment can be considered as a process in which two independent systems align to each other. The concept of entrainment goes back to the dutch physicist Chrisitan Huygens who observed the interaction of two independent clocks with different pendulum frequencies placed on a common surface in the year 1666 (Ross, Balasubramaniam 2014). After a while these clocks were swinging in synchrony due to modulations vice versa transmitted by the shared swinging surface. This interaction was called "entrainment". A more current definition of entrainment is the "*temporal locking process in which one system`s motion or signal frequency entrains the frequency of another system"* (Thaut et al. 2015). This process can involve systems that are physical, biological, human or sensory-motor systems. In the case of RAS, entrainment leads to synchronization of brain, body and environment, whereby the environment is carrying an auditory rhythmic signal. This brain-behavior coupling is also named "neuro entrainment" referring to a temporal relation of body, brain and the external environment (Ross, Balasubramaniam 2014). Since the nineties, entrainment-effects were utilized and investigated in the field of neurological rehabilitation. Therefore effects of rhythmically cued motor training for neurological patients were studied clinically applied to gait and arm training for stroke and Parkinson`s disease patients traumatic brain injury and cerebral palsy (Thaut et al. 1993; Thaut et al. 2002; Thaut et al. 2015). During RAS-training neural mechanisms cause a tight interaction between the auditory and the motor system: The firing rates of auditory neurons co-shape the firing rates of the motor system. By that the auditory system primes the motor system to be prepared to act in synchrony with the auditory rhythm (Patel 2014). This preparedness to act involves different steps of motor execution like movement initiation, timing and velocity. Recent research indicates that audio-motor synchronization activates a widely distributed network including sensory-motor-cortices, the supplementary motor area, basal ganglia and the cerebellum (Ross, Balasubramaniam 2014; Patel 2014). Already in the late 1960ies, Paltsev and Elner (1967) and Rossignol and Jones (1976) studied how a metronome-beat primes and times muscle activation patterns. Before that, motor control theories described other sensory domains such as the visual and proprioceptive systems as dominant domains influencing voluntary and involuntary movement (Thaut et al. 2015; Repp, Penel 2004). In the meantime it was shown that auditory perception plays a very important role as well: All senses, the visual, the tactile or the olfactory sense have different resolutions for specific parameters guiding perception. Regarding the phenomenon of entrainment and the ability to move in synchrony to an external time reference, the highest resolution in temporal precision of movement alignment to a cue can be achieved with sound (Hove et al. 2013): During exposure to a musical rhythm the auditory system generates stable temporal predictions and detects temporal changes with a high level of precision. This precision and speed is highly superior to the visual or tactile system (Thaut et al. 2015). Comparative studies on entrainment effects caused by visual and auditory rhythms showed that the auditory modality gains superior results in temporal precision than the visual modality. Visual cueing was just comparable in its outcome when stimuli were displayed as moving targets and not as static objects. Generally auditory-motor entrainment shows superior values for coupling auditory rhythm to motor behavior (Metcalf et al. 2014; Hove et al. 2013).

In summary, underlying mechanisms of sound- and music-induced effects that might play an important role for post-stroke motor rehabilitation were reported. A special focus was put on neural plastic changes caused by musical training, the influence of music on mood and motivation levels, and on the effect of RAS on motor functions.

2.2.3 Open questions in music therapy for post-stroke motor training for the paretic hand

In this section, open questions on the effectiveness of music therapy in the context of post-stroke motor rehabilitation are discussed:

Whether it was already shown that the music therapeutic technique of RAS as gait training gains better outcomes than conventional therapies, effects of RAS applied to arm training still lacks evidence (Whitall et al. 2000; Thaut et al. 2002). It is still unclear whether an auditory rhythmic cue applied to bimanual or unilateral arm or hand training (which was so far not observed at all), is effective or not. In addition, it is not known whether rhythmical music or a metronome-beat is more effective as cueing stimulus in arm training.

One of the most important questions regarding music is which kind of music could be used for RAS-training beside of march-music, western music or beat-based Big Band music. March-music was evaluated with Parkinson patients clinically showing positive effects on gait, but so far not with stroke patients (Ashoori et al. 2015). Furthermore, a study by Hayden et al. 2009 investigated rhythmic music as gait training with stroke patients which was either country, western or Big Band music with a 2/ 2 meter (Hayden et al. 2009). For the paretic arm or the hand, which might need other rhythmic or musical shapes to improve motor function post-stroke, there is a lack of empirical investigations showing positive effects of RAS with march-music, western music, Big Band music or other alternatives. Because of that, different musical genres and other meters could be taken into account in future research.

Beside of that, a musical piece can either be perceived as highly complex material consisting of single components or as a "whole". This depends upon the listener`s characteristics such as listening experience, the level of attention, emotional connotation and familiarity of a piece as well as the current mood state and situation of the listener (Brattico et al. 2010). Thinking of cultural aspects, music which was evaluated in RAS gait-training so far was rooted in western musical tradition and therefore might be perceived differently in other cultures. Because of that, cultural relatedness should be taken into account in the future when studying musical stimuli in the context of post-stroke rehabilitation. Moreover, music incorporates rhythm, meter, melodic contours, thematic accents, and a multidimensional structure of meaning. All these aspects might have power to induce a variety of emotional reactions isolated (just a beat) or together (as a whole musical piece). Concluding, complex music as well as single elements need to be observed carefully by taking listener characteristics into account. A systematic evaluation of each parameter within music is so far understudied in manners of therapeutic usage, more precisely which parameter of music causes what (Mainka 2015). This implies at the same time that there is a need to study the combination of different parameters to gain a better understanding on how and on which level parameters interact and which effects can just be caused when combined parameters, or music as a whole complex structure are used. Furthermore, it is unclear which kind of musical genre is best genre for a specific patient. The emotional impact of music has to be considered carefully as well. As music has the power to activate autobiographical memories what was shown by Eschrich et al. 2008 and by Jäncke 2008, it is important to be aware and to decide whether the activation of those memories are relevant for the therapeutic intervention at that point, or whether the treatment focus should be put on a different aspect (Eschrich et al. 2008; Jäncke 2008).

Regarding the terminology of "Rhythmic Auditory Stimulation" it might be interesting to extend the current concept of this music therapeutic technique by taking into account the differentiation of "stimulation" and "feedback": Van Vugt 2013 outlines that the term "feedback" describes a time-locked coupling of sound and movement resulting in a perceptual synchronization. In contrast, "stimulation" does not directly imply movement synchronization to a rhythm but an auditory stimulation can influence motor behavior and motor learning as well (van Vugt 2013). So far, entrainment and the synchronization-mechanism, which could be considered as a time-locked movement-beat coupling, are considered as central mechanisms in RAS. At a later stage in this thesis (see chapter 4), effects of another rhythmic structure on post-stroke motor recovery will be investigated, that does not induce a synchronization behavior but affect motor performance and motor training outcomes. The rhythmic structure will be considered as very important driver for the effect-induction. According, the current framework of RAS with a focus on entrainment and synchronization as main mechanisms could be extended. This extension could involve mechanisms of rhythmic stimuli that lead to "time-locked rhythmic feedback illusions" as well as mechanisms that are induced by a flexible rhythmic structure driving self-guided match-making of movement-to-accent.

Moreover, the reason why RAS is motivating needs a deeper exploration. During a successful coupling of a movement to a beat the fulfilment of expectancies and action is given. This might be rewarding (Huron 2006). Music-induced motor simulation might allow the prediction of a successful matchmaking of movement and sound what in turn could lead to an increase of motivation during RAS. It might be interesting to explore whether rhythmic disturbances embedded in RAS-training decrease the level of motivation. At the same time, such a study design allows to investigate a combination of RAS and error-based learning: Surprising events such as rhythmic disturbances might increase the level of attention and arousal which was already shown to promote motor-learning (error-based learning) (van Vugt, Tillmann 2015).

Whether Thaut et al. 1996 suggest musical criteria for an optimal RAS in gait training, these design features cannot directly be transferred to the upper extremity (Thaut et al. 1996). The reason for good outcomes of RAS as gait training might lie in the logic of easy-synchronization of bipedal gait to a 2/2 meter- or a 2/4- meter beat which facilitates regular walking. In contrast, hand or arm movements are most of the time unimodal and they differ from gait as they are not cyclic by nature. Whether movement sequences can also be performed in a cyclic way (e.g. repeated hand flexion and extension), arm and hand movements in real life tasks are most of the time more complex and not cyclic. Usually hand movements are related to grasping or manipulation of objects while the arm guides the direction of the hand as an end-point (Gentilucci et al. 1991). During a movement like grasping, many torques are turned with different velocities and forces interact antagonistically (Heinemann et al. 2015). When a grasping movement is subdivided into smaller units it involves single steps from reaching an object, opening the hand, closing the hand, sliding, transport and edge-release. This results in a complex rhythmical kinematic movement pattern. When an auditory rhythmic grid should support such a complex movement pattern, it is likely that a simple beat does not match, except from one condition in which the onset and endpoint of the overall-movement is synchronized. In this case, a rhythmic stimulus might influence the ecology of the movement in its onset and in its endpoint while subparts might be overcome with compensation strategies. In general, it is unclear whether such an approach promotes motor recovery and on which level of a subdivided movement sequence a beat could facilitate the movement.

One goal of this thesis is to suggest a specific sonic design for the application to the special case of robotic hand function training. Because RAS was so far indicated as the most effective music-based intervention for post-stroke motor training, it was taken into account to design an auditory environment for robotic training. An approach was chosen that extends the common RAS-design, based on the following assumptions: The complexity of hand and arm movements performed in the special case of robotic training lead to the conclusion that another metrical pattern is needed than in common RAS to facilitate movement training. Therefore an alternative metric grid is suggested. This grid contains a steady pulse and in addition an accent structure that might match to complex movements. Complex gross and fine motor movements usually consist of a multilayered accent structure. In this work, polymetric pattern music is introduced as experimental auditory environment intending to enhance robotic hand training. In polymetric music a stream of two or more meters is given simultaneously, including multiple accent structures at once, whereby none of these accent structures is dominant obviously (Large, Snyder 2009). Instead of an objective accent dominance, human perception constructs a comfortable accent structure. The rhythmic structure of the movement which is performed during exposure to polymetric music might shape the construction of the perceived accent structure. If so, a backwards oriented match-making is taking place. Another argument for the exploration of polymetric music is that it is a problem to suggest an optimal tempo for RAS applied to arm or hand training. As polymetric music likely induces the construction of an accent structure which is shaped by the movement accents, the question of tempo-matching is solved inherently by the listener (Large, Snyder 2009). So far it is unclear whether it is better to provide a tempo that encourages to speed up or to slow down. When a tempo is chosen which encourages to slow down or even causes relaxation, this might influence neurochemical effects which were shown in studies on relaxation music listening. In contrast, a fast tempo might cause stress to fulfill the task faster than it is possible. Stress can be a counterproductive factor, especially for patients suffering from spasticity. As it is not known whether motor learning post-stroke depends upon movement velocity, no conclusion can be drawn for a time modulating effector like RAS with a static tempo. Another open question is how "present" an accent or cue needs to be to induce an intended effect. More specifically, it is not known which level of consciousness is needed to affect movement qualities or motor learning. A metronome-pulse might be perceived very present and striking. But Rossignol and Jones 1976 already showed that the effect of rhythmic synchronization also takes place on low level or non-conscious response-levels (Rossignol, Jones 1976). In contrast to a metronome beep, the accent structure of polymetric music might rather be perceived as background music. What happens when sound or music is displayed in the background during motor training was never observed particularly for the context of robotic hand function training. When music is applied to arm or hand training as background stimulation, it is not known whether the impact of music, and precisely which parameters within this music influences the intended goal, namely to regain functions, best. Whether so far studies on RAS-training indicate that a simple rhythmic cue with a metronome improves spatiotemporal precision throughout reaching training, no conclusion can be drawn for metronome as more valuable experiment material than polymetric music for robotic hand training (Altenmüller, Schlaug 2015). In robotic training a stimulus has to fulfil an additional design aspect: The acceptance of a patient over a longer training period. Beside of that, the sound-stimulus interacts with the visual display of the training game. Because of this, polymetric music including a steady pulse and a flexible accent structure can be considered as equally valued as a starting point for experiments as a metronome. The metronome might be perceived as disturbing after some training sessions and by that it might cause incompliance of the patient or dissociate from the visual display.

The hypothesis in this thesis is that a match-making between a movement accent and an accent out of polymetric music substitutes motor learning by supplying kinesthetic information with a highly flexible accent structure and a fixed pulse. Polymetric music might assist motor learning post-stroke. Later in this thesis, an empirical evaluation on sound applied to robotic hand function training for stroke patients will be presented which refers to this summary. The goal of this evaluation is to gain knowledge on effects of polymetric music on motor learning post-stroke. When this sound design shows beneficial effects than the RAS-framework could be extended by an alternative meter structure beside of metronome and 2/2 music.

2.3 Robotic hand rehabilitation

2.3.1 Robotic tools for hand rehabilitation

2.3.2 Effectiveness of robotic hand function training

2.3.3 Open questions in robotic hand rehabilitation

2.3.1 Robotic tools for hand rehabilitation

First of all, a working definition of the term “rehabilitation robot” will be given: A rehabilitation robot is an electro-mechanical machine intended to provide technical assistance within a therapeutic environment. Usually these systems consist of a mechanical hardware part and a software environment. Robotic movements are controlled by the software or the human user. Most often the software includes a virtual reality scenario with training games, assessment software and algorithms that enable real-time assistance. Within such a virtual environment the mechanical device serves as controller that translates physical action into the virtual world. Robotic training can be carried out active, passive or assistive. Rehabilitation robots can be subdivided into end-effector systems, semi-exoskeleton and exoskeleton systems. End-effector systems are machines that have one contact only between machine and a user`s most distal part. Semi-exoskeleton and exoskeleton systems are mechanical skeletons that surround the whole body structure instead of one point only. The structure of an exoskeleton can be described as a mechanical negative shape of the body part. The design is based on the anatomical structure of the human body and includes all main ankle joints needed to actuate the surrounded body part (Maciejasz et al. 2014). The more ankle joints a system contains, the higher the variety of degrees of freedom is. The mechanical system can provide assistance ranging from actuation of movements (full, adaptive or assistive), to gravity support, to feedback. Feedback can be displayed in different styles ranging from error-feedback, to reward feedback, to real-time feedback which can be displayed visually, tactile, auditory, or multimodal. Generally those robotic rehabilitation systems are motor driven, pneumatic-, spring- or cable-based. Commonly a variety of sensors are applied to the robot that can assess the course of rehabilitation continuously. By that the patient can be informed about advances, and therapists can get new information to refine a therapeutic focus. Furthermore researchers can gain data that enables to evaluate the effectiveness of a specific treatment with a high resolution. These machines are considered as promising tools to extend conventional treatment, to enhance and refine treatment foci, to answer an increasing treatment supply, and to generally increase rehabilitation outcomes especially for patients suffering from severe or chronic movement related syndromes. Chronic and severely affected patients commonly need prolonged training that contains high-repetition and intensity. A robotic environment meets these needs at its best (Masiero et al. 2014; Riener et al. 2005; Riener 2007).

Since the late eighties, there is an increasing research interest of medicine, technology and economy on the effectiveness of rehabilitation robots (Rosati et al. 2011; Blank et al. 2014a; Mehrholz et al. 2008). This phenomenon goes along with a rising number of new devices, lots of them developed with a special focus on stroke recovery, a variety of research projects in this field, and the integration of rehabilitation robots in clinical institutions (Poli et al. 2013; Masiero et al. 2014; Kwakkel et al. 2008; Prange et al. 2006). These systems answer a need for effective treatment demanded by an increasing number of chronically ill patients within an ageing society including stroke victims (Heuschmann et al. 2010). As mentioned in chapter 2.1.1, age is main risk factor for stroke. In addition to that, in western-industrial countries 2-5% of all health costs are related to stroke (Heuschmann et al. 2010). Therapeutic techniques need optimization in manners of treatment-quality and its effectiveness. At the same time, it is highly important to collect new data on the course of recovery to generate predictive data. This data can be used to provide information for health care stake holders about sustainable techniques for prevention and treatment. Conventional therapy is cost- and labor intensive. Whether at this point robotic systems are still expensive, it is to expect that depending upon therapeutic qualities provided by robots and prolonged usage of these tools, prices will decrease. Such a price decrease might be furthermore related to an effective integration of robotic therapy extending conventional clinical settings (Blank et al. 2014; Maciejasz et al. 2014). As robotic tools provide an intelligent adaptive therapeutic environment which can be used in self-guided or group-settings, robot therapy might potentially change clinical schedules by increasing therapy intensity while lowering manual therapy hours: Patients could train on their own in therapy free time slots like in the weekends. Beside of that, different robotic tools could be placed in the same room. Like that, patients could play and train in multiplayer-settings or in circuit training with different devices in a group setting. Also in group settings a robot could ensure high quality training while social interaction is promoted. Social interaction was shown to increase motivation which is a very important factor influencing rehabilitation outcomes (Novak et al. 2014; Hesse et al. 2014). Moreover, severely affected patients not being able to move at all, could use robots to mobilize their bodies with repetitive passive movement practice. This patient population could train with high intensity and high repetition which cannot be provided by manual therapy. In the context of stroke recovery, so far robots were developed especially for gait training, for the upper extremity, for the wrist and the hands. In the case of post-stroke arm recovery, robot-assisted rehabilitation is considered as especially relevant for patients suffering from severe and chronic symptoms (Kwakkel et al. 2008; Prange et al. 2006). For these patients it is important to train high-frequent, intensive and repetitive. Robotic training can answer these demands: Robotic systems offer to train with a high intensity, highly repetitive, in different modes ranging from passive, to assistive, to active training with games encouraging patients to train longer than in other tasks (Balasubramanian et al. 2010; Kwakkel et al. 2008; Prange et al. 2006). Aspects like motor learning theories, well-studied therapy effects like high intensity, a high amount of movement repetition or error-feedback can be implemented into robot therapy concepts easily (Loureiro et al. 2011). Beside of this, motivational aspects can be integrated into these systems with games or by using the robots in circuit training scenarios with other technologies or in multiplayer settings (Novak et al. 2014; Dean 2012). Most often these systems allow to measure task performance with an objective and high resolution over longer time courses of treatment. This can be utilized to refine training strategies continuously, to inform the patient about advances and to serve as highly valuable data base for clinical examinations of pathological patterns reshaped by training.

Historical, the very early tools for arm rehabilitation were developed for shoulder and elbow training with end-effector devices that mainly guided movements in the horizontal plane. Later on, the wrist and the hand were taken into account as well: More specified devices were developed that were first end-effector systems and later on exoskeleton systems providing more flexibility (Blank et al. 2014). This thesis addresses hand rehabilitation and therefore will focus on hand rehabilitation robots only: Following Balasubramanian et al. 2010 who performed a comprehensive review on robotic hand function training, just a quarter of total 30 different robotic devices for hand training were so far evaluated clinically (Balasubramanian et al. 2010). Reasons for that could be the complexity of robotic hand systems, high costs, low level- quality of therapeutic implementation and the low-level of quality in studies (Lum et al. 2002). However, a small number of tools for the hand post-stroke were investigated. Here some of the most relevant robotic tools for hand rehabilitation that were evaluated clinically are presented:

The very first tool in this field was "Rutgers Hand Master II" (see Fig. 5). This device is a glove with a control unit which is placed at the palm of the hand. The fingers are actuated via pneumatic control cables that are attached to the finger tips with small rings. The device provides haptic feedback which is linked to a virtual-reality environment. This tool was evaluated in two different studies that both followed the same training protocol, once with four chronic hand paresis subjects, and once with three patients. Patients trained for 30 hours within a time span of three weeks with "Rutgers Hand Master" and gained positive effects in an increase of the active range of motion, movement speed and movement smoothness and in the Jebsen Taylor Test (Lum et al. 2012). Both of these small sized explorative studies lacked a control-group.

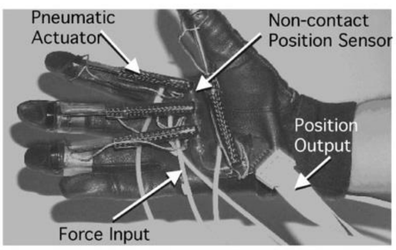


Fig. 5: "Rutger`s Hand Master II"

Another device is the "Hand CARE" which was developed by Dovat et al. 2008. This tool uses motor driven cables to actuate each digit separately (see Fig. 6). Training can be performed with the whole hand and with isolated finger movements. The device assists hand flexion and extension. The tool is adjustable to different hand sizes and hand shapes (Dovat et al. 2008). So far clinical evaluations just included two stroke patients that trained for 16 sessions each 20 minutes long. In this study hand flexion and extension was trained while "Hand CARE" facilitated movements by suppressing pathological muscle synergies. The small study indicated that finger coordination and isolated finger movements might be enhanced by such a training.

Fig. 6: "Hand CARE"

Two other devices were developed by Luo and colleagues: a body-powered orthosis based on prosthetic technology and a pneumatically powered glove (Lum et al. 2012). A clinical study with 15 stroke subjects was carried out in which subjects were training either with the body-powered orthosis, with the pneumatic glove or without any assistance. In this study, participants received 18 training sessions. In some assessments significant improvements were found for tool-based training compared to no assistance at all, but the active range of motion and movement velocity did not improve in the tool-based training group. The authors concluded that non-assisted versus robot assisted training would not lead to significant over-all differences. A refined version of the above mentioned pneumatic glove is the "PneuGlove" (see Fig. 7) which allows to control single fingers. In a clinical study effects of 18 sessions (1 hour) robotic therapy were evaluated with 14 stroke subjects suffering from chronic syndromes. Two groups were compared, whereby one group received training with "Pneu-Glove"-assistance and the other group trained without any assistance. Results showed that no significant differences occurred between training with glove-assistance and the non-assisted training (Connelly et al. 2010; Lum et al. 2012).

Fig. 7: "Pneu- Glove"

The glove-system "Cybergrasp" (see Fig. 8) is a system which is used in combination with a virtual reality environment. On each finger a cable is attached along the distal phalanx linking the back of the hand to the fingers. Each cable is controlled by a separate motor. By that, the tool allows to assist single finger extension. In a clinical evaluation involving eight stroke subjects, training effects of three training sessions (1 hour) with the "Cybergrasp" was evaluated. This training resulted in improved kinematics and some clinical scales for the upper limb (Lum et al. 2012). Again no control-group was assessed.

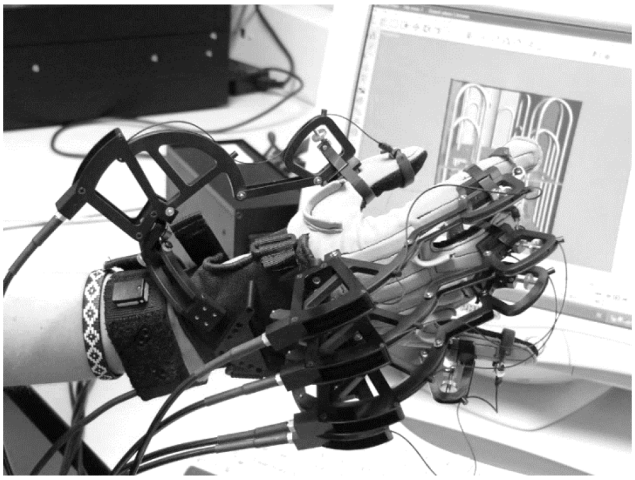


Figure 8: "Cybergrasp"

The "Haptic Knob" is a device which is based on an actuated parallelogram structure (see Fig. 9). It is designed similar to an exoskeleton that surrounds a dynamic interaction object. On one end of the device two flexible surfaces are attached that allow to interact manually with squeezing- or extension- movements (Lum et al. 2012).

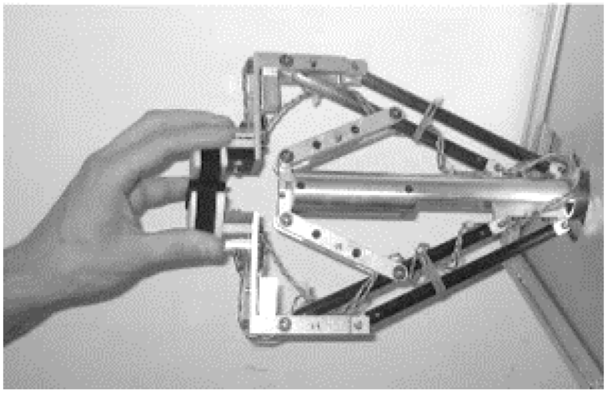


Fig. 9: "Haptic Knob"

The "In Motion Hand Robot" is a motor-driven device that utilizes a cylinder, surrounded by double cranks and a slider mechanism (see Fig. 10). The hand grasps a cylinder structure which can be actuated from inside and from outside. By that it can assist hand flexion and extension. A clinical study was performed with 127 stroke subjects training with the "In Motion Hand Robot" as one out of four robots which were compared to dose-matched conventional treatment. The results showed that robotic training gained comparable results to conventional therapy. Robotic therapy showed superior results in functional outcome measures 36 weeks follow- up (Lum et al. 2012).

Fig. 10: In Motion Hand Robot

The "Reha-Digit" is a device with a camshaft that rotates in the palm of the hand (see Fig. 11). It assists finger flexion and extension. Beside of mechanical rollers keeping the fingers in a stable position, abnormal hand postures are prevented. A pilot study was performed with eight stroke subjects that received either passive robotic training or bimanual training for 20 minutes on a daily base over a time course of four weeks. Results showed that the group that had received robotic therapy gained higher scores in the Fugl-Meyer Test and had a more reduced pathological muscle tone than the bimanual training group (Lum et al. 2012).

Fig. 11: “Reha-Digit”

The “Hand Wrist Assistive Rehabilitation Device” is an exoskeleton with three degrees of freedom (see Fig. 12). Assistance can be applied for single finger rotation, thumb abduction and adduction and wrist extension and flexion via forces applied to the metacarpophangal joints. A clinical trial was carried out with 13 stroke subjects suffering from chronic hand paresis. Two groups were compared whereby one group trained with the “Hand Wrist Assistive Rehabilitation device” with assistance and the other group without assistance. Results reveal that in both groups behavioral outcomes were improved. Furthermore, an increase in cortical activations related to the practiced task were found (Lum et al. 2012).

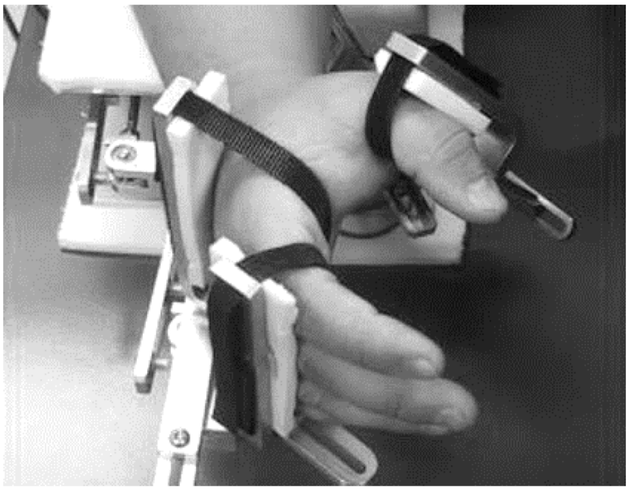


Fig. 12: “Hand Wrist Assistive Rehabilitation Device”

The “Hand Mentor” is a commercial exoskeleton system that assists finger and wrist extension and flexion (see Fig. 13). A clinical study was carried out in which 17 stroke subjects underwent 60 hours repetitive task training or 30 hours repetitive task training and 30 hours robot-assisted therapy. Both groups gained significant improvements in the Stroke Impact Scale (Lum et al. 2012).

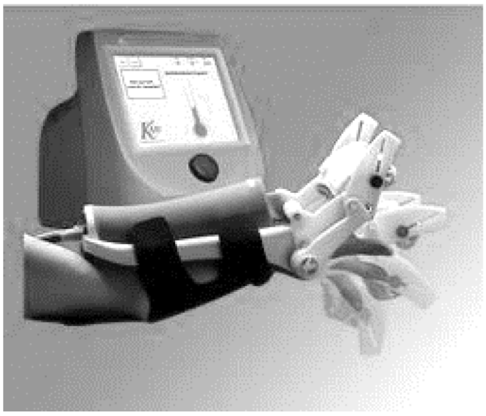


Fig. 13: “Hand Mentor”

Maxiejasz et al. 2014 performed a review on rehabilitation robots for the upper limb to generate an overview on current devices as a reference. This overview intends to inform about fields of application, target population, type of assistance, different types of mechanical design, control strategies and clinical evaluations of the tools. These author report about a higher number of devices than Lum et al. 2012 as they also review systems that are still under development like the independent linear movement system with five degrees of freedom for each finger or the portable orthosis-like commercial system “Hand of Hope” with five degrees of freedom (Susanto et al. 2015) (see Fig. 14).

Fig. 14: “Hand of Hope”

Because the robotic system “Amadeo” served as training environment within the later on presented clinical study, this tool is described here in detail: The commercial robotic hand function trainer “Amadeo” (Tyromotion GmbH) consists of a robotic hardware part which is connected to a computer. The computer screen is positioned on an adjustable platform displaying the virtual scenario including an assessment and gaming environment. The hardware part consists of a rack including a part with six sleighs. The affected arm is positioned on a track which predefines a stable arm position (see Fig. 15). The fingertips are connected to the sleighs via magnetic contacts taped around the finger tips. The sleighs actuate linear movements in flexion and extension and are equipped with sensors that can measure single finger forces and the range of motion of single fingers. Within the software an assessment module allows to adjust the sleighs to the individual finger size (calibration) and to measure single finger forces in two directions (flexion and extension). Training can be performed in three modes – passive, assistive, and active. In passive training the robot moves the fingers in a predefined range of motion into extension and flexion. The tempo of this movement is adjustable as well as the time span between single finger segmentation. In assistive training the patient controls movements in either flexion or extension. When a patient cannot perform 100% of the demanded task the robot continues the movement and takes over till 100% are reached. In active training the patient controls gaming actions within the virtual environment without any robotic assistance. The games are designed to train extension and flexion in either an isometric training mode or a range-of-motion mode. In the isometric training mode the sleighs are fixed and force application in both directions (flexion and extension) control actions in the gaming environment. In the range-of-motion-mode the sleighs are flexible. By moving the sleighs into either extension or flexion gaming actions can be controlled.

Stein et al. 2011 carried out a study with 12 patients suffering from a chronic to moderate hand paresis that received robotic hand function training 19 times within a treatment cycle of 6 weeks in the early phase post-stroke. Results of this open-label-study indicate that robotic hand therapy is feasible and safe. Beside of this improvements in multiple tests like the Upper Extremity Fugl-Meyer, the Motor Activity Log, the Manual Ability Measure-36, and the Jebsen Hand Function Test were documented (Stein et al. 2011).

Furthermore, Sale et al. 2011 performed a preliminary observer study to evaluate whether robotic hand therapy with "Amadeo" performed with high intensity would increase recovery results especially in the early phase following a stroke (Sale et al. 2012). In this study seven patients suffering from a moderate to severe hand paresis received 20 therapeutic interventions within a treatment cycle of four weeks. The authors reported significant improvements seen in the Ashworth Scale (that measures post-stroke spasticity), in the Fugl Meyer Test, and in the Motoricity Index (both tests asses upper limb function). This means that intensive robot-assisted treatment applied in the early phase after an insult might lead to a significant decrease of motor impairment in the hand.

In summary both studies, the study performed by Sale et al. 2012 and the study carried out by Stein et al. 2011 showed that robotic training with "Amadeo", applied in the early phase post-stroke with high intensity is beneficial. This is reflected in outcome measures like the Ashworth Scale, the Fugl Meyer Test, the Motoricity Index as also in the the Motor Activity Log, the Manual Ability Measure-36, and the Jebsen Hand Function Test. Both of the studies lacked a control-group. Following it remains unclear whether these effects could have been gained with conventional treatment as well, which is likely due to the time window in the early phase. Especially in this time window strong effects can be achieve. Because of that, future studies should focus on study designs involving control-groups.

Fig. 15: “Amadeo”

In this section, rehabilitation robots for the hand post-stroke were described that were evaluated clinically to provide a background that describes the current state-of-the-art in this field.

2.3.2 Effectiveness of robotic hand function training

Currently a huge number of devices for robotic hand rehabilitation are developed, investigated or are already included in clinical daily practices. So far, clinical studies evaluating the effectiveness of robotic arm training post-stroke indicate benefits for robotic training provided as add-on to conventional treatment. Here three systematic reviews, one by Prange et al. 2006, one by Kwakkel et al. 2008, and one by Mehrholz et al. 2012, and a meta-analysis by Mehrholz et al. 2008 are summarized that all share the objective to determine the effectiveness of robotic training for the upper extremity post-stroke. These reviews outlined that so far activities of daily living (ADL) were one highly relevant parameter that was not improved by robotic training yet (Lum et al. 2002; Kwakkel et al. 2008; Prange et al. 2006; Mehrholz et al. 2008). For ADL, fine motor skills involving the hand are necessary. The result of a lack in improving ADL reflects that the reviews observing effects of robotic therapy included clinical trials that investigated effects of arm robots and not of hand robots (Mehrholz et al. 2013). As mentioned before, the lack of ADL improvements might furthermore be related to hand training focusing on the finger combination thumb and index finger which was hypothesized to be counterproductive for spastic cases (see 2.1.5). So far comparative studies on active control versus unassisted training or conventional therapy did not show significant differences that would lead to the conclusion that one technique is to be regarded as superior to others (Lum et al. 2012). Till now, no superiority of robotic training compared to conventional therapy was found, except from studies in which the "Reha Digit" and the "Hand Wrist Assistive Rehabilitation device" were used (Lum et al. 2012).

Furthermore, Prange et al. 2006 carried out a systematic review to assess the effects of robotic arm therapy post-stroke on function (Prange et al. 2006). Prange et al. 2006 reviewed eight studies which showed that robotic arm therapy gained short-term mean changes in the Fugl-Meyer Test. Moreover they report that short and long-term motor control of shoulder and elbow in patient groups ranging from subacute to chronic states were improved. Prange et al. 2006 concluded that these studies did not show consistent effects in manners of an increase of arm function, while robotic therapy compared to conventional therapy achieved better outcomes in motor control. The included studies did not involve hand robots.

Also Kwakkel et al. 2008 performed a review on the effectiveness of robotic arm therapy (Kwakkel et al. 2008). These authors found similar results: Improvements of ADL were not found whether arm function and strength were shown to improve. This might be due to the orientation of robotic training on shoulder and elbow instead of hand training. As mentioned already before, hand function is needed to perform tasks that are related to ADL measures.

Another Cochrane review by Mehrholz et al. 2008 included 19 trials on electro-mechanical and robot-assisted arm training post-stroke. The results of this review showed that electromechanical and robot-assisted arm training post-stroke might improve ADL and arm function. Mehrholz et al. 2008 report that the muscle strength of the arm would not benefit from such a training (Mehrholz et al. 2012). These authors conclude that the results should be considered with caution due to a high variability in design and quality of the trials, type of treatment and patient characteristic. No study was included that focused on robotic hand training.

Mehrholz et al. 2012 performed an additional systematic review on the effectiveness of electromechanical and robot-assisted arm training devices with a special focus on ADL. In this review 11 trials with 666 patients total were included leading to the following results: The reviewed studies showed that robotic arm training is safe and does not lead to side effects. Furthermore, arm function and motor function can be increased with robotic or electro-mechanically guided therapeutic interventions while muscle strength of the arm was not shown to be improved. Beside of this, a lack of improvement was found for ADL measures.

Rosati et al. 2012 carried out a study that observed whether auditory feedback applied to robotic training could improve engagement, performance and learning. These authors suggest that sound feedback might be beneficial to facilitate the relearning process applied to grasp training post-stroke. Beside of this, Rosati et al. 2012 outline that sound feedback applied to the context of robotic neuro rehabiltiation might increase motivation (Rosati et al. 2011).

Studies observing effects of robotic training performed in a group setting showed that social interaction increases motivation and function outcome significantly (Hesse et al. 2014). Novak et al. 2014 observed whether different gaming strategies like competition and cooperation influences motivation and training performance. This study indicated that social interaction influences performance and motivation strongly (Novak et al. 2014). Because of that, social interaction should be considered as a key aspect for future devices.

Regarding studies observing the effectiveness of robotic hand training systems, two studies carried out by Sale et al. 2012 and by Stein et al. 2011 were already described in detail in chapter 2.3.1.

2.3.3 Open questions in robotic hand rehabilitation

Before a high level of evidence on the effectiveness of robotic hand rehabilitation training can be reached, still many open questions need to be answered: The so far biggest unsolved problem in robotic hand function training is that robotic training does not enhance ADL. Systematic reviews and meta-analysis on the effectiveness of robotic arm training post-stroke reported about a lack of ADL function as a central problem as well (Mehrholz et al. 2013; Kwakkel et al. 2008; Prange et al. 2006; Tatla et al. 2015). Whether some virtual reality environments were developed for robotic arm training providing ADL task training, there is still a need to increase results in ADL in the future (Guidali et al. 2011). ADL mainly demand fine motor skills which are performed with the hand. Reasons for this lack of ADL advances might be grounded in a lower number of studies with hand robots than arm robots. The reason why more arm robots than hand robots were so far evaluated clinically might be that hand robots are technically more complex than arm robots (Lum et al. 2002): Hand robots need 21 degrees of freedom compared to the whole arm that just needs 7 degrees of freedom. Another open question is, which joints of the hand should be the ones that are controlled by the robot or which movement patterns should be the ones that are trained specifically. Furthermore, it is still unclear whether training should focus just on the hand or combine hand training with the whole arm. Moreover, up to this point, no transfer training from robot to manual training was ever developed or evaluated. Potentially this might be a useful bridge to gain good outcomes with robot-therapy. Such an approach would also include the idea of Krakauer 2005. He suggests that training potentials improving ADL might lie in technical approaches that provide more naturalistic movement assistance (Krakauer 2005).

As it is furthermore not clear which conventional therapeutic technique is best for a specific patient population (grades of severity or time-span between insult and treatment), it is a big challenge to decide which therapeutic approach is the one which is most beneficial implemented into robotic training. This relies on lacking evidence on superiority of one conventional therapeutic technique among others. In the case of high-repetition training for the upper extremity contradictory effects were shown without robots, while with robots good outcomes were achieved (French et al. 2007; Sale et al. 2014). This is one example in which robotic therapy approaches adopt a therapeutic technique and amplify a positive effect. Other therapeutic techniques and evidence based concepts on motor rehabilitation should be implemented into robotic training by taking into account differences between self-guided and assisted movement training to refine and extend benefits of the machine. Commonly, high repetition training, goal-directed task training like pointing-tasks, performance feedback and passive training are implemented into robotic therapies, often translated into virtual gaming environments. This might be problematic as for example in the case of high-repetition training, it was already shown that high-repetition training is not gaining significant outcomes for the upper extremity (French et al. 2007).

Another important issue is, that so far study results lack information on a recommendable training intensity and frequency for a specific patient population (grade of severity, time-span between insult and treatment). Furthermore, it is not clear which grade of robot-assistance is most effective for these specific subgroups. It is not known whether robotic training is more effective when it is carried out in a bimanual or in a unimodal set-up. There might lie some interesting aspects in designs that would include the healthy hand to guide movements of the affected hand to promote bi-hemispheric interactions (van Delden et al. 2012).

Moreover, it is still unclear which kind of control strategy is most beneficial and whether new strategies are better than commonly used trigger-assist concepts in which a small movement triggers the robot to complete the movement. Therefore, systematic evaluations need to be carried out, that include new strategies such as intention detection via eye tracking, electromyographic or electroenzephalgraphic interfaces, or other new brain-computer-interfaces. These control strategies need to be studied into depth to enable detection of meaningful signals which can be translated into robotic movements (Novak et al. 2014; Elnady et al. 2015; Tong et al. 2010; Blank et al. 2014). Regarding the assessment possibilities of rehabilitation robots, high-resolution data on the recovery time-course could foster future technologies towards more intelligent treatment advices (Nordin et al. 2014).

So far it is unclear how to advance the technical design of hand rehabilitation robots in manners of material and costs. It might be relevant to use softer materials than commonly used static hardware systems. Soft robotics would offer a better wearing comfort and more flexibility (Laschi, Cianchetti 2014). Such a design would need to fulfil demands like easy adjustment, transportation, integration and adaptation to different environments, ideally even usability within day life. These soft material-based tools could allow to train the hand more continuously and to assist in day life at the same time. As it might get more important to lower costs for such devices, new production technologies like 3D printing could be explored taking into account new, cheaper and more flexible materials.

Because robotic therapy will be more and more integrated in clinical daily practice there will grow a need to rethink the education of therapists. It might get more relevant to study how manual therapy could contribute and interact with robotic therapies. Tatla et al. 2015 performed a study to identify critical factors influencing usage and effectiveness of new technologies in clinical practice in which they took account for the therapist`s perspective on the adoption of their patients (Tatla et al. 2015). The results of their study indicated that the adoption and usage of new technologies in clinical day life is complex due to patient- and therapist factors like the technical application of these tools, limited capacities, personality related aspects, the lack of transfer training, and a lack of access options to newest technologies. In contrast, they also found that new technologies contain beneficial factors that might increase social interaction within therapeutic environments. Anyhow, this study outlines that both sides, the therapist and the patient need to adopt to the new technology and therefore, special training for therapists with new technologies might enhance such a therapy.

It was already shown that motivation is a critical component influencing therapy outcome. Novak et al. 2014 showed that social interaction increases motivation in robotic training. Because of that, more devices need to be combinable to provide multiplayer training environments. If those technologies would provide an easy-to-use-design self-guided training could be performed.

It is furthermore unclear which kind of feedback extends robotic training effectively. Therefore, different types of feedback ranging from audio, visual, vibro-tactile feedback or combinations of them need to be evaluated systematically. It is still an open question, whether feedback should amplify errors, provide rewarding feedback, whether it should be displayed continuously or just shortly. Furthermore it is not known when, why and for which patient population feedback is most useful (Oscari et al. 2012).

Another important question is, how the interplay of robotic movements interacts with the virtual reality environment. It is very important to gain a better understanding on effects of single and combined parameters within such a complex system on motor learning or motivation. Therefore, studies need to be carried out that focus on effects of the visual, the tactile or the auditory modality separated as well as in a combined manner to understand how they interact.

2.4 Sound and music in robot-assisted rehabilitation technologies

2.4.1 Review of robot-assisted technologies using sound and music

2.4.2 Potentials and dangers of sound- and music applications in robot-assisted motor therapy

2.4.1 Review of robot-assisted technologies using sound and music

As it was already mentioned, usually robotic rehabilitation systems are combined with virtual reality scenarios including sound (Rosati et al. 2012; Colombo et al. 2005; Masiero et al. 2007). According to Rosati et al. 2012, so far potentials of auditory feedback applied to rehabilitation technologies are underestimated. In the following section current sound and music applications in the field of robotic rehabilitation systems are described, discussed and future possibilities are introduced.

First of all, it is important to outline that nearly all rehabilitation robots, especially most of the commercial hand robots such as the "Amadeo", the "Hand of Hope" or the "Hand Mentor" are used in combination with training games (Novak et al. 2014; Sale et al. 2012; Laver et al. 2015; www.rehab-robotics.com). Many of these robotic rehabilitation technologies that use gaming environments contain speech samples in order to provide guidance on how to perform a task and to display performance feedback (Rosati et al. 2012). In contrast, in commercial classic game environments speech is used very rarely. Commonly it is one of the main goals in commercial game environments to provide an intuitive self-explaining game design that does not need further verbal explanation. In the case of robotic rehabilitation training it might anyway be important to provide verbal explanations about rules of the game. This is important due to the age range of the patient population (going along with little gaming experience) as well as cognitive deficits caused by e.g. a stroke. Beside of speech samples, classic computer game sounds such as self-produced sounds that are related to a character`s movement or actions, reward sounds, ambiences, background atmospheres, environmental sounds and background music are used. Commonly, self-produced sounds are applied to illustrate the causality of an action within the virtual environment (Collins 2013). This could be an object collision of the controlled character with another object, contact or friction with a virtual surface or the execution of a gunshot. In robotic rehabilitation training games physical properties of virtual objects are simulated most often in a naturalistic manner to provide environmental realism (Guidali et al. 2011). Therefore naturalistic ambiences and background atmospheres are used that illustrate the characteristics of the visible environment. In contrast to classic computer games in which physical properties and background ambiences are often designed so that the player experiences a phantasy world which is not naturalistic, in most of the games in rehabilitation robotics a focus is put on real-world-relations. The reason for that might be that so far the research community considers the carry-over effect of a training to activities within the real world as very important. In robotic rehabilitation games, it is very common to provide reward sounds to motivate the patients during gaming. Reward sounds are most of the time abstract, simple and short sounds. They serve as symbolic markers in games and carry a positive emotional connotation. They occur to mark the start of a game, the end of a game, the successful collection of points or when score levels are presented. Furthermore, background music is displayed during the whole game. This background music varies in musical genre, tempo, complexity and instrumentation. It was already shown that different sound parameters, musical styles and different tempi can lead to changes in computer game performance what should be taken into account when sound is intended to achieve a therapeutic goal (Cassidy, Macdonald 2010).

Further possibilities for effective sound in robotic training systems could lie in analogue sonic features of the robot mechanics: When robotically-caused analogue sounds would be displayed in a filtered or amplified manner, they might represent a natural action-sound. Such a sound could enrich the real-time information about movement performance. Another option could be to explore auditory feedback for rehabilitation robotics more detailed. Auditory feedback could be provided as real-time feedback, error-feedback, corrective or adaptive feedback. It might be valuable to investigate different mapping strategies and sound materials that represent information on the position, velocity and errors of a movement. Since the eighties, a growing research body focusses on real-time sonification of movements. This research field could provide information on effects of sonification for rehabilitation technologies as well as it might be beneficial for this context (Dubus, Bresin 2013; Scholz et al. 2014; Schaffert, Mattes 2015). First Maulucci et al. 2001, than Effenberg et al. 2011, followed by Scholz et al. 2014, investigated different sound-to-movement mappings for arm rehabilitation training (Maulucci, Eckhouse 2001; Effenberg et al. 2011; Scholz et al. 2014). These studies indicate that sonified movement training might be effective for post-stroke motor rehabilitation training (Scholz et al. 2014). More research is needed to validate mapping strategies and to provide easy-technical set-ups for this purpose. Furthermore, it would be highly relevant to investigate the most obvious auditory environment - music-. Music is used in nearly all gaming environments and was shown to increase the perceived immersion during gaming. This immersion effect occurs because music illustrates specific gaming atmosphere or narrative characteristics of a game effectively (Collins 2009). Music can be perceived as rewarding, activating or relaxing, it can alter time perception and perception of effort (Fritz et al. 2013; Juslin 2013a). All this depends upon its placement within a game narrative, the general setting (how it is provided – as background or frontline activity), the tempo, the rhythm, the timbre, the melody, the orchestration, the complexity, the loudness, the familiarity or novelty (Salimpoor et al. 2014; Altenmüller, Schlaug 2015; Blood, Zatorre 2001). Personality related aspects like previous music listening experience, socio-cultural background, age, gender and taste could influence aesthetical judgement (Burger et al. 2013). Observations on effects of computer game music in the rehabilitation context should take into account that musical features might interact with the visual environment strongly. An example for that could be a war scene displayed with slow classical music. This scene might be perceived different with aggressive fast percussion-noise sounds. The high frequent noisy elements and percussion sound could induce stress, while slow classical music could arouse sentimental emotions and slow down movement performance. During robotic hand function training sound and music could influence the user`s attention, motivation, motor performance and in turn motor function. On the one hand, auditory displays could cause negative effects like distraction, fear, stimulus satiation or lead to superimposed patient-therapist interaction (Rosati et al. 2011). On the other hand, sonic displays could increase motivational states, improve movement qualities, lower the perceived size of effort and increase the perceived level of participation during training. It could cause flow-experiences, alter time perception and increase the level of enjoyment and concentration (Csikszentmihalyi et al. 2014). Following, the application of sound and music to robotic training might be a promising extension as it potentially promotes motor performance, function and motivation when it is designed adequately. To provide beneficial sound-and music-applications for robotic hand training, it is highly important to gain more knowledge about which kind of music causes what, whether musical parameter induce intended effects beneficial for motor training and whether auditory feedback is effective or not.

2.4.2 Potentials and dangers of sound- and music applications in robot-assisted motor therapy

As described in the previous chapters, music and sound can cause a variety of effects in domains ranging from emotion, to motor, to bio-physiological or social reactions. On the one hand, these reactions could extend and improve robotic hand function training. On the other hand, sonic applications have the potential to destroy therapeutic effects or to not show any effects at all. To prevent negative effects and to amplify positive effects sound and music need to be examined and in turn need to be applied carefully in regards of outcomes of these examinations. Here potentials and dangers of sound- or music applications to robotic training are discussed:

Before any sound is displayed in robotic training, the therapist needs to ensure that the patient does not suffer from any hearing loss or amusic deficits (Rosslau et al. 2015). Personality traits need to be screened to exclude patients with predictable incompliance. For example, some patients might dislike music, might get annoyed by sound easily, autobiographically negative connoted music could induce negative memories. Moreover some patients might react negative towards specific genres out of socio-cultural reasons or subjective taste. In such a case, sound or music should either not be used at all or the information should at least be taken into account in sound- and music- selection. Furthermore it was shown that music can cause different effects depending upon previous musical experiences. Rosslau et al. 2015 showed that stroke patients that had musical training before their insult performed better in receptive and expressive musical tests than patients without any previous training. These authors also investigated whether the location of the lesion would affect the level of skill in receptive and expressive musical tests. Results showed that a right-sided lesion led to weaker performance in fine melodic and rhythmic analysis. Because of that, Rosslau et al. 2015 recommend to screen stroke patients with such a test and to take into account information on the lesion location. This would allow to determine the level of musical ability in reproducing a previously displayed melody (Rosslau et al. 2015). This in turn could lead to an exclusion of sonic displays for patients identified with low levels of musical ability. Moreover, the therapist should keep track of the patient`s cognitive load throughout training to prevent from overload. Cognitive overload could be caused by continuous sound-exposure within demanding rehabilitation training and a complex setting. Stress might be counterproductive throughout such a training session. Furthermore, the auditory environment should be designed so that verbal interaction can take place without any effort. When the auditory design is displayed too loud, when sounds are too high-frequent or too complex verbal interaction might be superimposed between patient and therapist. Therefore the sound design should be provided with an adequate volume and frequency setting, and with a musical structure that is not cognitive too demanding or too complex. Another important point is that music is highly cultural (Cross 2003; Patel 2014). If sound or music used in robotic training is culturally familiar this might cause strong emotional reactions (Sammler et al. 2007; Pereira et al. 2011). Both, familiarity and unfamiliarity of music or sound can influence the focus during training. On the one hand, a foreign stimulus might cause a high level of interest and by that dissociate. On the other hand, it might be counterproductive to use music or sound which is familiar because familiar music can induce memories and by that also dissociate from the current task. At the same time familiar background music could increase mood levels, it could influence motivation positively and it could activate a widespread neural network which might improve neural plastic processes in a beneficial manner (Sammler et al. 2007). As both directions, familiar and unfamiliar sounds have potential to cause very strong effects, it is first of all important to investigate "neutral" sounds and music. "Neutral" sound and music could be designed by utilizing simple musical universals given in all cultures (Cross 2003; Patel 2014). Important universals would be a clear rhythmic pattern, two to three intervals with easy bell tones and a tempo of 120 beats per minute which is a tempo known as convenient tempo (MacDougall, Moore 2005). When it is intended to induce a specific effect by sound or music, different parameters as well as music as a complex material need to be considered carefully. To speed up or slow down a movement or to take influence on force production, it should be taken into account that the musical tempo or the volume could take influence. In order to affect a movement quality specifically, research on real-time sonification including systematic evaluations on mapping strategies could be considered (Dubus, Bresin 2013). Moreover it was shown that strongly rhythmical music induces rhythmic alignment of movements to a beat. Such a movement-to-beat synchronization might happen on different levels of a movement sequence. Independ of the complexity of a movement, any movement can be subdivided into smaller sub-sequences. When a beat or a rhythm is applied to the context of robotic hand function training post-stroke its potential influence on subsequences of hand movement should be taken into account.

AIMS AND OVERVIEW

3. METHODS

3.1 Research Design

3.1.1 Design approach for the development of sound and music applications for robot-assisted training

3.1.2 Design approach for the study set-up

3.1.3 Interrelation of studies 1-7

3.1 Research Design

In the previous chapters a theoretical background on the pathology and an overview on state-of-the-art treatment approaches for the paretic hand syndrome post-stroke was described. A special focus was put on technically-assisted rehabilitation and the role of sound and music in post-stroke motor rehabilitation and in robotic hand function training. In this chapter, the synthesis of an empirical research design is presented which aims to generate data that reflects the effects of specified sound applied to robotic hand function training post-stroke on function and motivation. Therefore, the previous chapters 1 and 2 serve as a theoretic reference.

3.1.1 Design approach for the development of sound and music applications for robot-assisted training

In order to design sound that extends robot-assisted hand function training effectively, several steps of theoretical assumptions, empirical tests and practical explorations were performed: In a first step, literature on sound and music interventions in post-stroke motor rehabilitation was reviewed. The aim of this review was to determine promising sound features for robotic hand training. Following, a set of sound features was concluded which was determined as promising to effectively extend robotic hand function training. The set contained rhythmic auditory stimuli known from the music therapeutic technique "RAS", auditory feedback and music. These parameters were identified as potentially strong effectors of function, motivation and attention in rehabilitation settings. Than an experiment series with four experiments (E1-4) was carried out with healthy subjects (E1-3) and stroke patients (E4) which will be described in chapter 3.2 in detail. Sound design prototypes showing strong effects on function or motivation were than discussed and modified as optimized sound material for robotic training. In the experiment series with healthy subjects and stroke patients, open questions regarding effects of rhythmic stimulation were tackled with a focus on different meters, materials and multisensorial display (metronome, speech-samples embedded in a rhythmic structure, waltz-music and a multisensorial beat). In a third step, the most promising designs determined in the experiments E1-4, metronome and waltz-music, and one additional concluded explorative design, polymetric music, were applied in a practical test phase to robotic training. As the experiment series with healthy subjects and stroke patients did not display conditions of a natural training setting with a robot including aspects such as a multimedia scenario and conditions demanding acceptance of a sound stimulus over a longer period, a practical test phase was carried out. The main goal of this practical test phase was to optimize the clinical study design material. In this phase spontaneous remarks, critics, feedback, observations and thoughts were collected and discussed. The main arguments behind the application of polymetric music as an additional auditory environment for the test phase was drawn from differences within the accent structure and movement rhythm of unilateral hand movements from cyclic gait patterns and from the experiments in which waltz-music as an alternative meter concept was explored. In the experiments in which waltz-music was observed it became obvious that it was not a cueing mechanism influencing qualities of fine motor performance. None of the test subjects synchronized movements to the beat. This was in line with previous considerations that the rhythmic pattern which is needed to support unilateral guided hand movements is different than 2/2, 2/3, or 2/4 meters. It was concluded that such a complex movement might need another metric structure suiting at any point of time. Therefore, polymetric music was suggested. After the practical test phase with the robot, all results and observations were summarized and reviewed. Polymetric music and game-related auditory feedback were concluded as auditory test environment for the clinical study design. Finally, a clinical study design was developed to detect whether specified sound for robotic hand function training would lead to changes in function and motivation in stroke-patients suffering from a hand paresis. Therefore, a two-armed not-blinded clinical study with 34 patients was carried out. In order to extend the perspective on training conditions additionally to this study, a series of single-case studies were performed. These three single-case studies observed an additional sound condition, self-selected favorite music, the influence of sound over a longer treatment period (consisting of three training phases each with nine sessions spread over three weeks) and the interaction of finger forces in rest and active extension forces. Moreover, single finger force profiles were examined to see whether training with the finger combination thumb and little finger was effective.

<u>3.1.2 Interrelation of Experiment series 1-4, practical test-phase with robot and clinical studies</u>

Empirical research design

The empirical research design was structured so that each result gained in E1-4 would provide information for the following experiment, the practical test-phase with the robot, the clinical study and the single-case studies. This step-by-step approach is displayed in the Flow-chart below (Fig. 16): The experiment series E1-3 aimed to observe effects of different rhythmic stimulation designs compared to no stimulation at all, on motor performance and mood throughout performance of a fine motor task on healthy subjects. The strongest effectors of this experiment series were chosen and evaluated in experiment E4 with stroke patients performing a fine motor task as well. The strongest designs were again discussed and, in a next step, tested applied to the robotic training system. Under that condition, new problems occurred that were taken into account to optimize the sound design for the clinical study. All in all, a sound design was concluded for the two-armed clinical study design (polymetric music and game-related sound feedback). The clinical study aimed to generate knowledge on two primary outcome parameters, one in the domain of function, and one in the domain motivation. In addition, secondary outcome measures on function and motivation and two different subgroup analysis differing patient profiles into three grades of severity and three time-span distances between insult and study participation were performed. To extend the perspective on gained results in the clinical study, single-case studies were carried out.

Conclusions from the experiment series E1-4, the 2-armed clinical study and the single-case studies can be drawn mainly on three levels: 1) The role of sound in robotic hand function training needs to be reconsidered by taking into account that specified sound shows ambivalent effects dependent on the grade of severity of a hand paresis. 2) The sound design is critical in achieving effectiveness for robot-assisted training and should therefore be applied carefully by relating function, motivation and social aspects which are shown to be influenced by sound. 3) This indicates that further research is needed to increase levels of effectiveness in sound-extended robotic training.

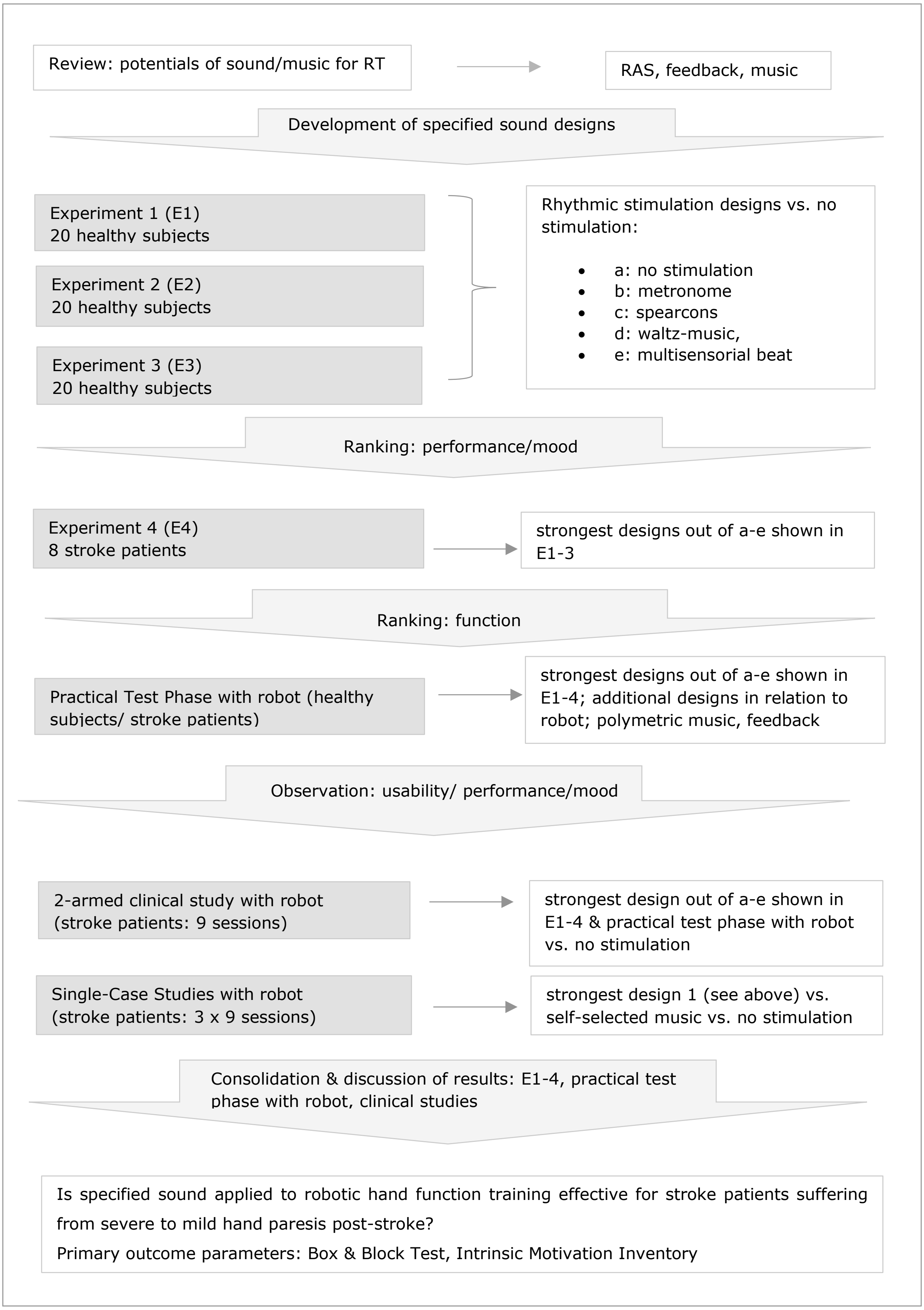


Fig. 16: Overview of overall research design and interrelation of Experiment 1-4, usability tests and clinical study.

EXPERIMENTS

3.2 Effects of sound on healthy subjects during performance of the Nine Hole Peg Test

3.2.1 Methods

3.2.3 Results

3.2.4 Discussion

3.2.5 Conclusions

3.2.1 Methods

Three pilot-experiments (E1-3) were carried out with healthy subjects. The goal was to investigate effects of four different rhythmic stimulation designs compared to a condition without sound on motor performance and mood during the performance of a fine-motor task. 20 subjects took part in the experiment series E1-3 (female = 11; male = 9; mean age = 27.15). Out of them, 19 had previous experiences in playing a musical instrument. All participants were right handed.

Technical set-up: The Nine Hole Peg Test (NHPT) was used as a fine motor task. In this test, subjects sit in front of a wooden block which is divided into two halves (see Fig.17: normal condition) (Oxford Grice et al. 2003). One side has nine small holes, the other side has one big hole in which there lie nine small pegs. The task is to grasp one peg after the other and place the pegs into the small holes on the other side. As soon as this is completed, the pegs, again one after the other, have to be transported back to the big hole. The time between the first and last peg-contact is measured. Furthermore, performance is assessed by counting mistakes such as dropping a peg.

The NHPT in the experiement series E1-3 had to be peformed under different conditions (see Fig.17, E2 and E3). In E2, a limiation was provided by elastic ropes pulling backwards; in E3, subjects had to use a mechanical grasp arm instead of their hands (see Fig.17, E3). These limitations were applied in order to simulate deficits that are related to an arm paresis post-stroke. More specifically, limitation 1 (elastic ropes pulling backwards) was applied to increase muscle effort for an arm extension and to make this task more demanding for motor control and coordination. Patients suffering from an arm paresis post-stroke suffer from muscle weakness, a loss of motor control and coordination. Limitation 2 (usage of a mechanical grasp arm) was applied to increase the level of difficulty for motor control, motor coordination and precision.

Four different stimulation designs were developed to be compared to a condition without sound (stimulation design a-e, see Fig. 18; sound-designs are attached in Appendix 9.2). The designs were suggested because of the following reasons: Metronome was applied to include a common RAS-design. So far, only metronome or march-music have been investigated clinically as sound material for RAS. Because of that, an alternative sound material, namely speech samples were observed. Therefore "spearcons" were chosen. "Spearcons" are speeded up speech samples that were evaluated in auditory displays by Walker et al. 2008. As "spearcons" were shown to increase the learning speed for navigation within a complex desktop system compared to other auditory or visual displays they were explored in the experiment series embedded into a rhythmic structure as alternative sound material in RAS. Usually, RAS training is carried out with metronome or march-music with 2/2 or 2/4 meter which suits easy-synchronization of bipedal gait. However, a direct application to robotic hand training with 2/2 or 2/4 meter was already discussed in chapter 2.2.4 as being problematic due to rhythms of unilateral robotically guided hand movements differing from gait patterns. As these experiments should generate data that provides information for robotic hand function training the common RAS- meter design was extended by the inclusion of waltz-music with a 3/4 meter as test stimulus. Furthermore, it was explored whether rhythm displayed in a multisensorial design can alter performance qualities. The tempo of all stimulation designs was 200bpm. This fast tempo was chosen to take into account the common velocity profile of the NHPT-norm value tables (Mathiowitz et al. 1985). A speed-up rate of 20% resulting in 200bpm was computed to investigate the influence of the rhythmic stimulation on performance velocity.

Procedure: Before the experiments started, participants were advised by an audio guide to rate their initial mood (condition 0). Than the task and test procedure were explained by the audio guide. Before each experiment, the task and the given condition was described. Before data recordings on each test condition (E1-3) started, one test trial was performed. During the performance of E1-3, four stimulation designs (condition b-e) were applied and compared to a condition without sound (condition a) (see Fig. 18): The stimulation designs a-e were displayed in each test condition in a randomized order.

The duration (d) of the task was measured with a stopwatch. The start and end were timed from the first to very last peg-contact. Performance quality (p) was assessed by counting the total amount of mistakes.

After each NHPT performance, the mood was rated via Visual Analogue Scale ranging from -10 to +10 in relation to the initial pre-assessed mood state (condition 0). All results were ranked to determine the strongest and the weakest stimulus-design of a-e for each condition in E1-3. A paired t-test (level of significance: 0,05%) was performed to compute whether effects of the strongest and the weakest stimulation design of a-e for E1-3 would differ significantly.

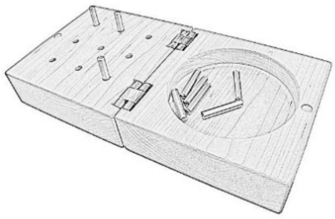
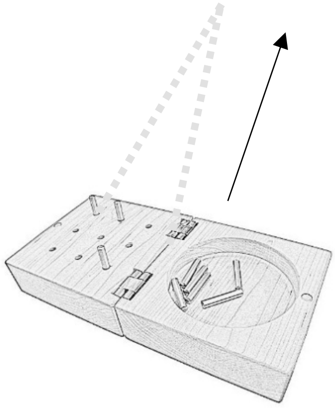
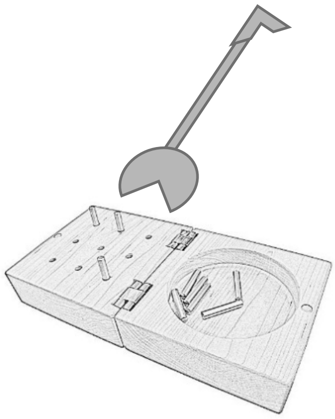
Experiment 1 (E1)	Experiment 2 (E2)	Experiment 3 (E3)
		
Normal condition	Limitation 1: Elastic ropes pulling backwards	Limitation 2: Mechanical grasp arm

Fig. 17: Technical set-up of Experiment 1- 3: E1: NHPT under normal conditions; E2: NHPT with limitation 1; E3: NHPT with limitation 2

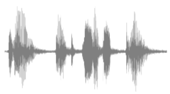
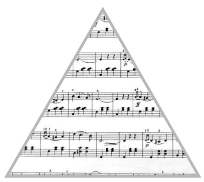
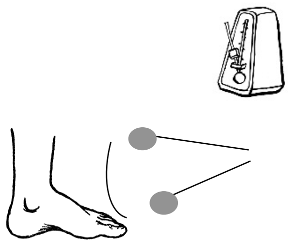
a control design	b metronome	c spearcon-beat	d waltz-music	e multisensorial beat
no stimulation				
	200 bpm	200 bpm “great, super, yeah”	200 bpm “Voices of spring”, J. Strauss	metronome: 200 bpm tactile beat: 100 bpm

Fig. 18: Design modes for rhythmic stimulation: a) control design: no stimulation, b) metronome beat, c) spearcon beat, d) waltz-music, e) multisensorial beat.

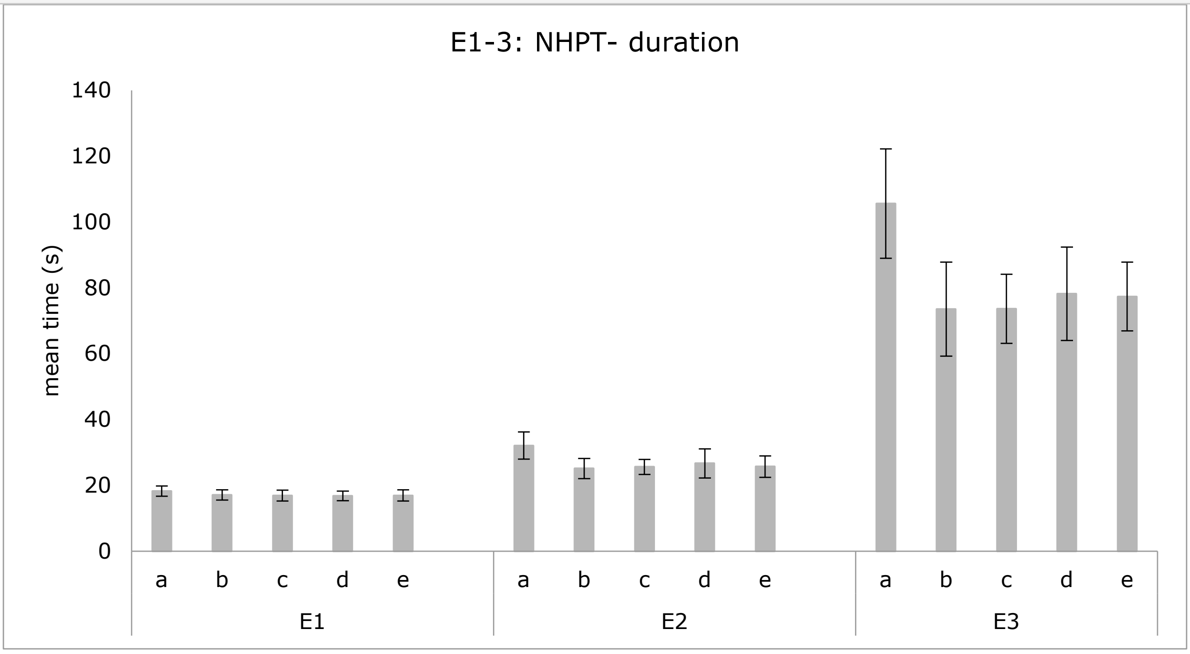
3.2.2 Results

Experiment 1 (see Fig. 19): In E1, duration was best with waltz-music (mean time (condition d) = 16,8s; sd = 1,42), followed by spearcon-beat (mean time (condition c) = 16,8s; sd = 1,67) and weakest without stimulation (mean time (condition a) = 18,3s; sd = 1,54). No significant difference was reflected in the outcome duration between the strongest and the weakest stimulation designs d) and a). Performance was best with waltz-music (mean performance (d) = 0,1; sd = 0,18) and with multisensorial-beat (mean performance (d) = 0,1; sd = 0,18) and weakest without stimulation (mean performance (a) = 0,35; sd = 0,49). No significant difference was found in the outcome performance comparing the strongest and the weakest stimulation designs d) and a). Mood was rated highest during waltz-music (mean mood (d) = 3,67; sd= 3,25) followed by no stimulation (mean mood (a) = 2,57; sd = 3,41). In relation to the pre-assessed initial mood (mean mood (0) = 3,2; sd = 4,02), waltz-music still gained higher values. Weakest results were seen with multisensorial-beat (mean mood (e) = -0,04; sd = 3,62). The effect of waltz-music on mood ratings led to significantly better mood ratings than the effect of multisensorial-beat in E1 ($p = 0,392$; $p < 0,05$). This means with a probability of 95% waltz-music increases mood ratings compared to multisensorial beat display during performance of the NHPT in healthy subjects.

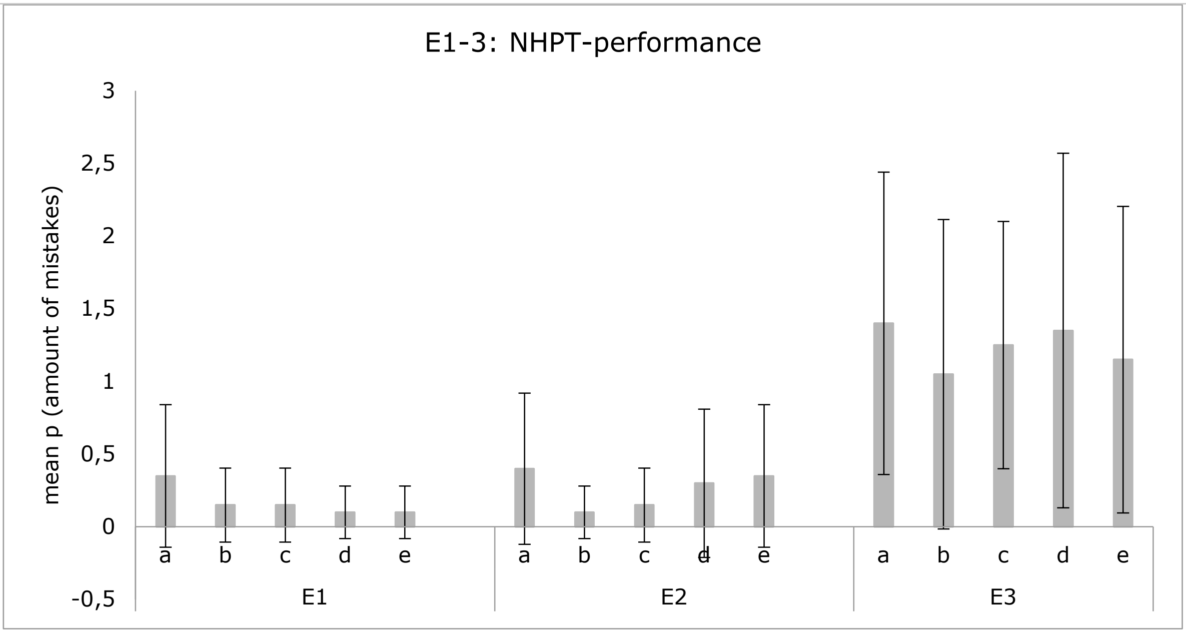
Experiment 2 (see Fig. 19): Best duration was measured with metronome (mean time (b) = 25,1s; sd = 3,02) and weakest without stimulation (mean time (a) = 32,1s; sd = 4,12). There was no significant difference reflected in the outcome duration between the strongest and the weakest stimulation designs b) and a) in E2. Performance qualities were best with metronome (mean performance (b) = 0,1; sd = 0,18), followed by multisensorial-beat (mean performance (d) = 0,1; sd = 0,49) and weakest without stimulation (mean performance (a) = 0,4; sd = 0.52). No significant difference was reflected in the outcome performance comparing the strongest and the weakest stimulation designs b) and a) in E2. Mood was rated highest during stimulation with waltz-music (mean mood (d) = 2,14; sd = 3,1) whereby the initial mood still was rated higher (mean mood (0) = 3,65; sd = 4,02). Weakest results were gained with spearcon-beat (mean mood (c) = -0,59; sd = 4,41). There was no significant difference reflected in the outcome mood between the strongest and the weakest stimulation designs d) and c) in E2.

Experiment 3 (see Fig. 19): Best duration was assessed with metronome (mean time (b) = 73,5s; sd = 14,26), followed by spearcon-beat (mean time (c) = 73,6s; sd = 10,51). Weakest duration was measured without stimulation (mean time (condition a) = 105,6s; sd = 16,63). No significant difference was reflected in the outcome duration comparing the strongest and the weakest stimulation designs b) and a) in E3. Performance was best with metronome (mean performance (b) = 1,05; sd = 1,06), followed by multisensorial-beat (mean performance (d) = 1,15; sd = 1,1) and weakest without stimulation (mean performance (a) = 1,4; sd=1,04). No significant difference was reflected in the outcome performance comparing the strongest and the weakest stimulation designs b) and a) in E3. Mood was rated highest with waltz-music (mean mood (d) = 2,09; sd = 3,19), whereby the initial mood was still higher (mean mood (0) = 3,65; sd = 4,02). Weakest results were assessed with spearcon-beat (mean mood (c) = -0,25; sd = 4,68). There was no significant difference reflected in the outcome mood between the strongest and the weakest stimulation designs d) and c) in E3.

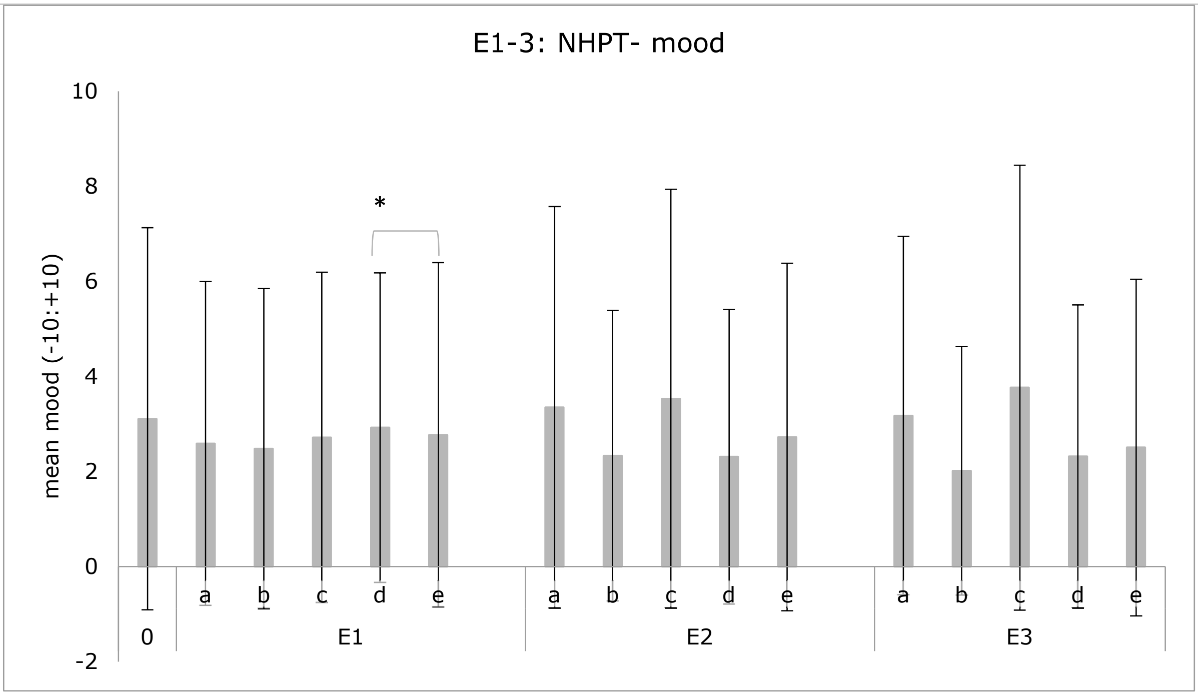
Experiment 1-3: NHPT- duration, performance, mood



Ranking of stimulation design gaining best and worst durations in E1-3:			
	E1	E2	E3
strongest	waltz-music mean time (d) = 16,8s; sd = 1,42	metronome mean time (b) = 25,1s; sd = 3,02	metronome mean time (b) = 73,5s; sd = 14,26
weakest	no stimulation mean time (a) = 18,3s; sd = 1,54	no stimulation mean time (a) = 32,1s; sd = 4,12	no stimulation mean time (a) = 105,6s; sd =16,63



Ranking of stimulation design gaining best and worst performance in E1-3:			
	E1	E2	E3
strongest	waltz-music mean performance (d) = 0,1; sd = 0,18 multisensorial beat mean performance (d) = 0,1; sd = 0,18	metronome mean performance (b) = 0,1; sd = 0,18	metronome mean performance (b)= 1,05; sd = 1,06
weakest	no stimulation mean performance (a)= 0,35; sd = 0,49	no stimulation mean performance (a) = 0,4; sd = 0,52	no stimulation mean performance (a) = 1,4; sd = 1,04



Ranking of stimulation design gaining best and worst mood in E1-3:			
	E1	E2	E3
strongest	waltz-music mean mood (d) = 3,67; sd = 3,25	waltz-music mean mood (d) = 2,14; sd = 3,1	waltz-music mean mood (d) = 2,09; sd = 3,19
weakest	multisensorial-beat mean mood (e) = -0,04; sd=3,62	spearcon-beat mean mood (c) = -0,59; sd = 4,41	spearcon-beat mean mood (c) = -0,25; sd = 4,68
T, P, p	T= 2,66251; P = 0,009798; p < 0,05.		

Fig. 19: Results of Experiment 1-3 (E1-3) with stimulation designs a-e (a: no stimulation; b: metronome; c: spearcons: d: waltz-music; e: multisensorial beat) of three outcome parameters 1)-3): 1) duration (mean time), 2) performance (mean amount of mistakes), mood (mean rate of VAS: -10: +10) displayed as block diagram (x-axis: stimulation design a-e; y-axis: mean outcome parameter 1)-3)); Ranking of best and worst stimulation designs a-e for outcome parameter 1)-3) in E1-3.

3.2.3 Discussion

In E1-3, duration and performance were weakest without any additional sound stimulation compared to the conditions with sound-stimulation. This indicates that a rhythmic sound stimulation can improve velocity and performance qualities when it is applied during performance of a fine-motor task (here: the NHPT) in healthy subjects. This improvement was independent of the level of difficulty which was more challenging in E2 and E3. Mood was rated highest in the condition in which waltz-music was applied. This effect was seen when waltz-music was compared to no sound, whereby the initial mood (condition 0) which was assessed before any task was performed, was still higher in E2 and in E3. In E1, mood was rated even higher with waltz-music than the initial mood rating (condition 0). This indicates that waltz-music potentially influenced the mood ratings positively. Although a more demanding task had to be performed in E2 and E3, the same effect was seen. This implies that music was perceived as motivating at all levels of difficulty from E1-3. Mood was rated second best with metronome. Under easy conditions as in E1, the second best results in mood ratings were achieved without any additional sound stimulation. In tasks that were more challenging (E2 and E3), mood ratings were second best with metronome. One reason for that could be that the metronome was perceived as most neutral stimulus and because it did not distract during performance of demanding tasks. This result could be related to positive outcomes with metronome-stimulation seen in E2 and E3, in which metronome influenced duration and performance best compared to other designs including no stimulation at all.

In order to provide sound designs for robot-assisted hand function training which enhances outcomes, more specifically, which increases function and motivation, several aspects need to be taken into account: The multisensorial-beat led to lower performance qualities than all the other designs in all settings. This might be due to technical limitations of the robotic prototype indicated by spontaneous comments of test participants. They described the hit on the foot as distracting. Mood ratings were negative under this stimulation design as well. Furthermore, effects on motor performance qualities were weaker than in the other designs. Because of that, the multisensorial rhythmic stimulation was excluded from further investigations. Moreover, the spearcon-beat did not generate strong effects, although it was described as distracting and unaesthetic by all test subjects. Consequently, the spearcon-beat was excluded from further examinations as well. A simple stimulus such as a metronome with an adequate tempo could provide a stable rhythmic pattern during difficult tasks. In all experiments, mood was rated highest with waltz-music independent of the level of challenge. A special focus in research on rehabilitation robotics is put on the proposition of an engaging technical environment that promotes motivation. Therefore, the positive effects of waltz-music on mood reflected in E1-3 are considered as very important.

3.2.4 Conclusion

The goal of this study was to explore whether auditory or multisensorial rhythmic stimulation designs have an impact on motor performance and mood during performance of a fine motor task in order to provide knowledge on an adequate sound design for robotic hand function training post-stroke. A review on effectiveness of sound and music in motor rehabilitation training was taken into account to identify promising stimuli and to transfer them to the context of robotic hand therapy: As "Rhythmic Acoustic Stimulation" (RAS) was shown to enhance motor control and movement initiation for neurological patients, and musical stimulation was shown to increase motivation and functional aspects during motor training, three pilot-experiments were carried. The objective of this experiment series was to examine effects of specified rhythmic stimulation designs and rhythmical music compared to no sound at all, in order to provide information on a promising sound designs for robotic hand function training. The rhythmic stimulation designs consisted of waltz-music with a 3/4 meter, metronome, a speech-based rhythmical pattern and a multisensorial beat. Three experiments were performed that varied in level of challenge, whereby the level of difficulty increased from E1 to E3. Throughout these three experiments, 20 healthy subjects performed a fine-motor task under four stimulation designs and a baseline condition without any sound stimulation. Results reflected in outcome parameters of duration to complete the task, performance and mood showed that specified RAS-designs influenced duration, performance and mood in all suggested designs positively compared to no stimulation at all.

Metronome led to a better performance, especially throughout difficult tasks. In the easiest task, best duration and performance results were achieved with waltz-music. In general, stimulation with waltz-music gained best mood ratings throughout all three experiments. This indicates that waltz-music influenced mood states positively independent of the degree of difficulty. Function was weaker with waltz-music under more difficult conditions than with metronome or the spearcon-beat. In a next step, the effects of metronome and waltz music applied during a fine motor test with stroke patients needs to be investigated. Such an investigation could lead to the suggestion of an effective sound design for further observations applied to robot-assisted hand function training. Future research on effects of sound and music applied in technology-assisted motor rehabilitation is needed to provide therapeutic meaningful auditory stimulation within a complex therapeutic environment that aims to engage motivation during training and to promote recovery effectively.

Study 2

3.3 Effects of sound on stroke patients during performance of the Box and Block Test

3.3.1 Background and goals of Experiment 4

3.3.2 Methods

3.3.3 Results

3.3.4 Discussion

3.3.5 Conclusions

3.3.1 Background and goals of Experiment 4

In E1-3, healthy subjects performed the NHPT, whereby the level of challenge was increased from E1 to E3 to simulate limitations given in arm paresis post-stroke (see Fig.17: E1-3). Four stimulation-designs (see Fig.18: a-e) were applied in a randomized order during the performance of each task. In E1-3, duration (t), performance (p) and mood (m) were assessed. Mood was ranked via the Visual Analogue Scale (-10:+10) in relation to the initial mood (condition 0). The two strongest RAS-designs determined in E1-3 were metronome (b) and waltz-music (d). In the here presented experiment E4 with 8 stroke patients suffering from an arm paresis waltz-music, metronome are compared to a condition without sound. Unlike in E1-3, in which stimulation designs were displayed during the performance of the NHPT, the stroke patients had to perform the Box and Block Test (BBT). The test task was changed because not all study participants were able to perform the NHPT.

3.3.2 Methods

In E4 the Box and Block Test (BBT), a validated clinical assessment tool for specification of manual dexterity and grasping skills served as experiment task for E4 in which different sound conditions and their effects on functional performance of the BBT are compared. In the BBT, the participant sits on a chair in front of a table on which a wooden box is placed. This box is subdivided into two parts by a wooden wall. In one side of the box, wooden blocks are placed (see Fig. 20). The test task is to grasp a block and transport it over the wooden wall to the other side as fast as possible and without throwing. The amount of blocks moved to the other side within 60 seconds reflects the manual skills, especially the ability to grasp and release an object (Mathiowitz et al. 1985). In E4, the function (n: amount of blocks) was assessed and the mean amount of achieved blocks was used as an outcome parameter. 8 stroke subjects suffering from an arm paresis post-stroke performed the BBT under different auditory conditions which were applied in randomized order. The stimulation conditions were a) no stimulation, b) metronome with 200bpm (the tempo was chosen in relation to the previous experiment), and d) waltz-music: “Voices of spring”, J. Strauss (see Fig. 20). The test was assessed once with the paretic side, and once with the non-paretic side.

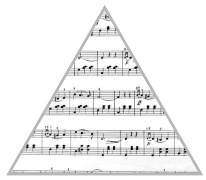
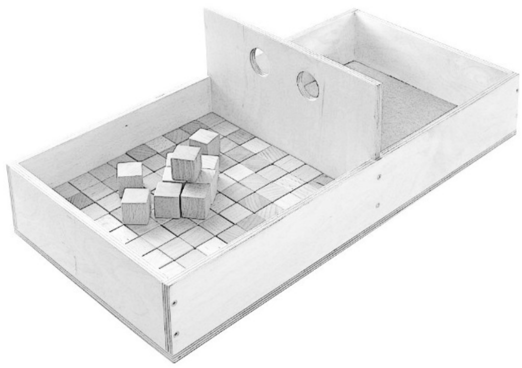
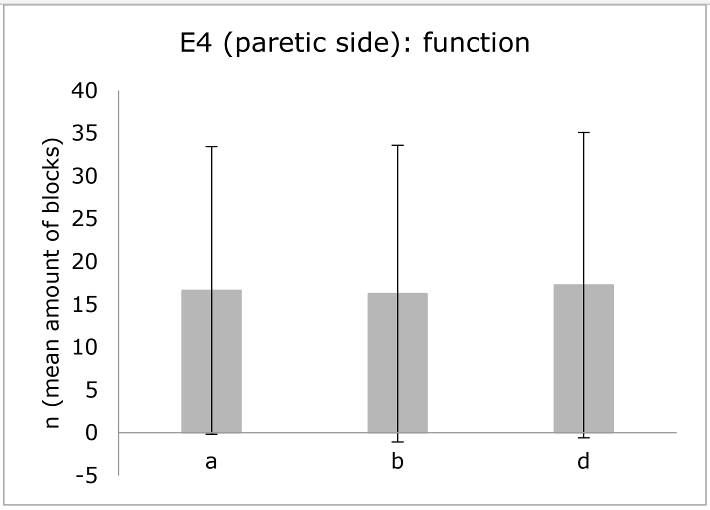
<table>
<tr><td colspan="3">Stimulation designs displayed in E4 in randomized order:</td></tr>
<tr><td>a: no stimulation</td><td>b: metronome
</td><td>d: waltz-music
(“Voices of spring”, J. Strauss
</td></tr>
<tr><td colspan="3"></td></tr>
</table>

Fig.20: Box and Block Test under three different sound conditions (a: no stimulation, b: metronome, d: waltz-music).

3.3.3 Results

Results of the performance of the BBT with the paretic side showed that the highest amount of blocks was achieved during stimulation with waltz-music (mean amount of blocks (d) = 17,25; sd = 17,84), followed by metronome (mean amount of blocks (b) = 16,625; sd = 17,34). The lowest amount of blocks was obtained with no stimulation (mean amount of blocks (a) = 16,25; sd = 17,84). The different stimulation designs a, b, d did not cause significant differences in the outcome of the mean amount of blocks in stroke subjects performing the BBT with the paretic side (see Fig. 21). E4 was furthermore carried out with the non-paretic side. Here the highest amount of blocks was achieved with waltz-music (mean amount of blocks (d)= 65,286; sd = 7,342), followed by metronome (mean amount of blocks (b) = 63,286; sd = 9,36), while the weakest outcome was gained without any stimulation (mean amount of blocks (a) = 63,286; sd = 8,85). The different stimulation designs a, b, d did not cause significant differences in the outcome of the mean amount of blocks in stroke subjects performing the BBT with the non-paretic side (see Fig. 21).

Experiment 4: Function (paretic side/ non-paretic side)



Ranking of stimulation designs in BBT in E4 (paretic side):

1) waltz-music

mean amount of blocks (d) = 17,25;

sd = 17,84

2) metronome

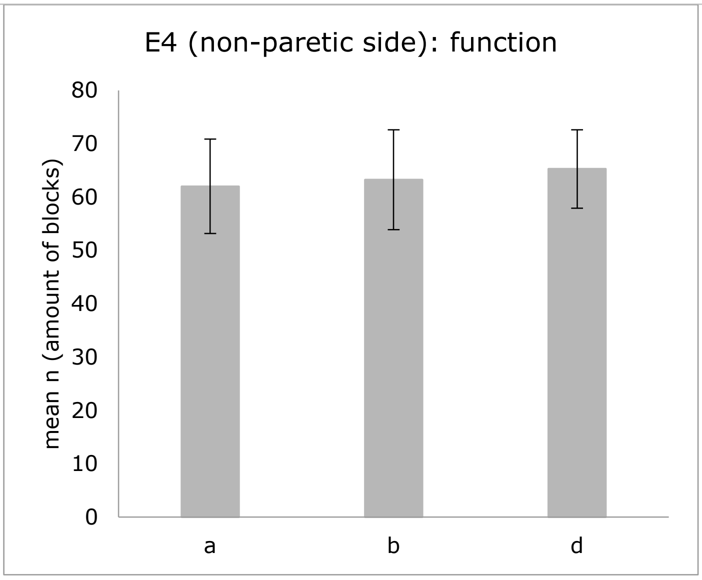
mean amount of blocks (b) = 16,625;

sd = 17,34

3) no stimulation

mean amount of blocks (a) = 16,25;

sd = 17,84



Ranking of stimulation designs in BBT in E4 (non-paretic side):

1) waltz-music

mean amount of blocks (d) = 65,286;

sd = 7,342

2) metronome

mean amount of blocks (b) = 63,286;

sd = 9,36

3) no stimulation

mean amount of blocks (a) = 62;

sd = 8,85

Fig. 21: Results of Experiment 4 (E4) with stimulation designs a, b, d (a: no stimulation: b: metronome; d: waltz-music) of the mean n (n= amount of blocks achieved in the Box and Block Test) of the paretic and the non-paretic side. Results are displayed as block diagram (x- axis: stimulation design a, b, d; y-axis: mean amount of n); Ranking of best and worst stimulation designs a, b, d for mean n in E4.

3.3.4 Discussion

The patients described the metronome stimulus as annoying and stressing. This might be due to the tempo of 200 bpm which was provided like in E1-3. Probably, this tempo was too fast for patients. Because of that, another experiment should be carried out in which the stimulation-tempo relates better to an individually pre-assessed performance tempo with a speed-uprate of 20%. In general, the remarks on aesthetical problems with the metronome sound also need to be taken into account when the overall-goal should be to provide sound for robotic hand function training. Aesthetical acceptance of an auditory environment is important to achieve patient compliance. This is especially critical when training is performed over longer time spans. Another important observation was that the patients did not synchronize their movements to the beat, neither to the metronome beat nor to waltz-music. Nevertheless, both the paretic and non-paretic side performed better with waltz music than without sound or metronome. This indicates that sound was better than no-sound, yet not the cueing mechanism but another adaptive phenomenon instead might influence task performance under stimulation of waltz-music or metronome. As shown in E1-3 that waltz-music was able to increase motivation while lowering performance qualities, while the results obtained with stroke patients showed contradictory results: Here, the outcome was better with waltz-music than with metronome. The positive influence of waltz-music points to another rhythmic-adaptive mechanism that might have influenced motor performance positively. Because of that, alternative metric structures to commonly used 2/2 meter in march music or metronome could be explored to extend the RAS concept. To clear out the importance of different rhythmic metrics, polymetric music is suggested for future evaluations. Another arguable point occurred during this experiment which was related to the familiarity of waltz-music. This leads to a more general concern on how to handle music-induced emotions, cultural markers and familiarity aspects. Waltz-music was known by all participants in this experiment which might be different in other countries with other cultural backgrounds. For further investigations, a musical stimulus is recommended that cautiously bypasses these aspects.

3.3.5 Conclusion

The results of E1-4 indicate that RAS enhances motor performance and motivation during fine motor tasks in healthy subjects and in stroke patients suffering from an arm paresis. In E1-3, function and mood gained better outcomes with rhythm than without. Best results in E1-3 with healthy subjects were achieved with metronome throughout difficult tasks (E2, 3). In the easiest task (E1), best functional results were obtained with waltz-music. Musical stimulation gained the highest mood ratings, independent of the degree of difficulty. Two sound designs were concluded from E1-3 for an experiment E4 with stroke-patients. In E4, patients showed best outcome with waltz-music, on both the paretic and the non-paretic side, followed by metronome stimulation. The weakest results were found in the condition without any stimulation. Because of that, waltz-music, and metronome are proposed for further observations applied to robotic hand therapy. As in all four experiments E1-4 sonic rhythmic stimulation resulted in better outcomes than no stimulation, this implies that such a stimulation might improve performance of fine motor tasks in healthy subjects and in stroke patients. More research on effectiveness of sound in technology-assisted motor rehabilitation is needed to promote recovery, to enhance given designs, and to provide information for further applications in the field of motor rehabilitation.

Study 3

3.4 Test phase: rhythmic stimulation designs applied in robot-assisted hand therapy

3.4.1 Technical description of the robotic hand function trainer "Amadeo"

3.4.2 Practical test phase of explorative sound designs applied to "Amadeo"

3.4.3 Concluded sound designs for clinical study design

3.4.4 Further observations - the role of the little finger

3.4.1 Technical description of the robotic hand function trainer “Amadeo”

The “Amadeo” system was already introduced in Chapter 2.3.1. Here, a short summary of the technical set-up is given which is extended with relevant details for the application of sound: The commercial robotic hand function trainer “Amadeo” (Tyromotion GmbH) consists of a robotic hardware part which is connected to a computer displaying a virtual environment.

The hardware part consists of a rack with six sleighs to which the fingertips are connected. These sleighs actuate linear movements in flexion and extension. Training can be performed in three modes – passive, assistive, and active. In passive training, the robot moves the fingers. The tempo of this movement, as also the segmentation of time between single finger actuation, is adjustable. In active training, the patient controls gaming actions within the virtual environment without any robotic assistance. The games are designed to train in two different modes: In the isometric training mode, the sleighs are fixed and force needs to be applied on one point to control gaming actions. In the range-of-motion-mode the sleighs are flexible. By moving the sleighs into either extension or flexion gaming actions are controlled. “Amadeo” provides different training games. All games are combined with background music varying in genre, tempo and musical style. Here training games that were played in the later on presented clinical study are described: The “balloon game” shows a balloon which is controlled by the player as described above (graphical display: see Fig. 22). This balloon has to be navigated in a virtual landscape without colliding with passing objects such as airplanes, clouds or the ground-floor. Collisions are displayed visually by a color change of the balloon as well as by a beep-sound. At the end of the game a score is displayed which reflects the total amount of collisions within a fixed time of 2 minutes play time. The presentation of the score as well as the game start and end are displayed with a short trumpet melody serving as reward sound. The game can be played at 10 levels of difficulty. Higher levels lead to an increase of the velocity of the balloon and with rising level the velocity of the balloon and the amount of objects one has to pass. The “collect apple”- game shows a bear placed in a garden with apple trees (see Fig. 22). The bear is equipped with a basket. This bear-character is controlled by the user. As soon as the game starts, apples drop down from the trees. The task is to catch the apples with the bear’s basket. When an apple is caught a short abstract reward sound is presented. When an apple is missed a short error sound is played back. The end of the game is marked by the same short trumpet-melody as in the “balloon game”. The game can be played at 10 levels of difficulty. The more advanced the level is, the smaller the basket gets is and the more apples fall down from the trees in a shorter time at a higher speed. The “collect trash”- game shows a grabber which travels back and forth above five trash cans of which each is marked with a symbol for its purpose such as a paper trash can, compost trash can and so on. As soon as the game starts, objects such as fruit, cans, bottles or paper objects are shown. The task is to make the grabber pick up an object and transport it to the matching trash can. A successful match goes along with a short reward sound. When the correct trash can is missed or an object drops beside of a trash can a short error sound is played back. The end of the game is marked by the same trumpet-melody as in the two other games. The game can be played at 10 levels of difficulty. The higher the level, the more objects are displayed and the faster the grabber travels from one side to the other. All games are displayed in colors, in 2D and contain sound. The sound ranges from error feedback, to performance feedback when scores are displayed, to background music.

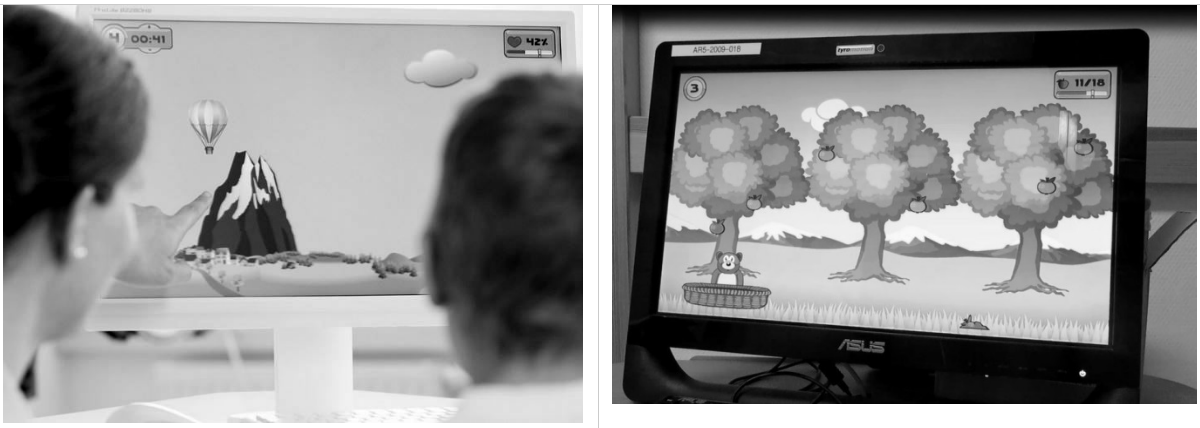


Fig. 22: Visual Display of "Amadeo"- games: 1) "Balloon game", 2) "Collect Apples-game"

<u>3.4.2 Practical test phase of explorative sound designs applied to "Amadeo"</u>

Throughout the practical test phase with 5 healthy subjects, and followed by 2 stroke patients, metronome, waltz-music, polymetric music and game related feedback were explored. These sounds were displayed via computer monitor speakers which are commonly used throughout training with "Amadeo". The sounds were applied to a training session containing passive training and active training. During passive training, the fingers were actuated in flexion and extension at different velocities and with different time intervals between single finger actuation over a time span of five minutes three times consecutively. Each time another sound was displayed: either no sound, waltz-music or polymetric music. In active training, three different games, the "balloon game", the "collect apples"- game, and the "collect trash"-game were played. Each of these three games was played three times with different auditory conditions. The navigation of gaming actions in the games was controlled by thumb and index finger in two modes, either in range-of-motion-mode or in the isometric mode. When test subjects commented the sound spontaneously, the observer took notes. All collected remarks are summarized in the next section.

3.4.3 Concluded sound designs for clinical study design

In the case of metronome, all participants described the metronome sound as annoying, irritating and distracting. Considering that training is performed with an intensity of daily practice over a time span of up to one year or more, acceptance of the auditory environment is highly important. The participants reported the metronome as annoying already after 5-10 minutes of training. An additional problem with metronome occurred during passive movement training. Due to technical limitations, the robot could not perform movements with an equally stable tempo like a metronome. Consequently, the auditory signal was not in synchrony with the movement already after 5-10 movement repetitions. This mismatch was noted by all test participants and by the observer. All in all, these problems led to the conclusion to exclude the metronome from further investigations in the clinical study. In the case of waltz-music, no obvious cueing mechanism was reported nor observed, neither in passive training due to the technical limitations described above, nor during gaming. For waltz-music participants, reported aesthetical doubts in thought of a prolonged training as well. Furthermore, they described waltz-music as emotional arousing and memory-inductive due to its associative nature. In the discussion section of experiments E1-4, it was already outlined that familiarity with music might cause problems when familiar music is applied to robotic hand function training. Because of that, waltz-music was also excluded from the clinical study design. In the case of polymetric music, no obvious cueing mechanism was observed. In contrast to waltz-music and metronome, acceptance and compliance was high for this musical stimulus. Subjects reported about a gaming experience in which they perceived themselves as focused, concentrated and in flow. The polymetric music was synthesized along design parameters that were concluded from E1-4 in order to provide an alternative metric structure than the commonly used in RAS training. RAS training is usually performed with metronome or with a 2/2 meter-based music. (In chapter 4.1 this musical stimulus is described more detailed; sound-designs b-d and the polymetric music are attached in Appendix 9.2.). Furthermore, the aspect of a cultural and emotional "neutral" design was taken into account for the design of the polymetric musical piece. Because music is cultural by nature, and because it is very difficult to tackle this complex topic, subjects were asked directly whether the music seemed familiar or culturally connoted. They described the stimulus as repetitive, but not as familiar. Moreover, they reported that this musical piece was emotionally neutral or calming. Because of the high level of acceptance and reports on attention, concentration and flow-inducing effects, this stimulus was concluded as an experimental auditory environment for the clinical study as well as game-related feedback sounds. Game related sounds that were already implemented in the games were perceived as informative, funny and motivating.

3.4.4 Further observations- the role of the little finger

Further observations in this test phase were related to patients in practice with the robot: Usually, the primary focus in hand therapy is to retrain grasping. Because of that, commonly this training starts with a focus on thumb and index finger. So far, no alternative finger combination as a starting point has ever been evaluated. In the case of a hand paresis syndrome, especially index finger and thumb are interconnected due to pathological muscle synergies. Typically the following pattern occurs: When the index finger is extended, the thumb is pulled into flexion automatically and vice versa. As soon as one of the fingers is in flexion the other one aligns this direction and extension cannot be performed anymore. Instead any motor control demand to the hand increases the muscle tone leading to an even stronger flexion pattern. It is unclear whether training with an alternative finger combination would improve hand function as well, more or less than the finger combination of thumb and index finger. The "Amadeo" offers to train with single finger actuation. In the clinical study, the combination of thumb and little finger was used instead of thumb and index in the first line. The little finger was chosen, because it is the most independent finger of the thumb muscle units that are related to flexion. Furthermore, the little finger might be less affected by spasticity compared to other fingers. To document the here suggested special role of the little finger within a spastic hand, a difficult fine motor balance task was designed in an explorative manner. The test was a "Twist-pencil"-task (see Fig.23 a,b). Therefore subjects were asked to twist a pencil between index finger and thumb. In most cases, a successful task performance was observed when the little finger was abducted (see Fig. 23 a).

a) b)

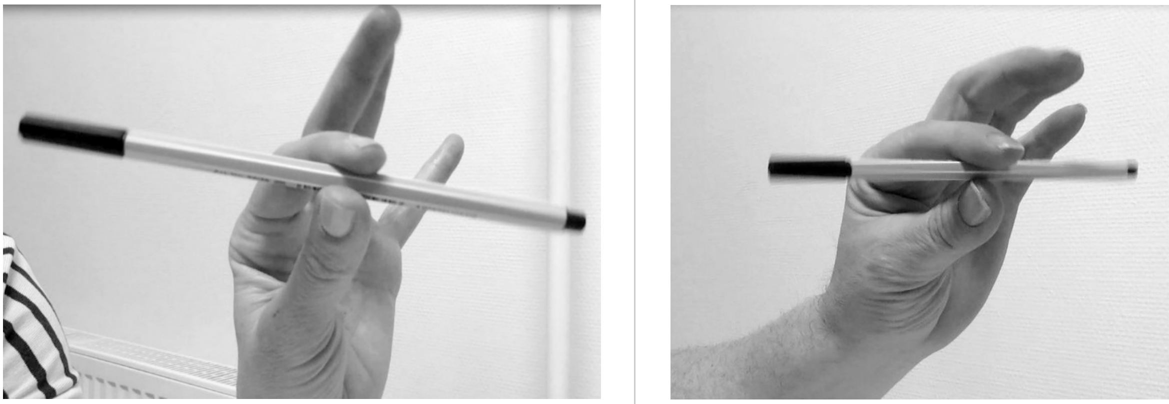


Fig. 23: "Twist-pencil"-task with thumb and index finger. The two pictures show a hand position in which the little finger is abducted.

The reason for this could be that the abduction of the little finger increases the stability of the hand posture. If this would be the case, such a stable posture would enable more flexible interaction needed for balance tasks between index finger and thumb. Beside of that, this posture indicates than when the thumb is in a flexed position the little finger can still be extended. Another interesting point when discussing the role of the little finger is that the cortical representation of the little finger is larger than the representation of all the other fingers except for the thumb (Koelsch 2012). The reason for this could be that little fingers have one muscle unit more than other fingers, which are the external extensors. Furthermore, the little finger is involved in grasping objects in a very multifaceted manner: When a round object needs to be grasped, the little finger can assist this task by stabilizing the object from below and from the side. Furthermore it can be extended to stabilize the hand posture.

In summary, investigations on different finger combinations might be valued when treating a paretic hand. A promising approach could be to train the thumb and the little finger instead of the thumb and index finger, which are muscle- synergistic interconnected.

CLINICAL STUDIES

4. CLINICAL STUDY: EFFECTS OF SOUND IN ROBOT-ASSISTED HAND FUNCTION TRAINING

4.1 Study Design and Test Battery

Here, a 2-armed non-blinded clinical study is presented which investigates the effects of specified sound applied to robotic hand function training on function and motivation of patients suffering from post-stroke hand paresis. As described in previous chapters, usually robotic rehabilitation technologies are combined with virtual reality scenarios including sound. So far, sound has never been specified for the context of robotic rehabilitation purposes. Furthermore, sound-induced effects were never evaluated with a focus on function and motivation. Therefore, a 2-armed clinical trial with 34 stroke patients suffering from a hand paresis syndrome was performed. The goal of this study was to examine whether robotic hand function training, extended with specified sound, shows clinically relevant changes with an impact on recovery compared to robotic hand function training without sound. One control-group received robotic hand function training without sound and one sound-group got sound-extended training. Both of the groups received robotic hand function training with the "Amadeo"-system for a three-week-training-cycle of nine 45-minute long therapy sessions. The sound which was displayed throughout training consisted of polymetric music and computer game-related feedback sounds. Outcomes of the control and sound-group were compared in function and motivation. More specifically, a 2-armed explorative clinical trial was designed to compare the effects of sound-extended robotic hand function training post-stroke on function and motivation (see Fig. 24), (n=34, control-group: n= 14; sound-group; n=20). The main endpoint measures for the domain function was the Box and Block Test (BBT) and in the domain motivation the Intrinsic Motivation Inventory (IMI) (Mathiowetz et al. 1985; McAuley et al. 1989). Secondary outcome measures in the domain function were the Nine Hole Peg Test (NHPT), Grip Force measurements with a dynamometer (GF), single finger forces in rest (F0) and maximal finger forces in extension (F ext) recorded with the commercial robotic training system "Amadeo" (tyromotion GmbH) (Oxford Grice et al. 2003; Hammer, Lindmark 2003). Secondary outcome measures in the domain motivation consisted of Experience Samplings (ES) which were carried out during the sixth therapy session (T1) and the Goal Attainment Scale (GAS) (T2,T3) which assessed two months after the ninth therapy session (T3) (Csikszentmihalyi et al. 2014; Turner-Stokes 2009). All tests on function were performed at baseline (T0) and one to three days after last intervention (T2). (For a detailed description of the test battery see Table 5). 34 stroke patients suffering from a hand paresis syndrome at least two months post-stroke took part in the study (patient characteristics see Table 3). All subjects were assigned to either the control-group (subject 1-15) or the sound-group (subject 16-34) (see Flow-Chart Fig. 24). All participants received nine therapy sessions of robot-assisted hand function training (RT) additional to conventional treatment.

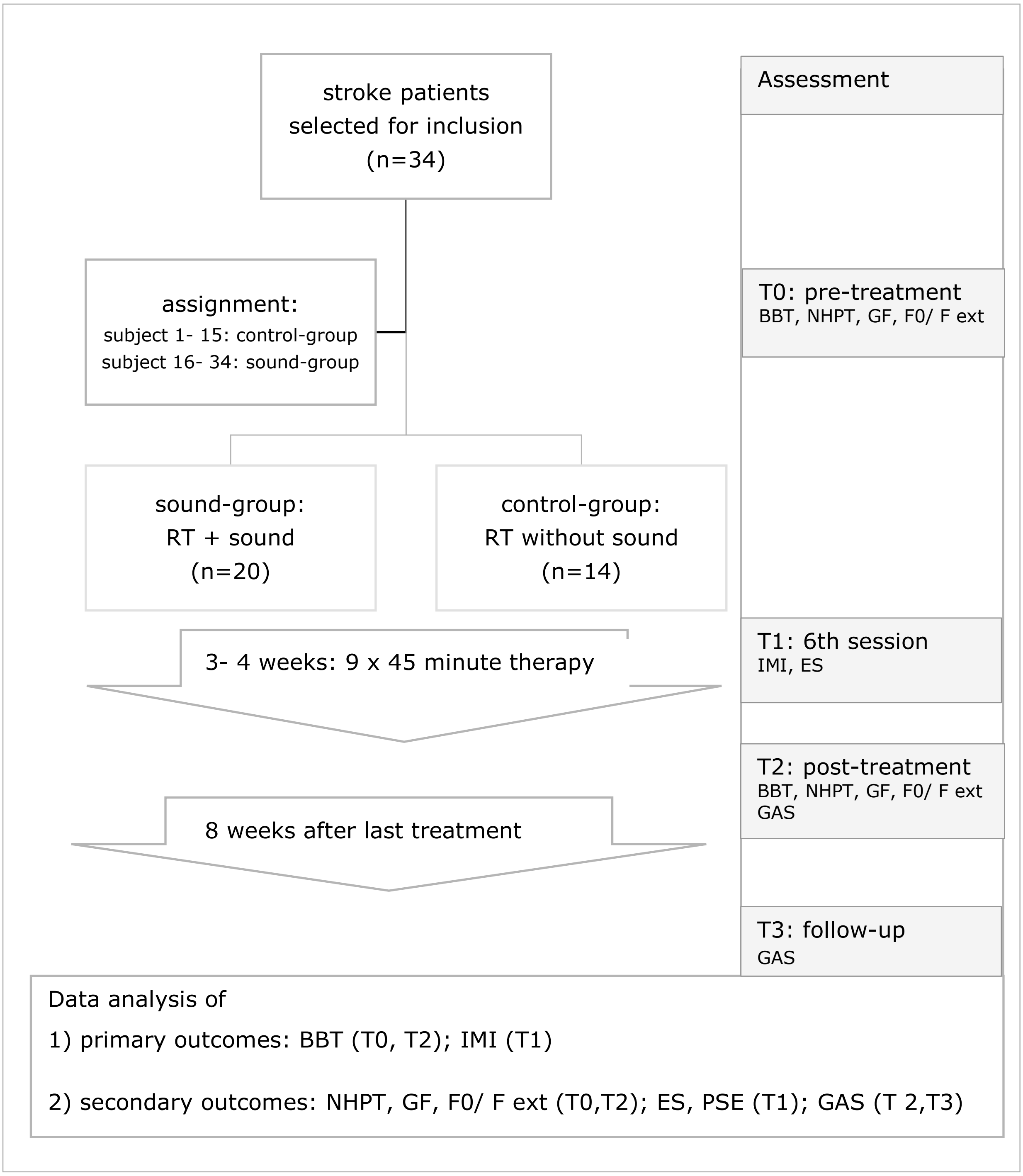


Figure 24: Study Design: 2-armed clinical trial (RT: robot-assisted hand function training; BBT: Box and Block Test; IMI: Intrinsic Motivation Inventory; NHPT: Nine Hole Peg Test; GF: Grip Force measure with dynamometer; F0: single finger forces in rest & F ext: maximal finger forces in extension; ES: Experience Sampling; PSE: Perceived Size of Effort; GAS: Goal Attainment Scale); T0: pre-treatment; T1: during session six, T2: after nine therapy sessions, T3- follow-up: 2 months after the last treatment session; Presentation of results of sound- and control-group are colored in this color scheme.

Ethics- This study was approved by the "Deutsche Ärztekammer".

Patient acquisition - 34 stroke patients suffering from hand paresis post-stroke who were meeting the inclusion criteria were recruited at the rehabilitation center "*Zentrum für ambulante Rehabilitation Berlin Mitte*" (see inclusion and exclusion criteria Table X). All study participants were selected by neurologists (Prof. Dr. med. Diethard Steube, Manoucher Omidvar) and ergo therapists and were treated in the "*Zentrum für ambulante Rehabilitation Berlin Mitte*" in a post-stroke therapeutic context with conventional ergo therapy during the time span of their study participation.

Inclusion & Exclusion Criteria - Stroke patients were included who were at least two months post-stroke, suffering from an arm paresis, showing minimal activity in the finger or hand of the affected arm, and who had signed the study participation agreement. Patients showing problems such as soft-tissue damage or joint contractures, orthopedic hand related problems, hearing deficits or amusia were excluded. For a detailed overview see Table 3.

Inclusion criteria	Exclusion criteria
• female/ male stroke patients • > 4 weeks post-stroke • hemiparesis of the upper extremity • minimal function in the upper extremity • minimal function in one finger or the hand • signed agreement on study participation	• soft-tissue or joint contractures in affected upper extremity • Chirurgic treatment on affected upper extremity 8 weeks before inclusion • amusia • hearing disorders/ deficits • other contra indications leading to exclusion (doctor, examiner)

Table 3: Inclusion/ Exclusion Criteria for study participation

Patient characteristics - In total, 34 stroke patients were included. 12 subjects were female and 22 were male. The age ranged between 15 and 80 years with a mean age of 52,1 years and a standard deviation of 16,1. All patients were at least two months post-stroke whereby the mean amount of months post-stroke overall was 14,9 months with a standard deviation of 16,4. 6 out of 34 patients had received music therapeutic interventions before the study participation. 13 patients had received robot-assisted therapy previously (10: with the tool "Amadeo", 2: with the tool "Armeo spring", 1 with the "Lokomat" gait trainer). 15 patients had practical experience with playing a music instrument, singing in a choir or dancing classes. 29 patients had experience with computer games. Two different subgroups were built (see Fig.25).

Baseline results of the Box and Block Test (BBT) were used to create three groups within subgroup A along the grade of severity. Therefore, the sum of the maximum amount of blocks achieved in BBT of all patients at baseline (max n = 51) and the minimum amount (min n = 0) was divided by three and mapped to a grade of severity (BBT all patients max n= 51; min n= 0): severe hand paresis (BBT: n < 16), moderate hand paresis (BBT: n > 16 < 32) and mild hand paresis (BBT: n > 32) (see Fig. 25). Furthermore, a second subgroup scheme for subgroup B was built which divided participants along different time-spans between insult and study participation into three groups (see Fig. 25). Group 1 included patients 2-6 months post-stroke, group 2 patients 7-12 months post-stroke and group 3 patients that were more than 12 months post-stroke. A subgroup analysis was performed for subgroup A and B on primary and secondary measures. A detailed overview of patient characteristics containing information on gender, age, months post-stroke, location of lesion, handedness, musical experience, previous experience in robotic training, computer gaming experience, grade of severity in relation to BBT outcomes and subgroup allocation to post-stroke group 1-3 are presented in table 4 a). Overall patient characteristics are displayed in table 4 b).

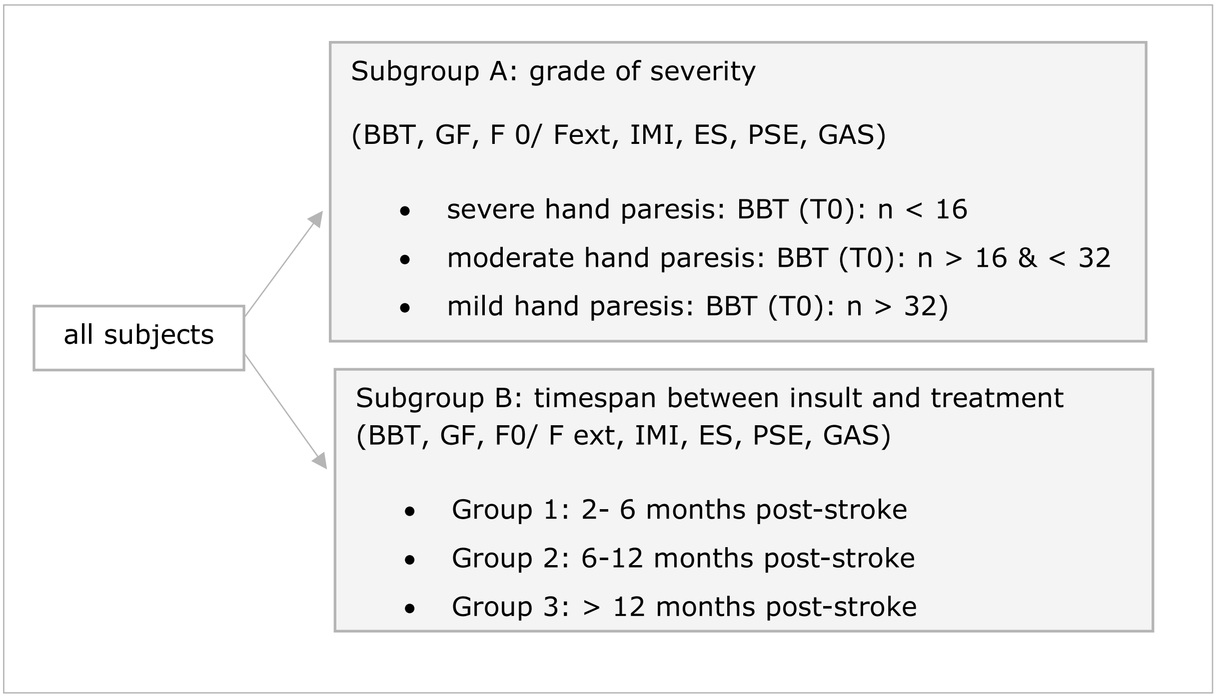


Fig. 25: Overview of grading system for Subgroup A (grade of severity) and B (timespan between insult and treatment); tests computed for subgroup A and B were BBT (Box and Block Test), GF (Grip Force measure with dynamometer), F0/ F ext (F0: single finger forces in rest & F ext: maximal finger forces in extension), IMI (Intrinsic Motivation Inventory), ES (Experience Sampling), PSE (Perceived Size of Effort), GAS (Goal Attainment Scale). A presentation of results of Subgroup A and B follow the above displayed color scheme.

Technical Set-Up - The commercial robotic hand function trainer "Amadeo" (Tyromotion GmbH) served as a technical training environment for the study. This system consists of a robotic hardware part which is connected to a computer. The computer screen is positioned on an adjustable platform displaying the virtual environment including assessment and gaming software (see Fig.26 a). The hardware part consists of a rack including a part with six sleighs. The affected arm is positioned on a track which predefines a stable arm position. The fingertips are connected to the sleighs via magnetic contacts which are taped around the finger tips (see Fig. 26 b).

a)

b)

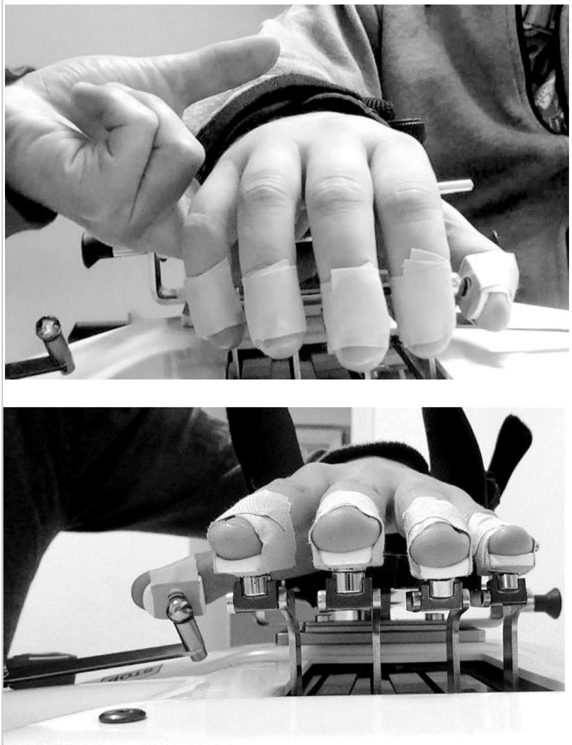


Fig. 26: a) "Amadeo" (Tyromotion GmbH); b) Fingertips with magnetic contacts connected to sleighs of "Amadeo" hand module in hand flexion and extension.

The sleighs actuate linear movements in flexion and extension and are equipped with sensors that can measure single finger forces and single finger ranges of motion. Within the software, an assessment module allows to first adjust the sleighs to individual finger size (calibration), and to measure single finger forces in two directions (flexion and extension). Training can be performed in three modes – passive, assistive, and active. In passive training, the robot moves the fingers in a predefined range of motion into extension and flexion. The tempo of this movement is adjustable as also the segmentation of time between single finger actuation. In assistive training, the patient first controls movements in either flexion or extension. When the patient cannot perform

100% of the demanded task the robot continues the movement and takes over until 100% of the intended range of motion is completed. In active training, the patient controls gaming actions within the virtual environment without any robotic assistance. The games are designed to train extension and flexion in either an isometric training mode or a range-of-motion mode. In the isometric training mode the sleighs are fixed and force application in both directions control the actions. In the range-of-motion-mode the sleighs are flexible and by moving the sleighs into either extension or flexion the gaming actions are controlled.

Stimuli- Polymetric music and game-related action sounds were used as auditory environment in the sound-group. Polymetric music was specifically developed to meet design parameters set up for the study: These parameters were rhythmic adaptability to multi-joint movements which are given in hand and finger movements, adaptability to different cultural- or age-backgrounds by trying to create a "neutral" genre, a simple tonal scheme, and a repetitive, calming melodic style. The rhythmic structure in polymetric patterns can be described as a pattern including multiple streams of meters at once (see Fig. 27). Such a rhythmic structure might suit multi-joint-determined hand- and finger movements. Hand and finger movements are organized rhythmically more complex than bipedal cyclic gait training which is commonly used in RAS gait training. The aim of this design approach using a polymetric rhythmical structure was to enable easy synchronization at any point of time independent of performance qualities such as total velocity, position or force production. The games, which were already described in Chapter 3.4.1., implemented in the "Amadeo"-system, already included action-related acoustic feedback sounds illustrating physical properties of objects within the virtual environment (e.g. a falling apple), error-feedback (e.g. object collision) and reward sounds illustrating the start and end of a game. These game- sounds were displayed additionally to the polymetric music in the sound-group.

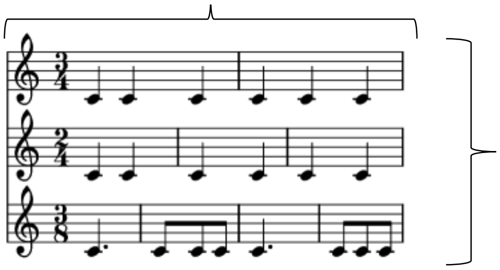


Fig. 27: Example of a polymetric pattern with multiple streams of meter: first voice with 3/ 4 meter containing 2 bars, second voice with 2/ 4 meter containing 3 bars, third voice with 3/ 8 meter containing 4 bars; all voices are played in one absolute time-frame.

Table 4 a) Individual patient characteristics										
No	gender	age	months post-stroke	location of lesion	right-/ left handed	musical exp.	robotic rehab exp.	gaming exp.	grade of severity	months post-stroke grouping
1	male	54	5	Media infarct right	r		x	x	mild	1
2	male	62	5	Stem ganglia right	r	x	x	X	mild	1
3	female	80	3	Arterria Cerebtri media	r				mild	1
4	female	21	21	ICB right parieta	r	x		x	severe	3
5	female	32	5	Media infarct left	r	x	x	x	moderate	1
6	male	43	4	Media infarct right	l	x	x	x	severe	1
7	female	49	7	Stem ganglia right	r			x	severe	2
8	male	62	17	AVM right temporo polar	r		x	x	severe	3
9	male	70	6	Stem ganglia left	r	x		x	moderate	1
10	male	54	3	Brain infarct MCA left	r	x	x		mild	1
11	male	50	3	Arteria cerebri left	r			x	moderate	1
12	male	57	5	Arteria cerebri media right				x	severe	1
13	male	34	48	Media infarct left	r	x			severe	3
14	male	75	22	Stem ganglia right	r				moderate	3
15	male	63	15	Media infarct left	r	x	x	x	mild	2
16	female	44	2	Media infarct right	r	x	x		mild	1
17	female	56	3	Media infarct left	r	x		x	moderate	1
18	female	80	20	Media infat left	r	x	x	x	severe	3

No	gender	age	months post-stroke	location of lesion	right-/ left handed	musical exp.	robotic rehab exp.	gaming exp.	grade of severity	months post-stroke grouping
19	female	46	17	Media infarct left	r			x	severe	3
20	female	62	22	Brain stem right	r	x	x	x	severe	3
21	male	57	3	Pons infarct caudal right	r			x	severe	1
22	male	57	28	Media infarct right	r		x	x	moderate	3
23	male	57	15	Media infarct right	r			x	severe	2
24	male	43	12	Stem ganglia right	r		x	x	severe	1
25	male	41	11	Arteria cerebri media left	r				severe	1
26	Female	30	44	Media infarct right	r		x	x	severe	3
27	male	58	84	Pons infarct	l		x	x	severe	3
28	male	50	18	Media infarct right	r			x	moderate	3
29	male	30	15	Media infarct left	l			x	mild	3
30	male	69	3	Media infarct right	r		x	x	mild	1
31	male	57	5	Media infarct right	r	x	x	x	moderate	1
32	male	33	13	AVW left thalamic	l			x	severe	2
33	female	68	15	Media infarct left	r	x		x	severe	3
34	female	15	10	Fronto parietal right	r	x	x	x	severe	2

4 b) Overall patient characteristics			
gender	mean age	months post-stroke	severity
m=22; f=11	51,67 years sd = 15,91	mean amount of months post-stroke= 14,971; sd = 16,412	severe: 18 moderate: 8 mild: 8

Table 4: a) Individual patient characteristics, b) Overall patient characteristics

Function					
test	target	test description	subjects	time point	outcome parameters
Box and Block Test (BBT)	manual/finger dexterity	grasp one block after the other as fast as possible and transport from one side to the other; (no throwing/ passing over the wooden wall)	N=34	T0, T2	n (amount of blocks)
Nine Hole Peg Test (NHPT)	manual/finger dexterity	grasp one peg after the other; one peg at a time only; place pegs into holes & back to big hole as fast as possible; (peg-drop = mistake)	N=16	T0, T2	d (time in s); p (amount of mistakes)
Grip Force (GF)	grip force	grasp dynamometer vertically measures grip with maximal force twice	N=34	T0, T2	f (N)
F0, F ext	F0: single finger forces in rest F ext: maximal single finger forces in extension	measures hand forces in predefined position in rest (mean of all single fingers: F0) and in maximal extension (mean of all fingers: F ext) with "Amadeo"-hand function trainer (tyromotion GmbH)	N=34	T0, T2	F0 (N) F ext (N)
Motivation					
test	target	test description	subjects	time point	outcome parameters
Intrinsic Motivation Inventory (IMI)	Multi-Dimensional Rating Scale on 7 sub-items reflecting intrinsic motivation	interest/ enjoyment, perceived competence, perceived choice, relaxation, value/ usefulness, man-machine relation rated with Liktert-scale (1:7); 1: no agreement, 7: full agreement;	N=34	T1	Likert Scale (1:7)
Experienc e Samplings (ES)	self-rating on mental states during therapeutic intervention via Visual Analogue Scale (-10: +10)	mood, involvement, motivation, fun rated with VAS (-10: +10).	N=34	T1	Visual Analogue Scale (-10:+10)
Perceived Size of Effort (PSE)	self-rating on perceived size of effort via Borg Scale (1:20)	perceived size of effort	N=34	T1	Borg Scale (1:20)
Goal Attainmen t Scale (GAS)	goal impact and attainment	self-rating on reaching rehabilitation goals within predefined time frame via a 5 point scale	N=34	T2,T3	(-2: +2)

Table 5: Overview Assessments on function and motivation

4.2 Therapy structure

In a first meeting, all patients were informed about the goals and risks of the study participation as well as the study procedure. After signing the participation agreement, every patient underwent the same study protocol either as a participant in the control-group or the sound-group. All subjects were assigned to the control-group or the sound-group. As the study period was limited to a time frame of one year with an uncertain number of study participants, the assignment to one of the two groups was not randomized. Instead, the first 15 subjects were assigned to the control-group, and from subject 14 upwards and up from subject 14 to the sound-group. This approach was chosen to ensure an adequate sample size for each group. Both groups received robot-assisted hand function training (RT) additional to conventional treatment.

The control-group (n=14) performed RT without sound, the sound-group (n=20) received RT extended with specified musical stimulation consisting of a polymetric music piece and game-related sound feedback. All subjects received nine robotic hand therapy sessions each 45 minutes long. Two additional sessions for assessments on function were performed before the treatment (T0) and after the ninth session (T2). Tests on motivation were performed during and after the sixth session (T1) and another test two months after the last therapy session (T3) (see Fig. 24).

The therapy structure was subdivided into five parts: 1) assessment, 2) passive training, 3) active training, 4) passive training, 5) assessment (see Fig.28).

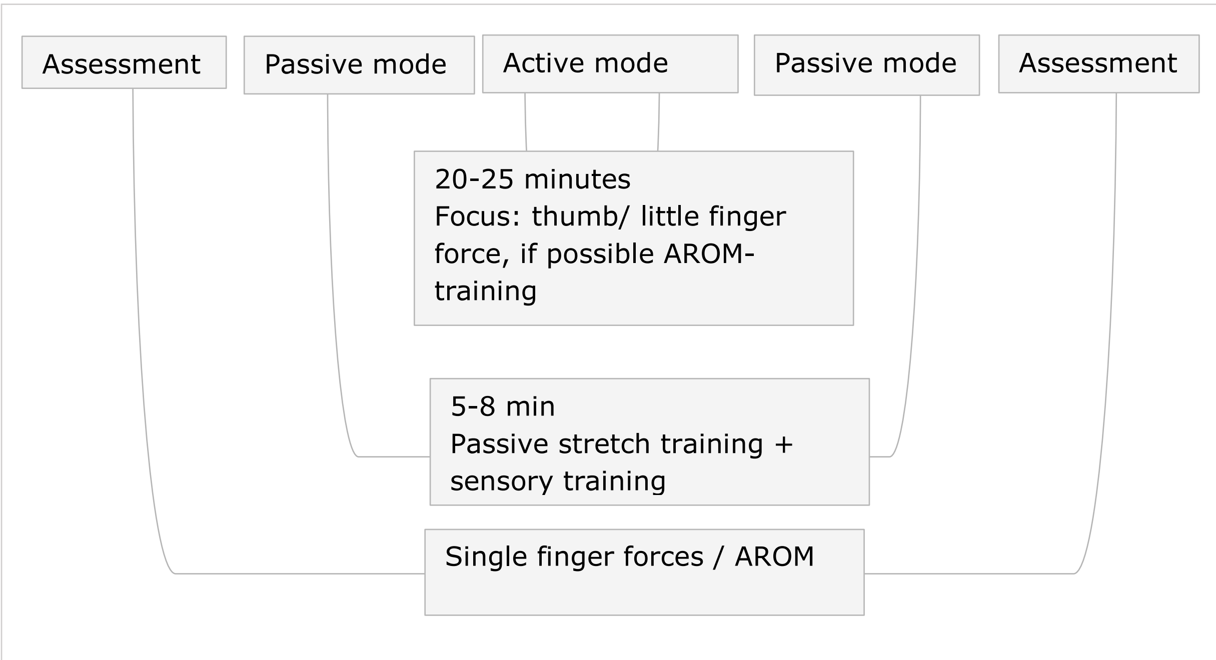


Fig. 28: Therapy Structure: 1) and 5) assessment of single finger forces in rest and maximal extension (F0/ F ext); 2) and 4) passive movement training, 3) active gaming.

In 1) and 5) single finger forces in rest (F0) and maximal extension force (F ext) as well as the active range of motion (AROM) of the hand from flexion to extension were recorded. In 2) and 4) 5-8 minutes passive training was performed. In 3) patients trained actively by playing games for 20-25 minutes. Depending on a patient's ability to extend the fingers, the training was either performed in the isometric task mode (severe cases) or in the active-range-of-motion-mode (AROM) (moderate to mild cases). A special focus was directed at given on thumb and little finger, based on the fact that these two fingers are least connected in manners of pathological muscle synergies. Extension of the thumb and the little finger at once shows the lowest level of co-activation compared to other finger combinations.

Statistical evaluation

Function: As endpoint in the domain function, the Box and Block Test was chosen. This test was performed by all 34 patients included in the clinical study (see Table 6).

Outcome	Box and Block Test - mean amount of blocks after 9 therapy sessions robot-assisted hand therapy (control-group versus sound-group)
F- H0= μ1= μ2	The control-group and the sound-group show no significant difference in the mean n (T2-T0) in BBT.
F- H1= μ1 ≠ μ2	The control-group and the sound-group show a significant difference in the mean n (T2-T0) in BBT.
Two intervention groups, primary endpoint	BBT- mean n (T2-T0)
Planned evaluation	co-variant analysis, power analysis based on t-test

Table 6: Overview of statistical evaluation; (F- H0: Function- null hypothesis; F- H1: function alternative hypothesis with μ1: mean n (T2-T0) sound-group; μ2: mean n (T3-T0) control-group).

For the suggested clinical study a sample size of at least 7 subjects per group (total 14 subjects) was computed as a requirement. The sample size calculation was based on computations related to the Altman's Nomogram for power calculations based on assumptions of a two-sided t-test with significance level of 0,05 and a power of 80% for a difference of two independent means of 22,5 and 29,5 blocks per BBT with a shared standard deviation of 5,5. The sample size was based on the following assumptions: The mean amount of blocks achieved in the Box and Block Test post-stroke is known to range between 24 ± 21, whereby after a treatment circle of 5 weeks it is known to range between 36 ± 23 (Higgins et al. 2005). The mean of border values of each mean (baseline and post-treatment) were taken and a shared standard deviation of 5,5 was computed. To have a power of 80% at the significance level 0,05, 14 patients are needed to be compared in two groups with each 7 test subjects. The calculated standard deviation relates to the mean of both computed means (baseline, after treatment) and has a value of 1,2727. Taking into account potential drop-outs, the sample size was adjusted upward from 7 to 10 per group (see Table 7).

Level of significance	0,05
Power	80%
Effect of treatment BBT	BBT: mean amount of blocks (n) Baseline (T0): mean (24± 21)= 22,5; sd =2,12; After treatment (T2): mean (36±23)= 29,5; sd = 9,19
Standard deviation	sd: mean 5,65
Subjects needed	14 (7 vs. 7)
t-test for two independent means	analysis of covariance (ANCOVA)

Table 7: Overview of level of significance, statistical power, treatment effect, sd: standard deviation, subjects needed, t-test for two independent means.

Motivation: As endpoint in the domain motivation, the Intrinsic Motivation Inventory (IMI) was chosen (see Table 8). This test was performed by all 34 patients included in the clinical study. The IMI consists of several sub-items that are related to intrinsic motivation. In our case, these sub-items were: interest/ enjoyment, perceived competence, perceived choice, relaxation, value/usefulness, man-machine relation. Each of these items is designed along statement - sentences that are rated on a Likert-Scale ranging from 1 for "no agreement at all" to 7 for "full agreement". The Likert-scale is an ordinal scale.

For the evaluation of an ordinal scale, nonparametric tests are recommended as well as parametric tests (Norman 2010). To evaluate data of IMI in our case, parametric tests were carried out. According to Sullivan and Artino 2013, this approach can be used when an adequate sample size with at least 5-10 subjects per group is given and when the data is nearly normally distributed. Also King et al. 2013 argued that the Likert Scale ranging from 1:7 can be analyzed with parametrics when the presumptions of a data-screening showing normality, homogeneity, and independence are fulfilled (King et al. 2013; Sullivan, Artino 2013). Norman 2010, reviewed the research discussion on statistical evaluation strategies of Likert Scales with either parametric or non-parametric tests. As Norman 2010 concluded, even a small sample size of unequal variances with a non-normal distribution can be evaluated with parametric tests in a robust manner. His main argument is that nonparametric tests often lack robustness which is provided by parametric tests (Norman 2010). Regardless of this, to ensure that the data would fulfil these presumptions, a data-screening was performed on the overall- study population in addition to parametric tests. (Plots showing the median and modus values of the overall- study population are presented in the Appendix 9.2).

Outcome	Intrinsic Motivation Inventory- mean rating on each sub-item (interest/ enjoyment, perceived competence, relaxation, perceived choice, value/usefulness, man-machine-relation) of IMI (1:7) in 6th therapy session of robot-assisted hand therapy (control-group versus sound-group)
M- H0= $\mu1 = \mu2$	The control-group and the sound-group show no significant difference in the mean rating of each sub-item of IMI (1:7).
M- H1= $\mu1 \neq \mu2$	The control-group and the sound-group show a significant difference in the mean rating of each sub-item of IMI (1:7).
Two intervention groups, primary endpoint	mean rating on Likert-Scale of each IMI-sub-item
Planned evaluation	t-test for 2 independent means of each sub-item of IMI

Table 8: Overview of statistical evaluation; (M- H0: Motivation- null hypothesis; M- H1: Motivation- alternative hypothesis with μ1: mean rating on each sub-item (interest/ enjoyment, perceived competence, relaxation, perceived choice, value/usefulness, man-machine-relation) of IMI (1:7) of sound-group; μ2: rating on each subitem (interest/ enjoyment, perceived competence, relaxation, perceived choice, value/usefulness, man-machine-relation) of IMI (1:7) of control-group).

4.3 Results

4.3.1 Function/Primary outcome measures

Results from Box and Block Test (BBT) Subgroup A (see Fig. 29)

The t-test for 2 independent means of the mean amount of n (T2-T0) gained with BBT was performed to compare whether severe cases in the sound-group or the control-group showed significant differences in BBT results. The t-value of 2,402074 and the p-value of 0,029704 indicate that the control-group gained significantly higher results in BBT than the sound-group at $p < 0,05$. This means that with a probability of 95%, training without sound will increase BBT-outcome measures significantly after nine sessions of training compared to sound-assisted training for severe cases of hand paresis post-stroke.

The t-test for 2 independent means of the mean amount of n (T2-T0) gained with BBT was computed to compare whether moderate cases in the sound-group or the control-group showed significant differences in the BBT results. The t-value of 2,310987 and the p-value of 0,060187 showed that moderate cases of hand paresis achieved significantly more blocks in the sound-group than the control-group at a level of significance of $p < 0,1$, but not at $p < 0,05$. This means that with a probability of 90%, sound-assisted training will increase BBT-outcome measures significantly after nine sessions of training compared to training without sound for moderate cases of hand paresis post-stroke.

The t-test for 2 independent means of the mean amount of n (T2-T0) gained with BBT was computed to compare whether mild cases in the sound-group or control-group showed significant differences in BBT results. The t-value of 1,911484 and the p-value of 0,097544 showed that the sound-group achieved significantly more blocks after therapy than the control-group at $p < 0,1$, but not at $p < 0,05$. This means that with a probability of 90%, sound-assisted training will increase BBT-outcome measures significantly after nine sessions of training compared to training without sound for mild cases of hand paresis post-stroke.

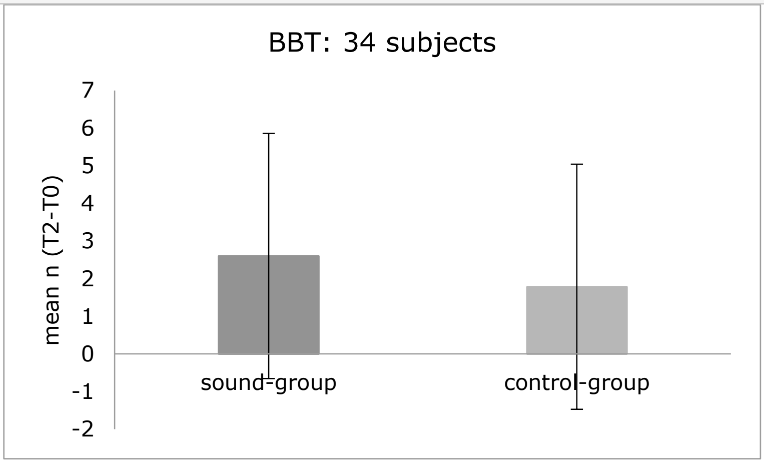
Results from Box and Block Test (BBT) Subgroup B (see Fig. 29)

The t-test for 2 independent means of the mean amount of n (T2-T0) gained with BBT was computed to compare whether cases in the phase 2-6 months post-stroke in the sound-group or the control-group showed significant differences in BBT results. The t-value of 0,046362 and the p-value of 0,963633 showed that there was no significant difference at $p < 0,1$. This means that with a probability of 90%, there will be no significant difference in BBT-outcomes dependent on sound-assisted training or training without sound in cases in the phase 2-6 months post-stroke.

The t-test for 2 independent means of the mean amount of n (T2-T0) gained with BBT was performed to compare whether cases in the phase >12 months post-stroke in the sound-group or the control-group showed significant differences in BBT results. The t-value of 1,137815 and the p-value of 0,277406 showed that there was no significant difference at $p < 0,1$. This means that with a probability of 90%, there will be no significant difference in BBT-outcomes dependent on sound-assisted training or training without sound in cases in the phase >12 months post-stroke.

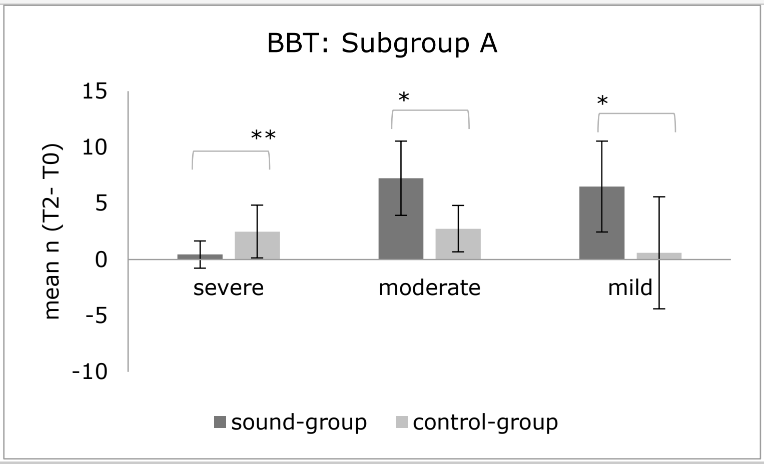
Results Box and Block Test all subjects/ subgroup A/ subgroup B- Plots:

Results BBT of all 34 subjects:



BBT: 34 subjects	sound-group (n=20) vs. control-group (n=14)
sound-group: mean n (T2-T0)/ sd	2,6
	4,50998891
control-group: mean n (T2-T0)/ sd	1,78571429
	3,25529396

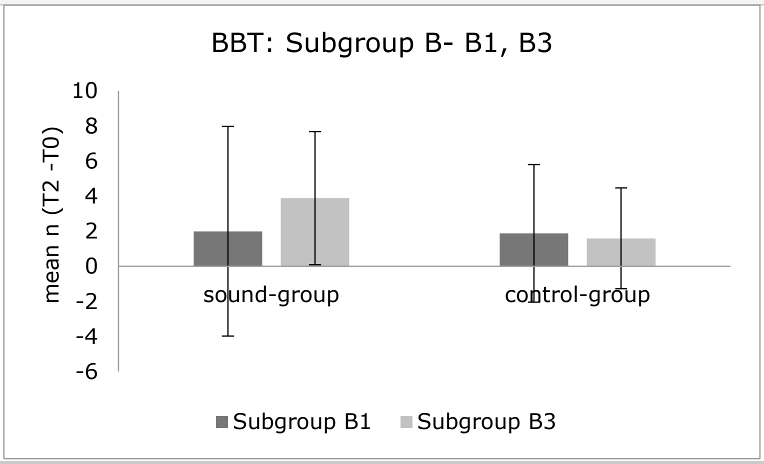
Results BBT of Subgroup A:



Subgroup A	severe sound-group (n=11) vs. control-group (n=6)	moderate sound-group (n=4) vs. control-group (n=4)	mild sound-group (n=4) vs. control-group (n=4)
sound-group: mean (T2-T0)/ sd	0,45454545	7,25	6,5
	1,21355975	3,30403793	4,04145188
control-group: mean (T2-T0)/ sd	2,5	2,75	0,6
	2,34520788	2,06155281	5,38052042

T,P, p	T = 2,402074 P = 0,029704 p < 0,05.	T = 2,310987 P = 0,060187 p < 0,10.	T = 1,911484 P = 0,097544 p < 0,10.

Results BBT of Subgroup B:



Subgroup B	B1: 2-6 months post-stroke; sound-group (n=8) vs. control-group (n=9)	B2: > 6 months < 12 months post-stroke; sound-group (n=3)	B3: >12 months post-stroke; sound-group (n=9) vs. control-group (n=5)
sound-group: mean n (T2-T0)/ sd	0,46875	-	3,75
	2,465611703		3,575711717
control-group: mean n (T2-T0)/ sd	0,027777778	-	5,35
	1,227576655		5,781435808

Fig. 29: Results from Box and Block Test (BBT) all subjects/ subgroup A/ subgroup B

(Results secondary outcome measures see 9. Appendix/ 9.2. a, b)

4.3.2 a) Motivation/Primary outcome measures

Results Intrinsic Motivation Inventory (IMI)- all sub-items- all subjects (see Fig. 33)
The t-test for 2 independent means of all subjects was performed on all sub-items to compare whether the sound-group or the control-group showed significant differences. Results indicate that sound-extended robotic hand function training post-stroke increases ratings of the sub-items "interest/ enjoyment", "perceived competence", "relaxation" and "perceived choice" significantly ("interest/ enjoyment": T = 2,792593; P = 0,009677; p < 0,05/ "perceived competence": T = 2,502845; P = 0,02065; p < 0,05/ "relaxation": T = 2,188839; P = 0,040048; p < 0,05/ "perceived choice": T = 2,873479 ; P = 0,00798; p < 0,01). The sub-items "value" and "man-machine-relation" did not differ significantly depending on training conditions with or without sound. This means that with a probability of 95%, the sound-group rates the sub-items "interest/ enjoyment", "perceived competence" and "relaxation" higher than the control-group. Furthermore, with a probability of 90%, the sound-group rates "perceived choice" higher than the control-group.
Results IMI- sub-item "interest"- all subjects (see Fig. 33)
The t-test for 2 independent means of the item "interest/ enjoyment" was computed to compare whether the sound-group or the control-group showed significant differences. The t-value of 2,792593 and the p-value of 0,009677 showed that "interest/ enjoyment" was rated significantly higher in the sound-group than in the control-group at p < 0,05. This means that with a probability of 95%, the sound-group rates "interest/ enjoyment" higher than the control-group.
Results IMI- sub-item "perceived competence"- all subjects (see Fig. 33)
The t-test for 2 independent means of the item "perceived competence" was computed to compare whether the sound-group or the control-group showed significant differences. The t-value of 2,502845 and the p-value of 0,020651 showed that "perceived competence" was rated significantly higher in the sound-group than in the control-group at p < 0,05. This means that with a probability of 95%, the sound-group rates "perceived competence" higher than the control-group.
Results IMI- sub-item "relaxation"- all subjects (see Fig. 33)

The t-test for 2 independent means of the item “relaxation” was computed to compare whether the sound-group or the control-group showed significant differences. The t-value of 2,188839 and the p-value of 0,040048 showed that “relaxation” was rated significantly higher in the sound-group than in the control-group at $p < 0{,}05$. This means that with a probability of 95%, the sound-group rates “relaxation” higher than the control-group.

Results IMI- sub-item “perceived choice”- all subjects (see Fig. 33)

The t-test for 2 independent means of the item “perceived choice” was computed to compare whether the sound-group or the control-group showed significant differences. The t-value of 2,873479 and the p-value of 0,00798 showed that “perceived choice” was rated significantly higher in the sound-group than in the control-group at $p < 0{,}05$. This means that with a probability of 95%, the sound-group rates “perceived choice” higher than the control-group.

Results IMI- sub-item “value/ usefulness”- all subjects (see Fig. 33)

The t-test for 2 independent means of the item “value/ usefulness” was computed to compare whether the sound-group or the control-group showed significant differences. The t-value of 1,549193 and the p-value of 0,145329 showed that “value/ usefulness” was not rated significantly higher in the sound-group or in the control-group at $p < 0{,}05$ or at $p < 0{,}01$. This means that there is no difference between ratings of the control- or the sound-group concerting the item “value/ usefulness”.

Results IMI- sub-item “man-machine-relation”- all subjects (see Fig. 33)

The t-test for 2 independent means of the item “man-machine-relation” was computed to compare whether the sound-group or the control-group showed significant differences. The t-value of 0,026262 and the p-value of 0,979242 showed that “man-machine relation” was not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- or the sound-group concerning the item “man-machine relation”.

Results IMI- Subgroup A- sub-item “interest/ enjoyment” (see Fig. 33)

The t-test for 2 independent means of the item “interest/ enjoyment” was computed to compare whether the sound-group or the control-group within subgroup A- severe cases showed significant differences. The t-value of 1,76617 and the p-value of 0,090086 showed that “interest/ enjoyment” was rated significantly higher in the sound-group than in the control-group at $p < 0{,}10$. This means that with a probability of 90%, sound will increase ratings of “interest/ enjoyment” in robotic hand function training in patients suffering from a severe grade of a hand paresis.

The t-test for 2 independent means of the item "interest/ enjoyment" was furthermore computed to compare whether the sound-group or the control-group within subgroup A- moderate cases or in mild cases showed significant differences. For moderate cases, the t-value of 0.888265 and the p-value of 0,385506, and for mild cases the t-value of 1,439689 and the p-value of 0,165425 showed that ratings of "interest/ enjoyment" did not differ significantly between sound-group and control-group.

Results IMI- Subgroup A- sub-item "perceived competence" (see Fig. 33)

The t-test for 2 independent means of the item "perceived competence" was computed to compare whether the sound-group or the control-group within subgroup A- severe cases, moderate cases or in mild cases showed significant differences. For severe cases the t-value of 1,100964 and the p-value of 0,283987, for moderate cases the t-value of 0,759793 and the p-value of 0,455824, and for mild cases the t-value of 0,530883 and the p-value of 0,602368 showed that ratings of "perceived competence" did not differ significantly between sound-group and control-group.

Results IMI- Subgroup A- sub-item "relaxation" (see Fig. 33)

The t-test for 2 independent means of the item "relaxation" was computed to compare whether the sound-group or the control-group within subgroup A- severe cases showed significant differences. The t-value of 1,910402 and the p-value of 0,070526 showed that "relaxation" was rated significantly higher in the sound-group than in the control-group at $p < 0{,}01$. This means that with a probability of 90%, sound will increase ratings on "relaxation" in robotic hand function training in patients suffering from a severe grade of a hand paresis.

The t-test for 2 independent means of the item "relaxation" was furthermore computed to compare whether the sound-group or the control-group within subgroup A- moderate cases or in mild cases showed significant differences. For moderate cases the t-value of 0,920741 and the p-value of 0,368729, and for mild cases the t-value of 0,152626 and the p-value of 0,880223 showed that ratings of "relaxation" did not differ significantly between sound-group and control-group.

Results IMI- Subgroup A- sub-item "perceived choice" (see Fig. 33)

The t-test for 2 independent means of the item "perceived choice" was computed to compare whether the sound-group or the control-group within subgroup A- severe cases showed significant differences. The t-value of 2,428111 and the p-value of 0,024738 showed that "perceived choice" was rated significantly higher in the sound-group than in the control-group at $p < 0{,}05$. This means that with a probability of

95%, sound will increase ratings of “perceived choice” in robotic hand function training in patients suffering from a severe grade of a hand paresis.

The t-test for 2 independent means of the item “perceived choice” was furthermore computed to compare whether the sound-group or the control-group within subgroup A- moderate cases or in mild cases showed significant differences. For moderate cases the t-value of 0,020961 and the p-value of 0,983475, and for mild cases the t-value of 0,951049 and the p-value of 0,355726 showed that ratings of “perceived choice” did not differ significantly between sound-group and control-group in patients suffering from moderate or mild grades of a hand paresis.

Results IMI- Subgroup A- sub-item “value/ usefulness” (see Fig. 33)

The t-test for 2 independent means of the item “value/ usefulness” was computed to compare whether the sound-group or the control-group within subgroup A - severe cases, moderate cases or in mild cases showed significant differences. For severe cases the t-value of 1,665333 and the p-value of 0,119747, for moderate cases the t-value of 0,762402 and the p-value of 0,463424, and for mild cases the t-value of 0,860425 and the p-value of 0,411889 showed that ratings of “value/ usefulness” did not differ significantly between sound-group and control-group in patients suffering from severe, moderate or mild grades of a hand paresis.

Results IMI- Subgroup A- sub-item “man-machine-relation” (see Fig. 33)

The t-test for 2 independent means of the item “man-machine-relation” was computed to compare whether the sound-group or the control-group within subgroup A - severe cases showed significant differences. The t-value of 2,847867 and the p-value of 0,008155 showed that “man-machine-relation” was rated significantly higher in the control-group than in the sound-group at $p < 0,01$. This means that with a probability of 90%, the control-group rates the sub-item “man-machine-relation” higher than the sound-group.

The t-test for 2 independent means of the item “man-machine-relation” was furthermore computed to compare whether the sound-group or the control-group within subgroup A - moderate cases or in mild cases showed significant differences. For moderate cases the t-value of 1,396391 and the p-value of 0,175379, and for mild cases the t-value of 0,869014 and the p-value of 0,397688 showed that ratings of “man-machine-relation” did not differ significantly between sound-group and control-group.

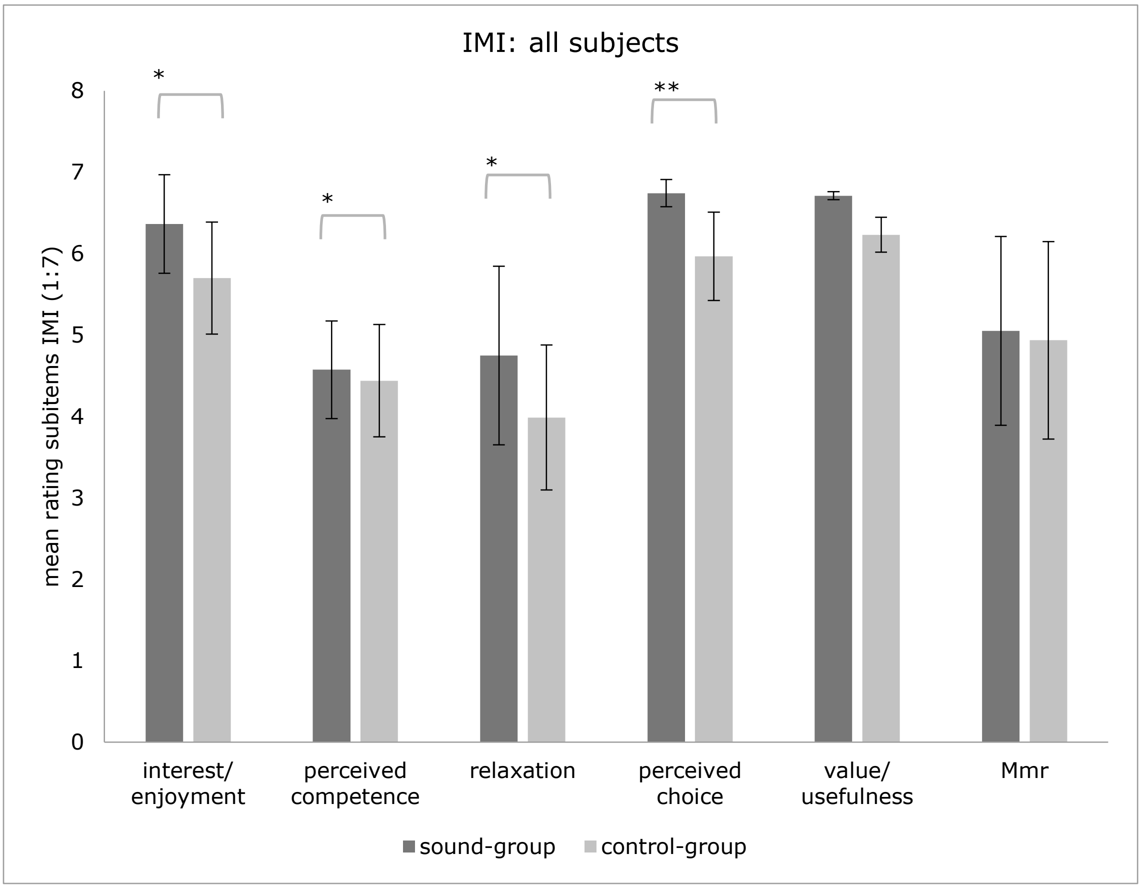
Results IMI- Subgroup B: B1, B3- sub-item “interest/ enjoyment” (see Fig. 33)

The t-test for 2 independent means of the item “interest/ enjoyment” was computed to compare whether the sound-group or the control-group within subgroup B1 or subgroup B3 showed significant differences. The t-value of subgroup B1: 0,4053 or subgroup B3: -0,44996 and the p-value of subgroup B1: 0,688229 or subgroup B3: 0,656781 showed that ratings of “interest/ enjoyment” did not differ significantly between sound-group and control-group.
Results IMI- Subgroup B: B1, B3- sub-item “perceived competence” (see Fig. 33)
The t-test for 2 independent means of the item “perceived competence” was computed to compare whether the sound-group or the control-group within subgroup B1 or subgroup B3 showed significant differences. The t-value of subgroup B1: 0,0484 or subgroup B3: -1,5908 and the p-value of subgroup B1: 0,961781 or subgroup B3: 0,126598 showed that ratings of “perceived competence” did not differ significantly between sound-group and control-group.
Results IMI- Subgroup B: B1, B3- sub-item “relaxation” (see Fig. 33)
The t-test for 2 independent means of the item “relaxation” was computed to compare whether the sound-group or the control-group within subgroup B1 or subgroup B3 showed significant differences. The t-value of subgroup B1: -0,40451 or subgroup B3: 0,0208 and the p-value of subgroup B1: 0,688229 or subgroup B3: 0,983587 showed that ratings of “relaxation” did not differ significantly between sound-group and control-group.
Results IMI- Subgroup B: B1, B3- sub-item “perceived choice” (see Fig. 33)
The t-test for 2 independent means of the item “perceived choice” was computed to compare whether the sound-group or the control-group within subgroup B1 or subgroup B3 showed significant differences. The t-value of subgroup B1: -0,17891 or subgroup B3: -1,99873 and the p-value of subgroup B1: 0,859643 or subgroup B3: 0,06097 showed that ratings of “perceived choice” did not differ significantly between sound-group and control-group.
Results IMI- Subgroup B: B1, B3- sub-item “value/ usefulness” (see Fig. 33)
The t-test for 2 independent means of the item “value/ usefulness” was computed to compare whether the sound-group or the control-group within subgroup B1 or subgroup B3 showed significant differences. The t-value of subgroup B1: -0,21442 and the p-value of subgroup B1: 0,832387 showed that ratings of “value/ usefulness” did not differ significantly between sound-group and control-group.

The t-value of 3,03109 and p-value of 0,00898 in subgroup B3 showed a significant difference at p < 0,05. This means that with a probability of 95%, ratings of "value/ usefulness" are higher in the sound-group than in the control-group in patients >12 months post-stroke.
Results IMI- Subgroup B: B1, B3 – sub-item "man-machine-relation" (see Fig. 33)
The t-test for 2 independent means of the item "man-machine-relation" was computed to compare whether the sound-group or the control-group within subgroup B1 or subgroup B3 showed significant differences. The t-value of subgroup B1: 0,7782 or subgroup B3: -0,50721 and the p-value of subgroup B1: 0,442754 or subgroup B3: 0,616281 showed that ratings of "man-machine-relation" did not differ significantly between sound-group and control-group.

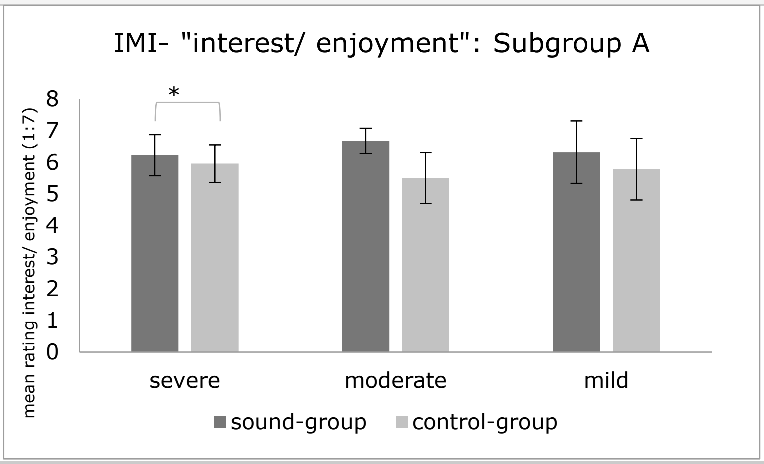
Results Intrinsic Motivation Inventory- all subjects/ subgroup A/ B- Plots:

Results Intrinsic Motivation Inventory (IMI) of all subjects and all sub-items:

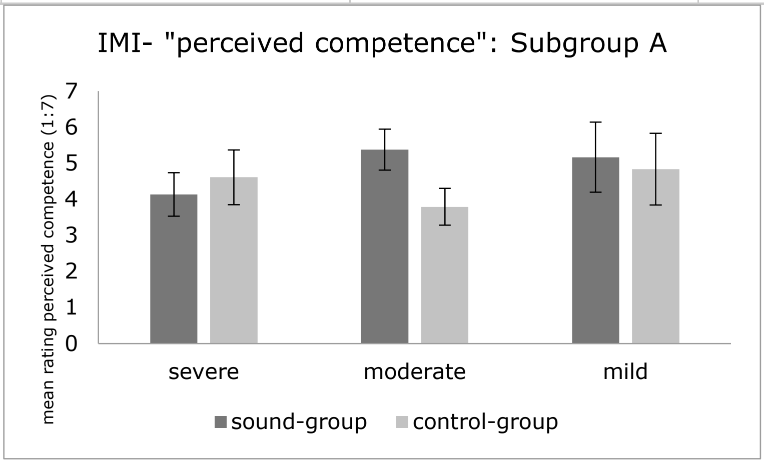


all subjects	interest/ enjoyment	perceived competence	relaxtation	perceived choice	value/ usefulness	Mmr
sound-group (n=20): mean/sd	6,36428571	4,575	4,75	6,74285714	6,7125	5,05357143
	0,68813687	0,68870874	0,89032976	0,54219437	0,2132913	1,21232919
control-group (n=14): mean/ sd	5,70015699	4,44047619	3,98809524	5,96938776	6,2321428 6	4,9375
	0,60602137	0,59812206	1,09772492	0,16690459	0,0478713	1,15979163
T,P, p	T = 2,792593 P = 0,009677 p < 0,05	T =2,502845 P = 0,02065 p < 0,05	T =2,188839 P =0,040048 p < 0,05	T =2,873479 P = 0,00798 p < 0,01		

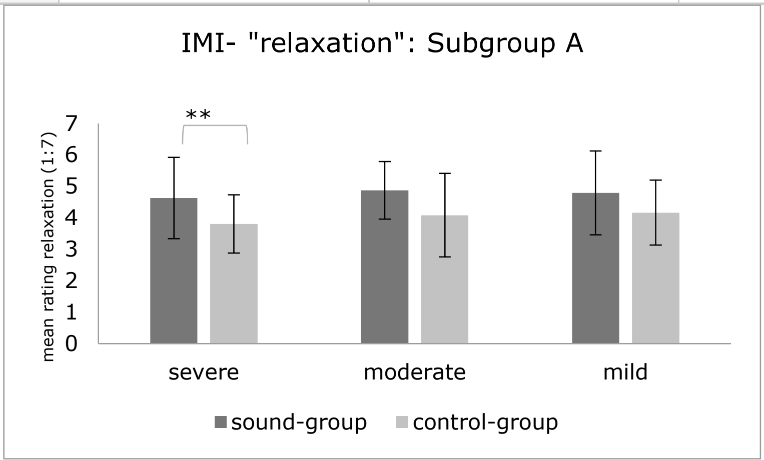
Results Intrinsic Motivation Inventory (IMI), subgroup A: subitems separated:



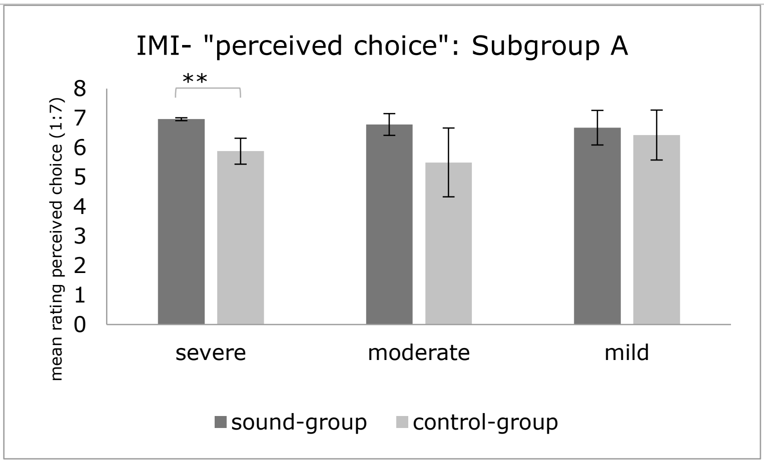
Subgroup A	severe: sound-group (n=12) vs. control-group (n=5)	moderate: sound-group (n=4) vs. control-group (n=4)	mild: sound-group (n=4) vs. control-group (n=5)
sound-group: mean rating „interest/ enjoyment"/ sd	4,13333333	5,375	5,16666667
	0,60553007	0,56457949	0,97039511
control-group: mean rating „interest/ enjoyment"/ sd	4,61111111	3,79166667	4,83333333
	0,75767676	0,51031036	0,99582462
T, P, p	T = 1,76617 P = 0,090086 p < 0,01		



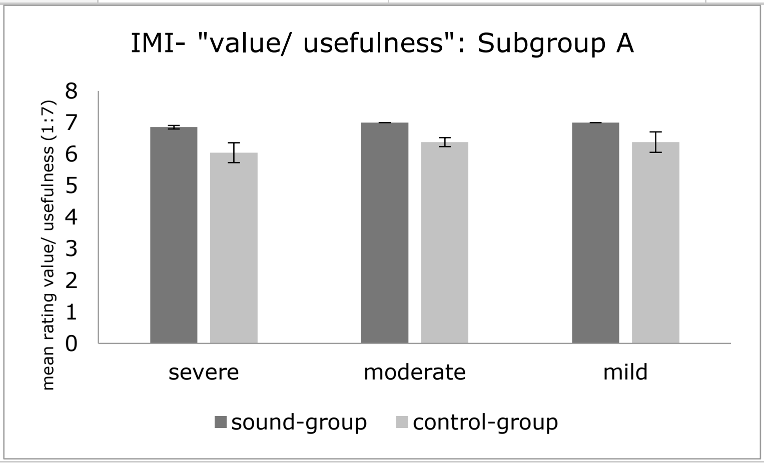
Subgroup A	severe: sound-group (n=12) vs. control-group (n=5)	moderate: sound-group (n=4) vs. control-group (n=4)	mild: sound-group (n=4) vs. control-group (n=5)
sound-group: mean rating „perceived competence“/ sd	4,13333333	5,375	5,16666667
	0,60553007	0,56457949	0,97039511
control-group: mean rating „perceived competence“/ sd	4,61111111	3,79166667	4,83333333
	0,75767676	0,51031036	0,99582462



Subgroup A	severe: sound-group (n=12) vs. control-group (n=5)	moderate: sound-group (n=4) vs. control-group (n=4)	mild: sound-group (n=4) vs. control-group (n=5)
sound-group: mean rating „relaxation“/ sd	4,63333333	4,875	4,79166667
	1,29254271	0,91855865	1,33619485
control-group: sound-group: mean rating „relaxation“/ sd	3,80555556	4,08333333	4,16666667
	0,92746169	1,32916014	1,03279556
T, P, p	T = 1,910402 P = 0,070526 p < 0,01		

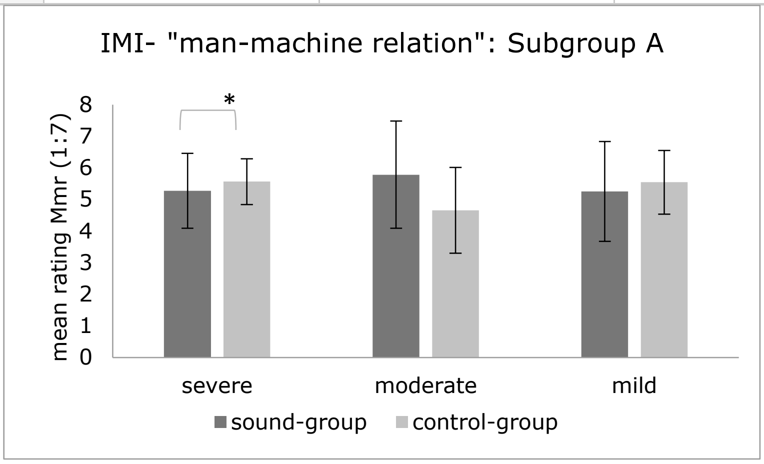


Subgroup A	severe: sound-group (n=12) vs. control-group (n=5)	moderate: sound-group (n=4) vs. control-group (n=4)	mild: sound-group (n=4) vs. control-group (n=5)
sound-group: mean rating „ perceived choice"/ sd	6,97142857	6,78571429	6,67857143
	0,048795	0,36596253	0,59009684
control-group: mean rating „ perceived choice"/ sd	5,88095238	5,5	6,42857143
	0,43794856	1,16240719	0,85042006
T, P, p	T = 2,428111 P = 0,024738 p < 0,05		



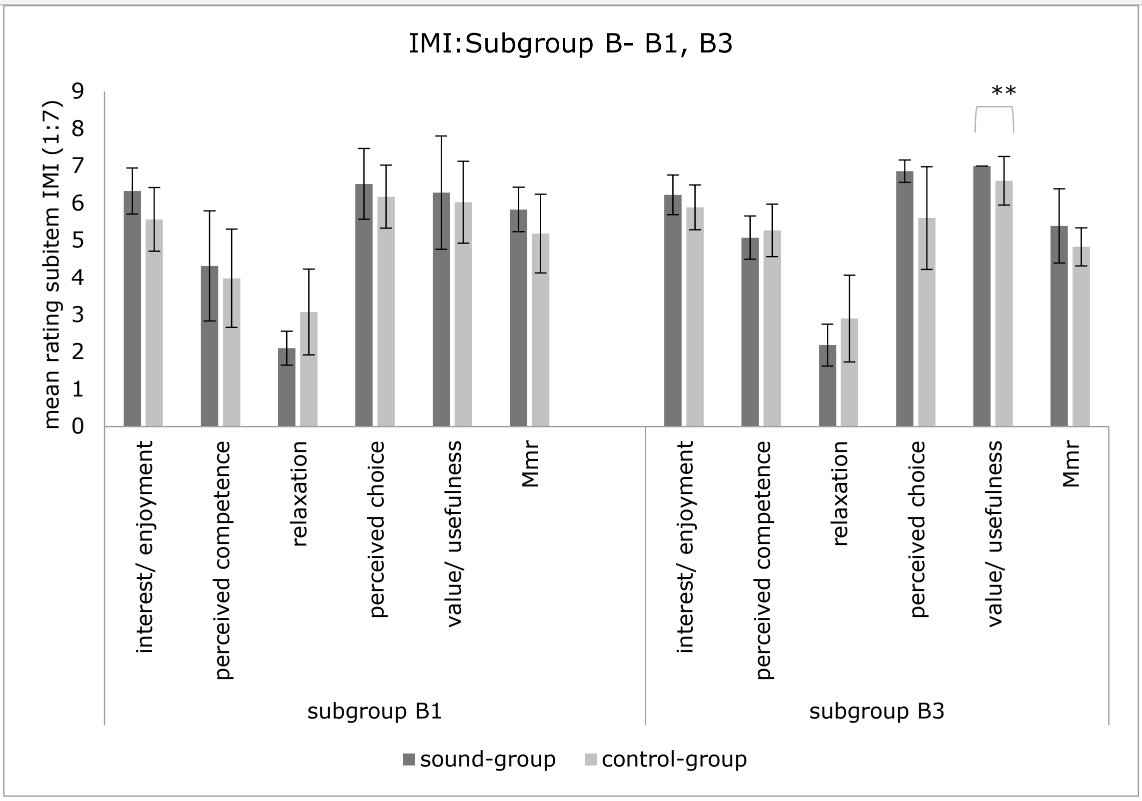
Subgroup A	severe: sound-group (n=12) vs. control-group (n=5)	moderate: sound-group (n=4) vs. control-group (n=4)	mild: s ound-group (n=4) vs. control-group (n=5)
sound-group: mean rating „value/ usefulness"/ sd	6,85	7	7
	0,05773503	0	0

control-group:	6,04166667	6,375	6,375
mean rating „value/ usefulness"/ sd	0,31549491	0,14433757	0,32274861



Subgroup A	severe: sound-group (n=12) vs. control-group (n=5)	moderate: sound-group (n=4) vs. control-group (n=4)	mild: sound-group (n=4) vs. control-group (n=5)
sound-group:	5,275	5,78125	5,25
mean rating „man-machine-relation"/ sd	1,18532696	1,69788471	1,58113883
control-group:	5,5625	4,65625	5,54166667
mean rating „man-machine-relation"/ sd	0,7234041	1,35579115	1,00519484
T, P, p	T = 2,847867 P = 0,008155 p < 0,01		

Results Intrinsic Motivation Inventory (IMI), subgroup B: subitems separated:



Subgroup B1: 2-6 months post-stroke: sound-group (n=9) vs. control-group (n=5)						
	interest/ enjoyment	perceived competence	relaxation	perceived choice	value/ usefulness	man-machine-relation
sound-group: mean; sd	6,321428571	4,3125	2,104166667	6,517857143	6,28125	5,828125
	0,619178427	1,481198303	0,453710452	0,950487062	1,520323626	0,597380816
control-group: mean; sd	5,563492063	3,981481481	3,074074074	6,174603175	6,027777778	5,180555556
	0,855984667	1,318786386	1,15202452	0,847498654	1,100031565	1,057176205

Subgroup B3: >12 months post-stroke: sound-group (n=9) vs. control-group (n=5)						
	interest/ enjoyment	perceived competence	relaxation	perceived choice	value/ usefulness	man-machine-relation
sound-group: mean;	6,222222222	5,074074074	2,185185185	6,857142857	7	5,388888889

sd	0,535052501	0,583994334	0,561770789	0,303045763	0	0,994996161
control - group: mean; sd	5,885714286	5,266666667	2,9	5,6	6,6	4,825
	0,601019542	0,703167437	1,16428328	1,382839433	0,65192024	0,512347538
T, P, p					T= 3,03109 P= 0,00898 p < 0,01	

Fig. 33: Results Intrinsic Motivation Inventory (IMI)- all sub-items- all subjects/ subgroup A/ subgroup B

(Results secondary outcome measures see 9. Appendix/ 9.2. a, b)

4.3.3 Summary results function, motivation primary and secondary outcome measures

(Results secondary outcomes see 9. Appendix/ 9.2. a, b)

Test	all	severe	moderate	mild	B1	B2	B3
BBT	F- H0 √	control-group	sound-group	sound-group			
NHPT							
GF							
F0							
F ext		control-group					
IMI	M- F1 √						
interest/ enjoyment	sound-group	sound-group					
perceived competence	sound-group						
relaxation	sound-group	sound-group					
perceived choice	sound-group	sound-group					
value/ usefulness	M- H0 √						sound-group
Man-machine-relation	M- H0 √	control-group					
ES- mood							
ES- involvement							
ES- motivation							sound-group
ES- fun							
PSE							
GAS							

Summary of results showing significant differences between sound- and control-group:

Primary outcomes BBT/ IMI:

BBT:

- In the evaluation including all study participant (sound-group (n=20)/ control-group (n=14)) in the primary outcome measure of BBT no significant difference between sound- and control-group was found. Therefore, the Function-null hypothesis is true: F- H0: "The control-group and the sound-group show no

significant difference in the mean n (T2-T0) in BBT." IMI: • In the evaluation including all study participants (sound-group (n=20)/ control-group (n=14)) in the primary outcome measure, the ratings of sub-items "interest/ enjoyment", "perceived competence", "relaxation" and "perceived choice" of IMI were significantly higher in the sound-group than in the control-group. Therefore, the motivation- alternative hypothesis is true: M- H1: "The control-group and the sound-group show a significant difference in the mean rating IMI (1:7)." • For the sub-items "value" and "man-machine- relation" of IMI no significant difference was computed. Therefore, the motivation-null-Hypothesis is true: M- H0: "The control-group and the sound-group show a significant difference in the mean rating sub-item "value"/ "man-machine-relation" IMI (1:7). "
Subgroup Analysis A and B on primary outcome measures BBT/ IMI: BBT: • Results of subgroup A- severe cases showed that BBT was performed significantly better in the control-group than in the sound-group. • Mild and moderate cases performed the BBT significantly better in the sound-group compared to the control-group. IMI: • Results of subgroup A- severe cases showed that ratings of the sub-items "interest/ enjoyment", "relaxation" and "perceived choice" were rated significantly higher in the sound-group than in the control-group. • The sub-item "man-machine-relation" was rated significantly higher in subgroup A - severe cases by the control-group compared to the sound-group. • In subgroup B- the group B3 (> 12 months post-stroke) rated the sub-item "value" significantly higher in the sound-group compared to the control-group.
Secondary outcome measures- F ext/ ES: F ext: • Results of subgroup A - severe cases showed that F ext was signficantly higher in the control-group compared to the sound-group. ES: • Results of subgroup B analysis of the sub-item "motivation" of ES showed that the sound-group rated "motivation" significantly higher than the control-group.

4.4 Discussion

A two-armed clinical study was presented to investigate whether specified sound applied to robotic hand function training post-stroke has effects on function and motivation compared to training without sound. The primary and secondary outcome of the study will be discussed in this section. The results will be compared and then reviewed in relation to the results gained in the experiment series E1-4.

Discussion of primary outcome measure- function:

The primary outcome measure of the Box and Block Test (BBT) computed for 34 subjects revealed that nine sessions of robotic therapy for paretic hand post-stroke accompanied by specified sound compared to therapy without sound do not cause significant changes in the domain function. Therefore, function- null-hypothesis (F- H0) stating that control-group and sound-group show no significant difference in function can be confirmed, indicating that sound-extension does not increase functional advances compared to training without sound-extension.

There might be several reasons for this outcome such as the diversity of the overall study sample comprising patient profiles with severe to mild grades of hand paresis and different timespans between insult and study participation. In chapter 2.1.1 - 2.1.5, both grade of severity and timespan after insult were reported as important influential factors of a treatment effect. Patients suffering from a severe grade of hand paresis are known to advance slower, therefore making less functional improvement than patients with a grade of moderate or mild hand paresis (Krakauer 2005). The strongest therapy effects can be achieved in the early phase post stroke, more specifically within the first three months after insult, as a result of a boost in neuro-plastic processes such as spontaneous nerve sprouting and fast growing neural pathways triggered by training in this time window (Hesse et al. 2014; Krakauer 2005, 2006; Nudo 2013). Sale et al. 2014 performed a study in which subacute patients were treated with either intensive robot-therapy or conventional therapy. This study showed that robotic therapy resulted in better functional outcomes than conventional therapy, yet only for subacute patients (Sale et al. 2014; Hesse et al. 2014). It may be concluded, that the factor grade of severity and timespan between insult and study participation might have influenced the outcome in our study. Therefore, two subgroups were formed; one, based on the grade of severity (subgroup A), and the other on the time-span between insult and study participation (subgroup B). The results of subgroups A and B will be discussed in the section on secondary outcome measures.

A second reason for explaining the outcome might be that the sound-specification did not meet adequate needs to effectively increase functional outcome of robotic hand training post-stroke. The used polymetric music structure does not contain an obvious cue along a repeated dominant accent structure, but consists of multiple streams of meter with multiple accents. To investigate whether this was the reason for the outcome, further comparative studies need to be conducted in order to observe the effects of different sound-designs. Thereby, a simple metronome cue should be compared to polymetric metronome cues or to the effects of 2/2 meter music and polymetric music. In RAS, a simple metronome cue or march music, which has a clear accent structure on 2/2 is commonly used (Thaut et al. 2015). This music therapeutic technique has already led to positive outcomes in gait, speech and arm-training of neurological patients (Thaut et al. 2015; Bradt et al. 2013). The decision to use polymetric music instead of a metronome beat or march-music was based on theoretic assumptions which and drawn from conclusions from the practical test phase.

A third reason to explain the outcome is based on the results from E1-4 revealing that sound had a positive effect on performance in all four experiments (see Chapter 3.2). Performance qualities, however, reflect how an activity is executed in one specific situation in contrast to functional outcome, which is measured by comparing baseline measures with post-treatment measures. A better performance during sound-extended robotic training with patients does not necessarily have a functional effect. Therefore, the relation of performance and function would need to be studied separately. Malcom et al. 2009 studied the effects of RAS on performance during a reaching task of hemiparetic patients. The difference between performance and function was outlined while discussing this study in chapter 3.2 (Malcolm et al. 2009).

Discussion of primary outcome measure- motivation:

In the domain motivation, the Intrinsic Motivation Inventory (IMI) was used as a primary outcome measure to study whether specified sound applied to robot-hand therapy causes changes in motivation compared to the same training without sound. Results of IMI showed that sound had a significant positive effect on motivation. This was reflected in significant higher ratings of the IMI-sub-items "interest/ enjoyment", "perceived competence", "relaxation" and "perceived choice" by the sound-group compared to the control-group. The ratings of the sub-items "value/usefulness" and "man-machine-relation" were not different between sound- and control-group. The motivation-alternative hypothesis (M- H1) stating that control-group and sound-group show a significant difference in motivation concerning the sub-items "interest/ enjoyment", "perceived competence", "relaxation" and "perceived choice" was confirmed. The motivation- null-hypothesis (M- H0) stating that control-group and sound-group show no significant difference in motivation concerning "value/usefulness" and "man-machine-relation" was also confirmed.

The reasons for better ratings of the items "interest/ enjoyment", "perceived competence", "relaxation" and "perceived choice" by the sound-group compared to the control-group might lie in the motivational nature of music. Music as a motivating auditory environment was already discussed in chapter 2. Särkämö et al. 2008, reported that listening to music improves cognitive recovery as well as mood. The positive rating of "interest/ enjoyment" and "perceived competence" indicates a similar effect for sound applied to robot-assisted hand function training. Jäncke 2008, sees the emotional impact of music closely related to memory formation, a cognitive process. Therefore emotional modulation mediated by music might support learning (Jäncke 2008). It can be concluded that both mood and cognition may benefit from sound and its impact on motivation.

Another reason for the better ratings of IMI by the sound-group is possibly a result of an increased liking of the played polymetric piece due to repeated exposure. Over the time-course of six therapy sessions the same polymetric music piece was played at least 33 times, thereby it was becoming familiar to the patient. Pereira et al. 2011 conducted a study in which they observed the relation of familiarity and liking throughout a listening test. These authors showed that familiarity of a piece influenced emotional reactions positively (Pereira et al. 2011). Also van den Bosch et al. 2013 studied the relation of emotional arousal, pleasure and familiarity during music listening. They performed a study in which participants were presented unfamiliar music pieces and familiar music. The same music piece used as an unfamiliar piece was presented more often, thereby its familiarity was increased. The results showed that expectation and predictability increased emotional arousal (van den Bosch, Iris et al. 2013). It can be concluded that a repeated exposure to the polymetric piece of music may be responsible for positive ratings of "interest/ enjoyment", "perceived competence", "relaxation" and "perceived choice" by the sound-group.

The ratings of "value/usefulness" and "man-machine-relation" did not differ between the sound- and control-group. In the case of "value/usefulness", an explanation might be that the stimulation with sound does not influence how the value of the therapeutic intervention is perceived. In general, this item was rated with very high values in both groups. To increase the ratings of value and usefulness mediated by the role of sound, it might be interesting to investigate whether this parameter would change when music is generated or controlled by the patient instead of displaying music as stimulation. The aspect of creating music as a further motivation strategy for robot-assisted training for the upper limb post-stroke will be discussed in chapter 6.

The item "man-machine-relation" reflects the attitude towards the machine during training. The item itself was developed along the commonly used item "relatedness" by replacing the word "human" with "robot". Instead of assessing interpersonal interactions, friendship formation with another human being and the relation to a machine was tested. This part of the IMI was found irritating by many patients due to the fact that aspects of social relations to humans were replaced by the word machine and might have affected both groups in the same way so that no difference between sound- and control-group was found. Presumably, the suggested sound-design did not have any impact on the attitude towards the machine-relation. Dautenhahn 2007 outlined that multisensorial aspects co-shape the formation of an attitude towards the machine while interacting with a robot and that attitude depends on adequate design (Dautenhahn 2007). As the attitude towards the machine was not influenced by sound in our study, this might be due to sound-design that did not directly use interactive modes. A robotic-voice or musical real time control via the robot could change this relationship by providing an interactive experience of sound. Both of these ideas will be discussed in chapter 6.

In summary, the results of the primary outcome measures in function and motivation point in different directions. On the one hand, sound did not show effects on function. On the other hand, sound increased the ratings of motivation. Regarding the overall population, this indicates that sound has an impact on motivation, but not on functional effects.

It is surprising that the positive effect of sound on motivation does not directly induce functional advances. Maclean and Pound 2000 discussed the influence of patient motivation on function as a highly important factor (Maclean, Pound 2000). This effect might be discovered when training is carried out longer than just over a timespan of three weeks. Furthermore, results gained in the subgroup analysis will show that differences in function occurred as well.

Discussion of secondary outcome measures- function:

A huge body of research indicates that the grade of severity of a hand paresis syndrome has an effect on treatment outcome (Knecht et al. 2011; Smania et al. 2007; Wissel et al. 2014). Because of that, subgroup A was built by dividing the overall study population into three groups with different grades of severity. In computations on subgroup A, it was discovered that the grade of severity had a significant effect in the domain function and motivation. More specifically, moderate and mild cases, benefited from sound significantly, whereas the sound condition for severe cases even worsened the therapeutic effect gained with robotic therapy significantly. This was independent of significant higher motivation ratings achieved with sound-extended training. Furthermore, severe cases were weaker in finger extension forces (F ext) in the sound-group compared to the control-group. All in all, it can be concluded that severe cases did not benefit from sound-stimulation. The reason for the negative effect caused by sound in severe cases might be the result of an increase of muscle tone. High muscle tone is likely to cause strong muscle couplings, known as muscle synergies, which counteract the development of flexion forces measured with F ext over a treatment period of three weeks. This increase in muscle tone might also explain the weak performance in the BBT of severe cases in the sound-group. A high muscle tone is usually accompanied by an increase in synergistic muscle activity. Clinically, this can be characterized as post-stroke-spasticity (PSS), which can include problems such as muscle weakness, co-activation, over-excitability and spastic reflex responses. This was discussed in detail in chapter 2.2. Synergies between thumb and index and the co-activation of muscles limiting isolated finger movements cause limitations for grasping and release-function needed for execution of the BBT. Although severe cases showed significantly higher results in motivational scores with sound-extended training, the function did not increase, indicating that a higher motivation in severe cases does not improve function.

One possible explanation for the contradictory effect with high ratings of motivation and weak functional outcome in the severe patient-group could be that music-induced emotional arousal was counterproductive, especially for this group. It was already shown that music can cause a heightened emotional arousal resulting in an increase of muscle tone additionally to other physiological responses such as blood pressure, heart rate, breathing frequency and cortisol levels (Blood, Zatorre 2001; Juslin 2013a, 2013b; Pereira et al. 2011; van den Bosch, Iris et al. 2013). An emotional reaction leading to an increase in physiological parameters such as muscle tone is likely be counterproductive for recovery in this severe patient group. In contrast, exactly this effect might be beneficial for moderate to mild cases in which the problem of synergistic activities is not a central pathological problem. Thereby, the increase of muscle tone in moderate to mild grades of hand paresis could modulate muscle units needed to extend the hand in a beneficial manner.

Another possible explanation for the increase of muscle tone in severely affected patients in the sound-group could be drawn from problems with the intra-spinal processing of primary afferent inputs. This is a clinically well-known part-symptom of a spastic hand paresis post-stroke (Wissel et al. 2013). In PSS, muscle co-activation patterns are caused by the hyper-excitability of spinal reflexes such as the stretch reflex or flexor withdrawal reflexes. This can also occur during rest or be induced by sensory input (Sheean, McGuire 2009). When music is regarded as primary afferent input, a potential increase in spastic reflexes is possible. Within music, the parameter rhythm was already shown to induce audio-spinal coupling by Rossignol and Jones 1976, indicating that a reflex can be modulated on a spinal level via rhythmic sound (Rossignol, Jones 1976). Rossignol and Jones 1976 showed that the Hoffmann-reflex, a reflex induced by electric stimulation showing strong muscle activation as a response, can be boosted with rhythmic auditory stimuli. This would support the idea that an auditory rhythm is likely to increase spinal activity. This in turn could lead to an increase of a spastic reflex response. When music causes changes in spinal processes and intra-spinal processes are disturbed after a stroke, there might be a relation between these two aspects and the problem of an increased muscle tension in spastic patients exposed to rhythmic music. This idea is also supported by a study by Thaut et al. 1993. In this study EMG - activity of the leg of hemiparetic stroke patients was measured during walking under two conditions - with RAS stimulation and without stimulation. Results showed that with RAS stimulation, the onset of muscle activation occurred earlier and with a higher amplitude (Thaut et al. 1993). It can be concluded that auditory rhythmic cues lead to a change in muscle activation onset and intensity. The fast muscle response to rhythmic cues might be counterproductive for patients suffering from a spastic paresis post-stroke. As PSS involves the problem of muscle over-excitability, a rhythmic-cue-induced increase of muscle activation amplitudes might counteract the ability to release muscle tension and thus increase spasticity.

Another study performed by Ramasubriania and Arumugam 2006 extends this argument as well. These authors carried out a study in which they observed muscle recruitment under different sound conditions throughout the performance of repetitive arm movements in healthy subjects. Results showed that, compared to a setting with relaxing music, more muscles were recruited accompanied by an earlier onset of muscle energy and higher amplitudes in a setting in which activating music was presented (Ramasubramania, Arumugam 2006). When bigger muscle units are activated under the condition of activating music, this might mean that for patients showing spasticity and co-activation-symptoms the problem of regaining access to voluntary muscle control without co-activation could increase.

Furthermore, Aluru et al. 2014 performed a study which can be related to our outcome. In this study effects of auditory constraints on motor performance during a wrist extension task in stroke patients at different stages of recovery were compared to a condition without sound (Aluru et al. 2014). Results showed that metronome stimulation increased wrist extension in patients suffering from a spastic paresis accompanied by an increase of muscle co-activation in the wrist. In a patient group mainly suffering from spastic co-contraction, the condition without sound led to an increase of wrist extension and reduced co-activation. The group suffering from minimal paresis did not show improvements under any condition. Aluru et al. 2014 concluded that auditory environments might influence motor learning depending upon the stage of recovery. They hypothesized, that within the recovery period different neural substrates are recruited. The results of contradictory effects of sound on motor learning in different groups of severity are in line with the results of our presented clinical study. Severe patients which are named "spastic paresis" group in the study of Aluru et al. 2014 benefited from metronome in wrist extension, but showed counterproductive increased co-contraction at the same time. The "spastic co-contraction"-group might be comparable to subgroup A - moderate cases in the here presented clinical study. Results differed in our study from results gained by Aluru et al. 2014. The subgroup A-moderate cases benefited from sound whereby Aluru et al. 2014 described that no sound was best for the spastic co-contraction group. A reason could be that different sounds were used by Aluru et al. 2014 and in the here presented clinical study. In contrast to our study, in which polymetric music and game-related sound feedback was displayed, Aluru et al. 2014 used metronome, non-musical happy sounds and self-selected music. Furthermore, performance effects of a bimanual wrist extension task were examined. In the here presented clinical study a unilateral robotic hand function training task was observed and data on function and not on performance was assessed. Nevertheless, the findings by Aluru et al. 2014 are similar with our findings in one central aspect, namely that sound has different effects on stroke patients suffering from hemiparesis depending upon the stage of recovery. The study results of Aluru et al. 2014 extend this view by exploring effects on performance.

The above discussed reasons for the negative effects of sound on patients that were graded as severe cases are most likely a result of a sum of reasons such as the interplay of emotional arousal reflected in positive ratings in IMI and malfunctioning processes at different levels of the reflex bow including the cortical level as well as the spinal level. The main new finding is that patients suffering from PSS should not train with sound. To better understand the mechanism behind this, future studies should observe whether the increase of muscle tone is directly related to sound.

Therefore EMG-measurements of sound-induced effects, the comparison of different musical parameters such as strong rhythmical music and relaxing music without any beat could be explored. Furthermore, it might be important to investigate music in the role of a motivational and functional primer displayed before training or not displayed at all. This might induce an energized state that increases the training focus and could be perceived as rewarding before and after exhausting training.

In other secondary outcome measures in the domain function including the NHPT, GF and F0, no significant differences were recorded between the sound- and the control-group. Furthermore, no differences were found in subgroup computations taking into account the grade of severity and the timespan between insult and study participation. In the case of the NHPT, a possible reason for the results might be that severe cases were not able to perform this test at all as the NHPT requires the ability to grasp small pegs, to place them with high precision involving balance, and the release of the peg. The BBT measures the ability to grasp and release as well, but the blocks are bigger and only need to be released without precise placement. Positive effects of sound versus no-sound were found in E1-4 with the NHPT and also with the BBT (see Chapter 3). In these tests, no severe cases of hand paresis were included and performance effects were assessed. As outlined before, the transfer from performance to function is questionable. In GF measures it was reflected that the grip force was not increased or decreased in treatment with sound-extended robotic training or robotic training only. Both groups showed advancements in this measure. This indicates that sound does not directly influence the maximum force in grip tasks.

F0 was measured to detect whether the resting hand showed flexion forces in rest typical for PSS. PSS usually leads to flexion forces that are also visible in a resting position. Furthermore, F0-measures could show whether there is a difference between the sound- and the control-group. Sound did not have an effect on these measures while in a resting position in the overall study population or in subgroups A and B, however a significant difference was seen in subgroup A for severe cases in F ext measures. As mentioned before, there was a possibility of F0 and F ext interacting, generally described as muscle co-activation. As soon as the hand muscles do not further counteract in antagonistic force directions due to PSS, the hand can increase in F ext while F0 stays at a stable value around 0-3N. The relation of F0 and F ext will be discussed in chapter 5 more detailed when single-case studies are presented in which these two measures are central. There was no significant difference between sound- and control-group in the BBT, NHPT, GF or F0/ F ext measures in subgroup B which anticipated that the timespan between insult and study participation might have influenced whether sound was beneficial or not. The results reveal that the timespan does not have an impact on whether sound or no-sound-conditions are better or worse.

It was generally surprising that subgroup B3 gained better results than subgroup B1 in all of these measures independent of being in the sound-group or in the control-group. Subgroup B2 was not computable due to the small sample size and the results of subgroup B were contradictory to commonly presented studies that showed an especially effective treatment window for B1 (Hesse et al. 2014; Sale et al. 2014). The outcome here might be based on a very small sample size in both groups B1 and B3.

Discussion of primary outcome measure- motivation:

In secondary outcome measures in the domain motivation, the IMI was analyzed for subgroup A and B. ES, PSE and GAS were also evaluated for the overall-study population and both subgroups A and B. The results showed that in subgroup A, again severe cases showed significant differences in ratings of IMI-items in the sound-group compared to the control-group. More specifically, the sound-group rated "interest/ enjoyment", "perceived choice" and "relaxation" higher than the control-group. This indicates that sound influenced motivation in severe cases positively. This had already been associated with the potential danger of emotional arousal-increasing muscle tone. Generally, the aim was to increase motivation by sound. This was confirmed for the overall-patient population as well as for subgroup A - severe cases.

In subgroup A - severe cases, the control-group rated the IMI-item "man-machine-relation" significantly higher than the sound-group. This could mean that in a setting without sound, participants had a better relation to the machine while requiring a higher focus on the training task. If so, than music might have been distracting patients during training. Furthermore, the musical stimulus might have led the focus away from training to music-listening. This aspect was already discussed in chapter 1.3. and in 2.2.2.

Another interesting outcome was found in subgroup B3. The control-group of subgroup B3 rated "value/ usefulness" higher than the sound-group. The reason for this might be that music created a relaxed and pleasurable experience, whereas without sound, the training was perceived as more serious. Moreover, the same argument as described above, that music was likely to be distracting, could be considered as a reason for this result. In ES, PSE and GAS, neither the subgroups A and B nor the overall-study population showed a significant difference between the sound- and the control-group. Except for motivation, one item in ES, that was rated significantly higher in the sound-group than in the control-group, thus indicating that sound increased motivation, which is in line with arguments discussed in results gained with IMI. It is surprising, that motivation-related items of ES, PSE or GAS were not rated higher in the sound-group than in the control-group. In ES, the items measured were mood, involvement and fun. These results indicate that the sound stimulation affected neither mood nor the feeling of being involved in the task nor the perception of fun compared to training without sound.

This might be due to the belief that the gaming experience with a robot itself already increases mood, fun and the feeling of being involved in the task. This might have had a similarly effect on the outcomes in PSE and GAS. Generally, the results shown in subgroup A - severe cases indicated a special relation to sound and its impact on this group. This was confirmed by the outcomes of the BBT, F ext and the IMI. Regardless of the sample size of this group containing in total test subjects, the question is whether sound is beneficial for this group or not. Interestingly, this group showed a higher motivation in the sound-group than in the control-group. However, the high grade of motivation did not influence functional advance, indicating a need for a specification of the relation between function and motivation in patients suffering from a high grade of severity. It might be important to take into consideration, that patients with severe grades of hand paresis are generally more excited during training and thus show higher ratings in motivation. This "excitement" might be based on the fact, that the new therapy approach is perceived as promising, especially when advances are not visible over a longer time course in other therapies. The level of expectancy unequivocally differed in the group of severely affected patients compared to patient groups that advanced in function. In order to determine whether excitement and the suggested psychological issue of severely affected patients might have influenced the results, future studies should assess personality traits. Furthermore, in-depth research on the level of expectation of advances should be conducted.

Limitations of the study:

The presented clinical study has several limitations, those being that the same person was responsible for performing the assessments, evaluating the results, and carrying out the therapeutic interventions. This can lead to a person-related bias, in addition to the fact that blinding was not possible.

Another limitation is that the sample size for statistical evaluation was calculated for two groups only, the sound-group and the control-group along the primary outcome measure in function which was the BBT. The sample size within the subgroups was much smaller. Therefore, the statistical power of outcomes shown in subgroup analysis is reduced.

Furthermore, in current research on therapeutic effects post-stroke, a special focus is put on the early phase after the insult. Patients that were included in this study were treated in an ambulant center. Therefore, subgroup B-1 (2-6 months post-stroke) did not contain patients showing very severe cases of a stroke. These cases are commonly treated in rehabilitation clinics in-house.

Another limitation of this study was that the total amount of therapeutic interventions was limited to nine sessions. So far, the best outcome in robotic hand function training has been documented with training over at least 5-6 weeks with daily training sessions. Possibly, a longer time-span of training might have shown more distinct differences between the sound- and the control-group.

Finally, the fact that the Likert-scale ranging from 1:7 used in IMI, the VAS ranging from 1:10 used in ES, and the two-graded five-point-scale used in GAS were evaluated with parametric and not with nonparametric methods. The decision to use a parametric approach to evaluate the data was based on arguments by Norman 2010, Sullivan and Artino 2013 and by King et al. 2013, stating that parametric tests display a high resolution with more robust results (Sullivan, Artino 2013; Norman 2010; King et al. 2013). To ensure that non-parametric tests would not have led to different conclusions, the median and modus values are added to the Appendix showing fulfilment of presumptions mentioned by Sullivan and Artino 2013 and King et al. 2013 (see 9.2.).

<u>4.5 Conclusion</u>

A 2-armed clinical study was presented which compared effects of specified sound versus no-sound applied to robotic hand function training post-stroke on function and motivation. The main goal was to investigate whether specified sound consisting of polymetric music and game-related sound feedback has the power to effectively extend robotic hand function training for stroke patients. According to the presented study results, it can be concluded that sound has an impact on both function and motivation.

The results revealed furthermore, that sound needs a careful application, one that is sensitive to patient characteristics in order to be immediately effective in both domains. It was shown that motivation can be increased by including specified sound to the overall study population. In contrast to motivation, the functional outcomes showed ambivalent effects when sound was applied. In the overall study population, there was no difference found in regard to the effects of sound-extended robotic hand function training compared to training without sound.

However, the results of a subgroup analysis indicate, that the effects differ depending on the grade of severity of the hand paresis syndrome, showing that sound can either destroy or boost therapeutic effects. In the past, music and sound were applied to robotic therapies without further evaluation of their effects on function, performance or motivation, and sound was also never particularly specified for the context of robotic training in virtual environments. It might be relevant to consider the interaction of sound as one part of the complex training scenario with a robot, a virtual scenario, and a therapist alongside. Moreover, it would be important to differentiate sound-related aspects in each parameter such as the impact of musical genre, rhythmicity, tempo, cultural or age-related factors as well as the specific needs of the stroke population. This study was the first approach to specifically develop music and sound for the purpose of increasing function and motivation in robotic hand training post-stroke and is based on a scientific background indicating that sound features might have beneficial effects. The design consisting of polymetric music and game-related sound feedback was suggested as a first sound-environment for this context to promote motivation and function. The fact that musical stimulation increases motivation supports the intention with which sound is commonly applied to therapy robots, namely, as a motivating design factor within virtual training environments (Novak et al. 2014; Friedman et al. 2014). In the introduction and in chapter 2, a lack of empirical investigation on the effects of sound and music applied to robotic therapy was discussed. The effect of sound and music as a motivating factor was confirmed empirically by the here presented study. Also the results gained in the experiment series E1-4 indicate that musical stimulation with waltz-music can increase not only performance qualites, but also mood. Independent of the promising effects of music and sound on patient motivation, it was emphasized in chapter 1 and 2 that the impact of sound and music on function is underestimated in regard to its widespread usage in robot therapy and as a powerful therapeutic tool, currently being outlined by a huge body of research (Altenmüller, Schlaug 2015; Bradt et al. 2010; Gebauer, Vuust 2013). The experiment series E1-4 showed that sound can have an effect on the performance quality of fine motor tasks in healthy subjects and stroke patients. Furthermore, it was clarified in the discussion section that the effects on performance are not directly related to the impact on function. Therefore, the clinical study focused on effects of treatment. The outcomes were assessed before and after treatment and then compared. The results illustrate that sound compared to no-sound did not cause a significant difference in the overall study population in functional outcomes.

Interestingly, the subgroup analysis comprising a differentiation of the grade of severity of the hand paresis syndrome post-stroke indicates a different matter, that is, that depending on the grade of severity, function either decreased or increased. More specifically, it was shown that for patients suffering from a severe grade of hand paresis, the sound-extension destroyed therapeutic effects. This effect was also seen in the secondary outcome measure observing the ability to extend the fingers. However, for patients suffering from a moderate and mild grade of severity, the training effects of robot therapy were boosted with sound. It can be concluded that sound may show ambivalent effects on function, independent of positive effects on motivation.

These findings emphasize that the role of sound in robotic hand function training needs to be explored further by taking into account the grade of severity of a hand paresis post-stroke. Moreover, the interaction of motivation and function has to be reconsidered in the subgroup of patients suffering from a severe grade of a hand paresis. According to Aluru et al. 2014, auditory constraints can promote motor learning post-stroke when the stage of recovery is taken into account by mapping groups that benefit from sound such as patients with a spastic paresis and groups that do not benefit from sound such as patients suffering from spastic co-contraction or minimal paresis (Aluru et al. 2014). Aluru et al. 2014 argue that the reason for different reactions to sound and music stimulation during motor performance post-stroke might lie in a distinct recruitment of neural substrates at different stages of recovery. A similar conclusion can be drawn from the presented clinical study showing that the grade of severity interacts with the usefulness of auditory constraints.

Another subgroup analysis focused on the variables of the timespan between the insult and study participation which was shown to be critical in robotic training (Hesse et al. 2014). Thereby no differences were seen that were dependent on sound or no-sound robotic therapy. This implies that not the time-point, but the grade of severity is essential when considering the effects of sound in this context. Limited conclusions can be drawn from this result as no severely affected stroke patients in the acute or subacute phase were included in the study.

Another important finding of this study was that whether motivational aspects can be boosted by sound, functional advancement is not directly related to this sound-induced motivation increase. In contrast to the above mentioned outcome, severely affected patients showed an increase in motivation but not at all in functional improvement. In this group, the relation between motivation and function is contradictory and implies that a high motivation might even interfere with functional recovery. Therefore, the relation between functional and motivational advance needs to be further observed, in particular with regard to the group of severely affected subjects. In summary, the presented study results imply that it is necessary to have sound applied in a specified manner until the functional effects of sound have become more effective for all subjects and the effect-mechanism has been studied more carefully.

In order to prevent negative side-effects and to achieve effects that are beneficial, the application of sound needs a clear differentiation between grades of severity. According to the presented study, it is recommended to assess the grade of the hand paresis before applying sound. The Box and Block Test could serve as screening tool to differentiate severe, moderate and mild cases of a hand paresis post-stroke. Patients achieving less than 17 blocks should not receive any sound stimulation applied to robotic training. For patients achieving more than 17 blocks, sound-stimulation with polymetric music and game-related sound feedback is recommended, as it was shown to improve function and increase motivation.

For the first time, negative side-effects of music and sound applied to rehabilitation were reported, and with regard to the strength of music influencing cognitive, emotional, social and motor functions this is surprising. In chapter 1, music was introduced as a therapeutic tool with clinical relevance (Altenmüller, Schlaug 2015; Bradt et al. 2010; Gebauer, Vuust 2013; Thaut et al. 2015; Särkämö, Soto 2012). When music is used as a therapeutic tool, the effect on each domain such as cognition, emotion, social and motor domains needs to be evaluated carefully. Furthermore, the complexity of the musical stimulus has to be investigated by determining those elements within this complex material that are responsible for causing the specific effects. This is highly important as the power of music and its effects on human behavior were shown to be extremely powerful.

This study proposes the use of a specified sound environment consisting of a polymetric musical piece and game-related sound feedback, as its results reveal that a specified sound environment is beneficial to improve function and motivation. When using commonly applied sound-environments of commercially available therapy robots, music might cause different effects than showed in this study which used music with specific design features. Therefore, polymetric music and game-related sound feedback are recommended for the application in robotic hand function training post-stroke for patients suffering from moderate to mild grades of a hand paresis. Polymetric music combined with game-related sound feedback is the first empirically evaluated sound-environment.

The study revealed negative effects of a sound application on severe grades of hand paresis, and it is likely that different music or sound environments will also have such an effect. The main conclusion drawn from this study is that sound and music influence function and motivation. Sound-induced effects are ambivalent depending upon the grade of severity of a hand paresis post-stroke. Music and sound have an impact on both motivation and function. On the one hand, the results support the idea that motivation can be increased by sound applied to robotic hand therapy. However, the results also indicate that although the motivational aspect is positive, the functional effects need to be considered carefully, as they can increase or decrease rehabilitation outcome.

In order to achieve positive outcomes and to prevent negative side-effects, patient characteristics need to be taken into account as well as an adequate sound design, specified in regard to the application context. Patients suffering from a severe grade of hand paresis should not receive any audio displays during robotic training as negative side-effects could occur. In cases of moderate and mild hand paresis, it is indicated that sound increases function compared to training without sound and therefore should be applied. As one goal was to provide further arising technology with information on the benefits and dangers of sound for robotic therapy post-stroke, it is recommended to take into account these findings, firstly, by applying the BBT as a screening tool to enable a determination of the grade of severity, thus preventing severe cases from the negative side effects of sound, and secondly, to use polymetric music and game-related sound feedback, as this sound-environment has so far been the only one evaluated clinically, proving its beneficial impact on function and motivation for mild to moderate cases of hand paresis.

Study 5

5. SINGLE-CASE STUDIES

5.1 Background of single-case studies

5.2 Methods

5.3 Results

5.4 Discussion

5.5 Outlook

5.1 Background and study design

In the previous chapter, a 2-armed clinical study was presented in which effects of specified sound for robotic hand function training post-stroke on function and motivation were compared to training without sound. Results from the clinical study showed that patients suffering from a severe grade of a hand paresis did not benefit from sound. This patient population is investigated more particularly in the following presented three single-case studies. The goal of these single-case studies is to extend the perspective on effects of sound applied to robotic hand therapy on the patient population suffering from a severe grade of the hand paresis post-stroke by exploring measures on the hand in a rest position (F0) and active hand extension forces (F ext). Furthermore, an additional sound condition, self-selected favorite music, is investigated. Because all patients in the previously presented clinical study trained with the finger combination thumb and little finger, a special focus is put on finger forces in rest and extension of single fingers. This aspect is taken into account to determine strong and weak muscle interactions between single fingers.

More specifically, in the single-case-studies, three patients suffering from a severe grade of the hand paresis post-stroke (> 12 months post-stroke), performed robotic hand function training over three training phases, each phase consisting of nine therapy sessions carried out within three weeks, with different sound conditions (phase 1: no sound, phase 2: polymetric music + game-related sound feedback, phase 3: self-selected favorite music + game-related sound feedback). Between each phase, a 4 week wash-out phase was applied. Outcome measures of the hand and single finger forces in rest (F0) and in active extension (F ext) were recorded in the first and last session of each phase. Three aspects are of special interest within these single-case studies: 1) A special focus is put on the interaction between muscle tone in rest (F0) and the ability to extend the fingers (F ext). 2) Furthermore, effects of different sound environments applied to robotic hand training post-stroke on F0 and F ext are considered. 3) Moreover, profiles of single fingers forces are ranked and related among each other. All three aspects 1)-3) are reported in relation to the previously presented clinical study in the following section.

1) According to the previously discussed clinical study, one finding was that patients suffering from a severe grade of a hand paresis post-stroke showed an unexpected sound-induced effect which was negative. In the discussion section of chapter 4.4., several reasons for this outcome were suggested. As one possible explanation for the negative sound-effect on this patient population, an increase of muscle tone via sound was discussed. To observe the development of muscle tone in rest (F0) and the ability to extend the fingers (F ext), three single-cases suffering from a severe grade of the hand paresis post-stroke were investigated under different sound conditions with a special focus on these two measures. It was expected that the

interaction between F0 and F ext would reveal that a plateau value range between 0-3N for F0 is a premise for an increase of F ext- values.

2) Music was shown to promote motivation in all patients that took part in the before presented clinical study. Patients suffering from a severe grade of the hand paresis did not benefit from the sound stimulation independently of positive ratings in the domain motivation. In the single-case-studies the aspect of familiarity, liking and selecting music is taken into account to see if motivation impacts functional outcomes in a different way than the before used polymetric music and game-related sound feedback.

3) In the previously described clinical study and in the following single-case studies, all patients trained with a special focus on the finger combination thumb and little finger. In conventional hand therapy the common finger combination for training is thumb and index finger whether these two fingers show a strong muscle-co-activation pattern post-stroke (Bhardwaj und Sabapathy 2011). The finger combination of thumb and little finger was suggested in the here presented studies, because these fingers might show least muscle-coupling counteracting extension due to the anatomical distance and muscle unit distance of little finger and thumb. Furthermore, both combinations, index and thumb as well as little finger and thumb, allow to perform grasping with two fingers in opposition. Following, the finger combination thumb and little finger might be a promising treatment approach extending the common training focus in hand therapy on thumb and index finger. To explore this finger combination more specifically, in the single-case studies, F0 and F ext profiles of single fingers are observed.

5.2 Methods

Participants- Three patients suffering from a severe grade of a hand paresis syndrome post-stroke took part in the single-case studies (patient characteristics see Table 4 a): No.8, No. 27, No.33; Table 9).

Procedure- All three single-case-study participants underwent the same training- and test-protocol. They took part in three treatment phases, each consisting of nine therapy sessions robotic hand therapy with "Amadeo". The therapeutic intervention was carried out as described in chapter 4.2. Each of these three phases was performed with different sound-conditions. In relation to the previously presented clinical study, an additional musical stimulus, self-selected favorite music, was explored. The order of the sound-conditions was for all three single-cases the same: phase 1- no sound, phase 2- polymetric music and game-related sound feedback, and phase 3- self-selected favorite music and game-related sound feedback (titles of self-selected favorite music are presented in the result- section of each patient profile). After each training phase, a 4 week wash-out phase was applied (see Table 10). The primary outcome measures were F0 and F ext assessed with the "Amadeo"-system. F0 and F ext were recorded before the first session of each phase and after the final session of each phase. In total, F0 and F ext were measured six times at T0, T1 for phase 1, T2, T3 for phase 2 and at T4, T5 for phase 3.

Evaluation- Descriptive statistics were used to display the relation of F0 and F ext of the mean F0- and mean F ext- values of the hand. F0 and F ext values of all single-fingers are shown, and a ranking on strongest and weakest values in phase 1 to phase 3 for all fingers are outlined. Moreover, the impact of sound on the outcome parameters F0 and F ext of the mean of the hand from phase 1 to 3 are presented. All graphical displays shown in 5.3. are used to provide a ground for an outcome discussion. Furthermore, they are related to outcomes of the clinical study presented in chapter 4.

Summary of the goals- In summary, the central questions of these case-studies are 1) whether there is an interaction between F0 and F ext which shows that a plateau-value of F0 which ranges between 0-3N, is a premise for an increase of F ext, 2) whether the different sound conditions showed to impact outcome measures of F0 and Fext in severe cases, and 3) whether the little finger shows least F0 values compared to index, third and fourth finger.

	No.	gender	age	Months post-stroke	Location of lesion	Right-/ left handed	Musical exp.	Robotic rehab exp.	Gaming exp.	Grade of severity	Months post-stroke grouping
Single-Case 1	8	male	62	17 months post-stroke	AVM right temporo polar	r		x	x	severe	3
Single-Case 2	27	male	58	84 months post-stroke	Pons infarct	l		x	x	severe	3
Single-Case 3	33	female	68	15 months post-stroke	Media infarct left	r	x		x	severe	3

Table 9: patient profiles of single-case-study- participants

Single Case studies 1-3		
phase 1:		
assessment of F0 / F ext: T0, T1	T0 9 therapy sessions T1	RT + no sound
wash-out phase > 4 week		
phase 2:		
assessment of F0 / F ext: T2, T3	T2 9 therapy sessions T3	RT + polymetric music & game-related sound feedback
wash-out phase > 4 week		
phase 3:		
assessment of F0 / F ext: T4, T5	T4 9 therapy sessions T5	RT + self-selected favorite music & game-related sound

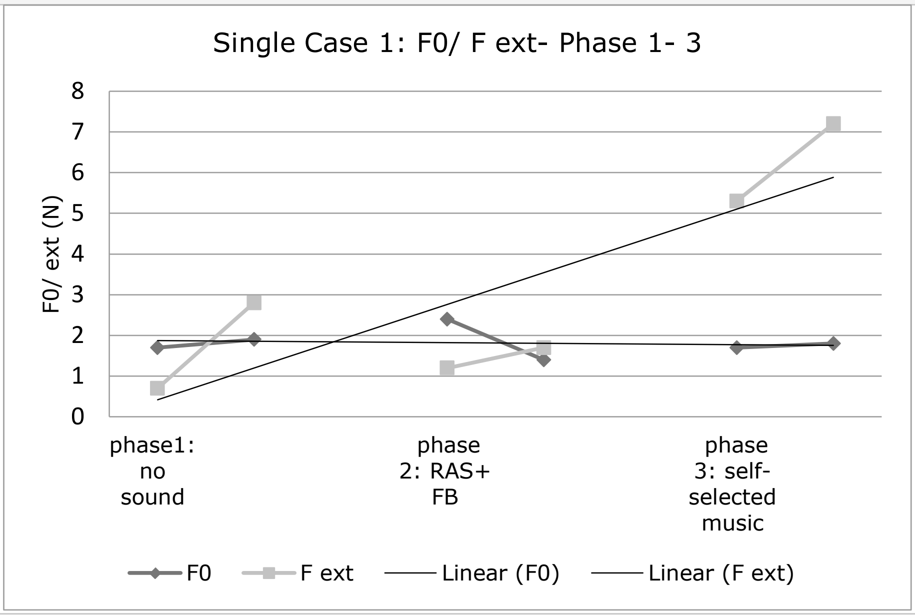
Table 10: Study procedure Single –Case Study 1,2,3

5.3 Results

Single-Case 1 (Subject 8)

self-selected favorite music:

Hans Harz, ”Die weißen Tauben sind müde”.



F0:

Within phase 1, subject 8 increased F0 from T0 to T1 from 1,7N to 1,9N by 0,2N. In phase 2, from T2 to T3, a F0-decrease of 2,4N to 1,4N, in total by 1N, was measured. In phase 3, F0 was assessed at T4 with 1,7N and at T5 with 1,8N. This is a F0-increase by 0,1N. From T0 to T5, F0 ranged between 1,7N and 2,4N with a total range of 0,7N.

F ext:

Within phase 1, subject 8 increased F ext from T0 to T1 from 0,7N to 2,8N, in total by 1,1N. In phase 2, an increase of F ext from T2 to T3 from 1,2N to 1,7N, in total by 0,5N was measured. In phase 3, an increase of F ext from T4 to T5 from 5,3N to 7,3N, in total by 2N was recorded. Following, this patient increased F ext from phase 1 to phase 3 from 0,7N at T0 to 7,2N to T5.

From T0 to T5, F ext ranged between 0,7N and 7,2N with a total range of 6,5N.

F0 and F ext:

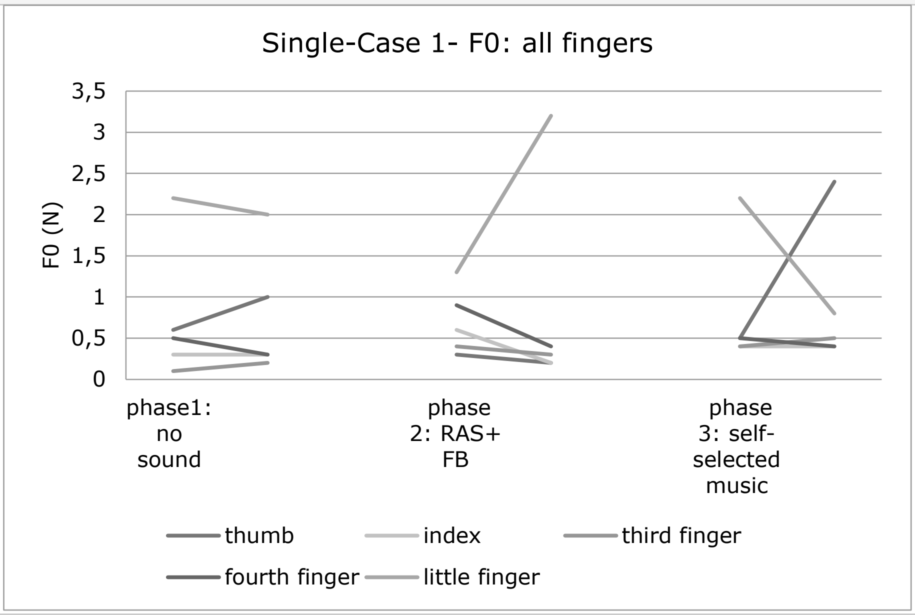
Subject 8 showed an increase of F ext with a total range of 6,5N and a stable F0-plateau ranging between 1,7N and 2,4N.

The strongest decrease of F0 was seen in phase 2, and a very slight increase of F0 was recorded for phase 1 and phase 3.

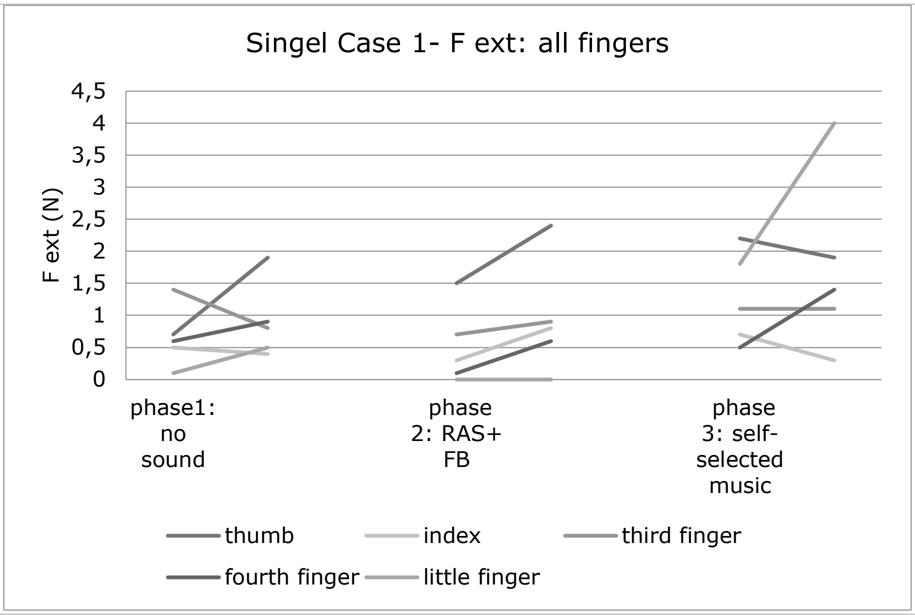
The strongest increase in F ext was measured in phase 3, the weakest increase within the phases of F ext was seen in phase 2.

F0- and F ext- values were used to generate a linear relation of all values. The crossing of these linear functions from F ext and F0 occurs at 1,8N.

Single-Case 1 (Subject 8): Single finger force measurements F0/ F ext:



Ranking of lowest (o)/ highest (x) F0-values	phase 1	phase 2	phase 3
thumb		o	x
index			o
third finger	o		
fourth finger			
little finger	x	x	

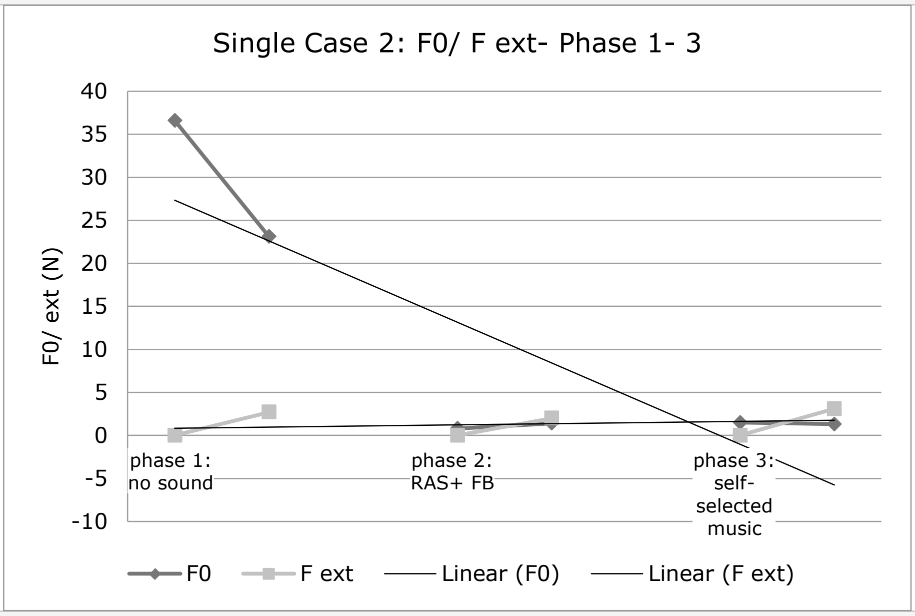


Ranking of lowest (o)/ highest (x) F ext-values	phase 1	phase 2	phase 3
thumb	x	x	
index			o
third finger			
fourth finger			
little finger	o	o	x

Single-Case 2 (subject 27)

Self-selected music:

Bonny Tyler, "Hide your heart"



F0:

Subject 27 decreased F0 from T0 to T1 from 36,6N to 23,1N, in total by 13,5N. In phase 2, an increase of F0 from T3 to T4 with 0,8N to 1,4N, in total by 0,6N was measured. In phase 3, F0 was assessed at T4 with 1,5N and at T5 with 1,3N. This is a slight decrease of F0 by 0,2N.

From T0 to T5, F0 ranged between 36,6N and 0,8N with a total range of 35,8N.

F ext:

Subject 27 increased F ext from T0 to T1 from 0N to 2,7N. In phase 2, an increase of F ext was measured from T2 to T3 from 0N to 2N. In phase 3, from T4 to T5 an increase from 0N to 3,1N was recorded. Following, this patient increased F ext from T0 to T5, from 0N to 3,1N.

From T0 to T5, F ext ranged between 0N and 3,1N with a total range of 3,1N.

F0 and F ext:

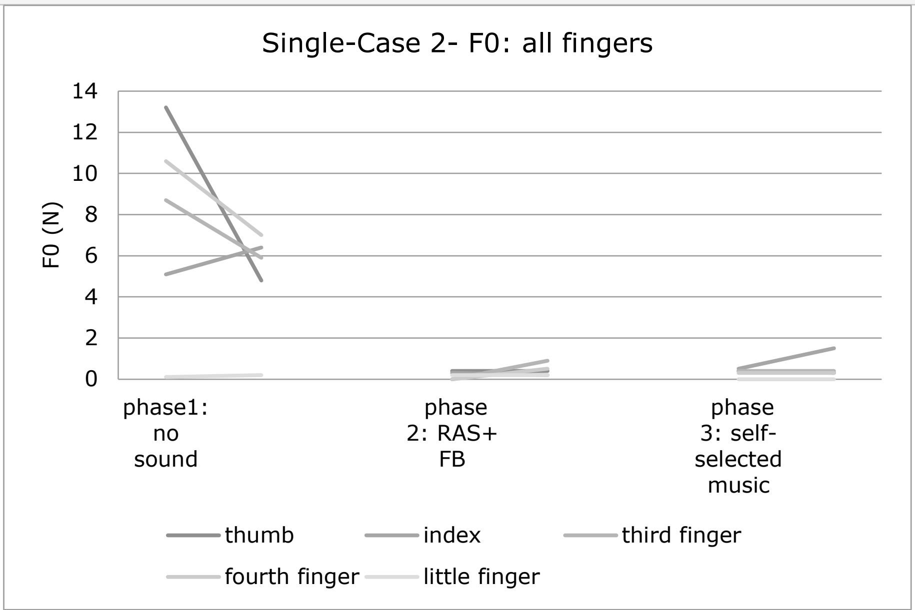
Subject 27 showed an increase of F ext with a total range of 3,1N and a decrease of F0 from 36,6N to 0,8N in the timespan T0 to T5.

The strongest decrease of F0 was seen in phase 1, and a very slight increase of F0 was recorded for phase 1 and phase 3.

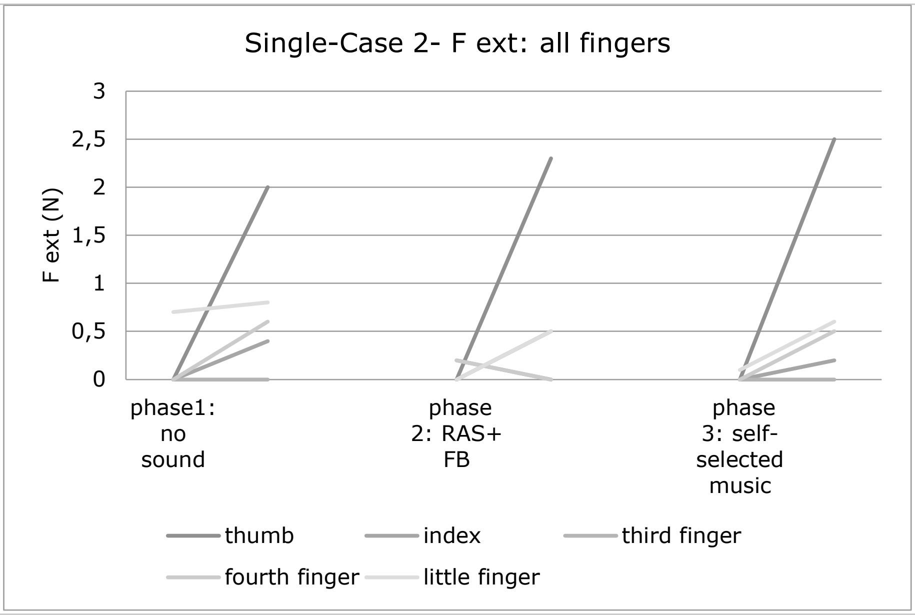
The strongest increase in F ext was measured in phase 3, the weakest increase within the phases of F ext was seen in phase 2.

F0- and F ext- values were used to generate a linear relation of all values. The crossing of this linear functions from F ext and F0 occurs at 1,9N.

Single-Case 2 (subject 27): Single finger force measurements F0/ F ext:



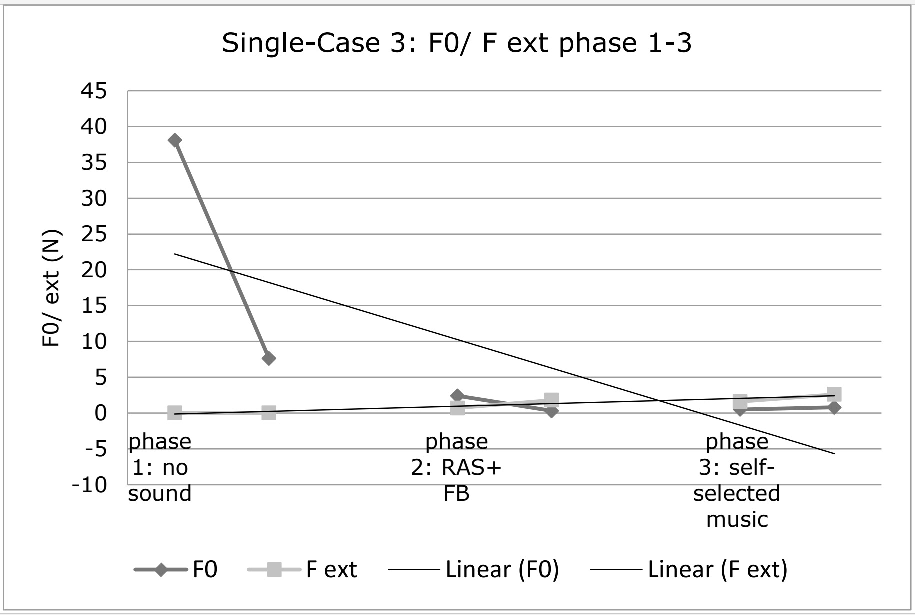
Ranking of lowest (o)/ highest (x) F 0-values	phase 1	phase 2	phase 3
thumb	x		
index			x
third finger		x	
fourth finger			
little finger	o	o	o



Ranking of lowest (x)/ highest (xx) F ext-values	phase 1	phase 2	phase 3
thumb	x	x	x
index			
third finger	o		o
fourth finger		o	
little finger			

Single-Case 3 (subject 33)

Self-selected music: The patient did not have any personal suggestions. Because of that waltz-music "Voices of spring" by Johann Strauss was explored. This piece was used as musical stimulation environment in E1-4.



F0:

Subject 33 decreased F0 from T0 to T1 from 38,1N to 7,6N by 30,5N. In phase 2, a decrease of F0 from T2 to T3 from 2,4N to 0,3N was measured. In phase 3, F0 showed a slight increase from T4 to T5 with 0,5N and 0,8N.

From T0 to T5, F0 ranged between 36,6N and 0,8N with a total range of 37,6N.

F ext:

Subject 33 did not increase F ext from T0 to T1. In phase 2, from T2 to T3 an increase of F ext was assessed from 0,7N to 1,8N, in total by 1,1N. In phase 3, F ext increased from T4 to T5 from 1,6N to 2,6N, in total by 1N. Following, this patient increased F ext from T0 to T5, from 0N to 2,6N.

From T0 to T5, F ext ranged between 0N and 2,6N with a total range of 2,6N.

F0 and F ext:

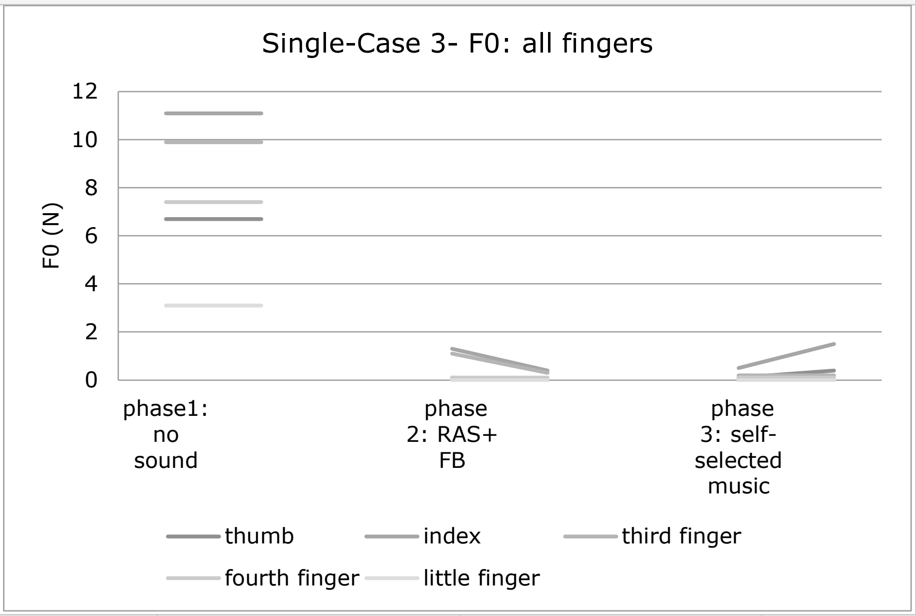
Subject 33 showed an increase of F ext with a total range of 2,6N and a decrease of F0 from 37,6N to 0,8N in the timespan T0 to T5.

The strongest decrease of F0 was seen in phase 1, the weakest results of F0 was a slight increase in phase 3.

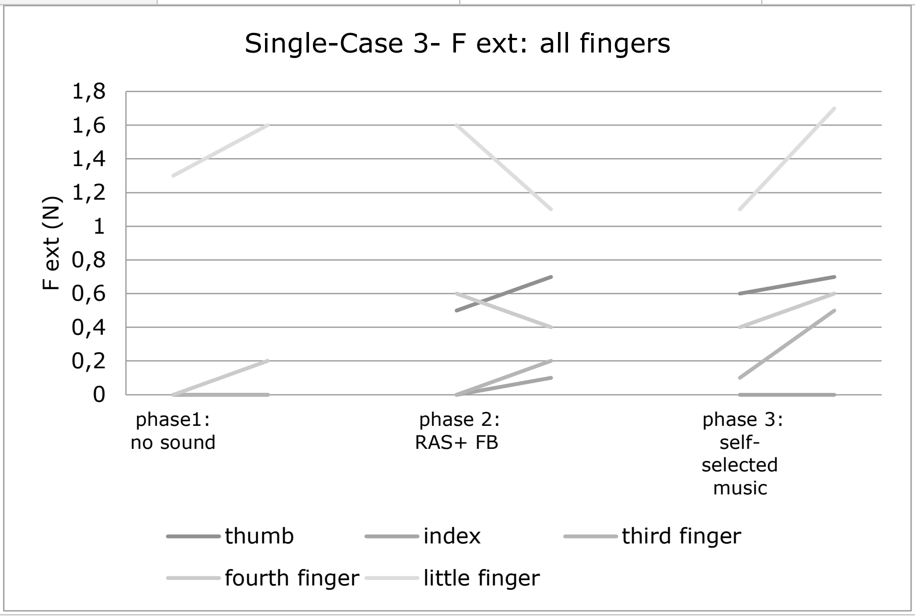
The strongest increase in F ext was measured in phase 3, the weakest increase within the phases of F ext was seen in phase 1.

F0- and F ext- values were used to generate a linear relation of all values. The crossing of these linear functions from F ext and F0 occurs at 1,9N.

Single-Case 3 (subject 33): Single finger force measurements F0/ F ext:

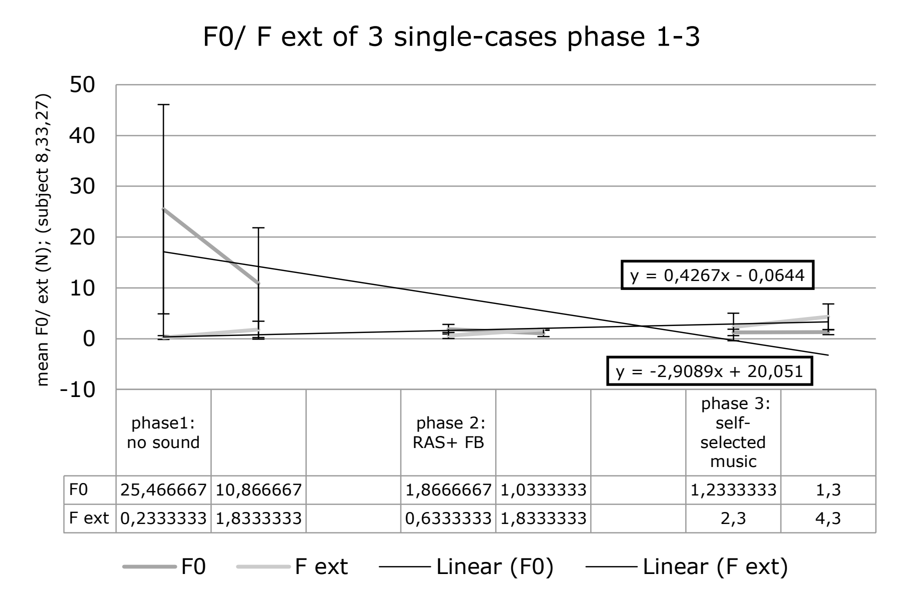


Ranking of lowest (o)/ highest (x) F0- values	phase 1	phase 2	phase 3
thumb			
index	x	x	x
third finger			
fourth finger			
little finger	o	o	o



Ranking of lowest (o)/ highest (x) F ext- values	phase 1	phase 2	phase 3
thumb			
index		o	o
third finger	o		
fourth finger			
little finger	x	x	x

Overview F0/ F ext- single-case 1-3 in phase 1-3:



	phase1: no sound			phase 2: RAS+ FB			phase 3: self-selected music	
F0	25,466667	10,866667		1,8666667	1,0333333		1,2333333	1,3
F ext	0,2333333	1,8333333		0,6333333	1,8333333		2,3	4,3

In summary all three subjects taking part in the single-case studies, showed a F0-decrease and an F ext-increase from T0 to T5.The standard deviation for F0 and F ext was highest in phase 1 and lowest in phase 2.The mean F0 and F ext values of all three subjects were connected with a linear function. The crossing of the two linear functions of F0 and F ext for the timespan T0 to T5 occurs at 1,2N.

Overview single-case 1-3 in phase 1-3:

Ranking of lowest (o)/ highest (x) F 0- values	phase 1	phase 2	phase 3
thumb	x	x	x
index	x	x	o / x / x
third finger	o	x	
fourth finger			
little finger	x / o / o	x / o/ o	o / o
Ranking of lowest (o)/ highest (x) F ext- values	phase 1	phase 2	phase 3
thumb	x / x	x / x	x
index		o	o
third finger	o / o		o
fourth finger		o	
little finger	o / x	o / x	x

For all three cases F0 and F ext maximum- and minimum-values for single-finger recordings were assessed.

F0-values:

Lowest F0-values for phase 1 were assessed for third and little finger. Highest F0-values for phase 1 were assessed for thumb, index and little finger.

Lowest F0-values for phase 2 were assessed for thumb and little finger. Highest F0-values for phase 2 were assessed for index, third and little finger.

Lowerst F0-values for phase 3 were assessed for index and little finger. Highest F0-values for phase 3 were assessed for thumb and index finger.

F ext-values:

Lowest F ext-values for phase 1 were assessed for third and little finger. Highest F ext-values for phase 1 were assessed for thumb and little finger.

Lowest F ext-values for phase 2 were assessed for index, fourth and little finger. Highest F ext-values for phase 2 were assessed for thumb and little finger.

Lowest F ext-values for phase 3 were assessed for index and third finger. Highest F ext-values for phase 3 were assessed for thumb and little finger.

5.4 Discussion

In this section, the three single-case studies are discussed in regards of 1) whether there is an interaction between F0 and F ext which shows that a plateau value range between 0-2N for F0 is a premise for an increase of F ext-values, 2) whether the different sound conditions showed to have an impact on F0 and Fext in severe cases, and 3) whether the little finger shows least F0 values compared to index, third and fourth finger.

Single-case 1:

1) Single-Case 1 showed a positive development from phase 1 to phase 3 with a F0-decrease and an F ext-increase. The interaction between F0 and F ext was characterized by a F0-plateau-value-range between 1,7- 2,4N. F0 regarded as a function for each phase 1-3, crossed the F ext-function in phase 1 and in phase 2. Whether F0 did not change a lot in phase 3, F ext increased with a starting point value above F0-values. Therefore, the interaction of F0 and F ext indicates that F ext increases for single-case 1 up from the F0-plateau level between 1,7- 2,4N. Because this range is contained in the

suggested 0-3N range, this result supports the idea that a plateau-value-range for F0 between 0-3N could be considered as a premise to develop F ext-improvements.

2) The reason for the high F ext-value as starting point value in phase 3 might stem from a general improvement resulting from two previous training phases. This effect might be considered as promising effects that can also be gained in patients suffering from a severe grade of the hand paresis post-stroke. Krakauer 2006 outlined that also chronic cases more than one year post-stroke do respond to rehabilitation training by showing motor improvement after treatment with novel techniques (Krakauer 2006; Page et al. 2004). Furthermore he states that cases more than six months post-stroke can improve when the training is executed more extended (Krakauer 2005). This effect was also seen for single-case 1 in manners of the positive F ext-value at T4 with a strong increase to T5 as possible result from total three training phases (Krakauer 2005).

Moreover, the positive effect gained in phase 2 with polymetric music could be discussed as premise for the high F ext-value at T4. If this would be the case, polymetric music could be considered as a sound environment that stabilized functional effects gained in phase 1 and phase 2.

Single-Case 1 showed a strong F ext-increase in phase 3 with favorite self-selected music. This patient had chosen a german pop song from the 80ies with a political song text. He talked a lot about his personal relation to the piece and emphasized the political meaning of this song. This patient seemed shy and insecure especially in phase 1. He had very sweaty hands, not just on the affected side, especially in phase 1 and 2 which was seen by the observer when applying the magnetic contacts to the finger tips. In phase 3, he was more motivated and seemed to feel more self-confident during training. One possible reason for that might be, that the self-determined action to choose a piece, to introduce this piece to the therapist, and to listen to it during training, increased self-confidence of the patient. Jäncke 2008 outlined a close relation of music, emotion and the formation of memories. The memories induced by listening to music of his past, might have influenced the patient`s emotional and cognitive system (Jäncke 2008). This could have supported the positive development of functional outcomes in phase 3.

As in the clinical study results showed that the sound-group had higher ratings in the IMI-subitem “perceived choice” than the group training without sound, maybe sound affects whether patients feel self-determined and in turn motivated or not. To feel self-determined by having the option to choose something as well as making a decision was already shown to influence intrinsic motivation positively by Ryan and Deci 2000. Ryan and Deci outlined that competence, autonomy and relatedness modulate strongly whether a subject is motivated intrinsically or not (Ryan und Deci 2000).

3) The recordings of single-finger forces in single-case 1 showed that lowest F0-values were achieved in phase 1 for the third finger, in phase 2 for thumb and in phase 3

for the index finger. The highest F0-values were recorded in phase 1 for little finger, in phase 2 for little finger and in phase 3 for the thumb. F ext-values were highest in phase 1 and phase 2 for thumb and in phase 3 for the little finger. Lowest extension forces were seen in phase 1 for little finger, in phase 2 for little finger and in phase 3 for the index finger. This result does not support the idea that the little finger would be affected lowest from involuntary muscle tension in general, as in phase 1 and 2 this was the finger which was recorded with the highest F0-value. But in phase 3, the little finger showed the highest value for F ext and lowest F0-values for the thumb. In this phase the patient was also generally advancing most in manners of an F ext-increase and a F0-decrease. The change from phase 1 and 2 to the phase 3 was interesting and differed from results seen in the other single-cases. A possible reason for that might be that this patient was insecure and psychological aroused due to inner stress in phase 1 and 2. This was different up from the point when this patient trained with self-selected favorite music. This indicates that in patients showing nervous and insecure behavior, it might be helpful to involve them into the process of therapy design. One possible way could be to offer them to suggest training music. Therefore, these patients should still fulfill an adequate score of the Box and Block Test, suggested in chapter 4.

Single-Case 2:

1) In Single-Case 2 the interaction of F ext and F0 was characterized by a strong Fext-decrease in phase 1, followed by a crossing of F ext- and F0-values in phase 2 and in phase 3. The F0- value-range was between 36,6-0,8N. Crossing of F ext and F0 occurred at a level of 1,9N. Like in the single-case 1, this crossing might indicate that a value-range of F0 between 0-3N could be considered as premise to develop F ext-improvements. The crossing of the linear function of F0 with the linear function of F ext occurred in phase 2 and 3 in which the level of F0 was below 1,5N.

The F0-value at T0 was extremely high. One possible reason for that might be that till to this point, the patient was not familiar with the therapeutic setting with a robot. Furthermore, this patient was in general more excited and nervous, especially in the very first session. This might be reflected in the high F0-value of T0.

2) In single-case 2, the recordings of F ext and F0 differed in phase 1 to phase 2 in manners of an extremely strong F0-decrease in phase 1 which was followed by a stable F0-value-range of 0,1-1,5N in phase 2 and 3. The extension forces increased in all three phases, which was strongest in phase 3. This was the phase in which self-selected music was applied. This patient had chosen an American song from the 70ies which he, as well as the patient in the single-case study 1, introduced to the therapist very detailed by explaining the personal meaning of this song and the socio-political circumstances of the time when it was released. The positive effect reflected as F ext-increase in phase 3 might be related to the positive mood induced by this song. According to Jäncke 2008

and Eschrich et al. 2008, familiar music can cause automatically a state of being awake, high arousal and it can induce emotions that in turn influence cognitive processes (Eschrich et al. 2008). This supports the idea that self-selected favorite music might have induced a general high level of motivation. Furthermore, the F ext-increase might result from the two previous training phases. If so, than this again supports Krakauer 2005, who suggested that also chronic patients can benefit from therapy when training is carried out longer.

3) The recordings of the single-finger forces in F0 and F ext displayed that lowest F0-values were achieved in all three phases 1-3 for the little finger. Highest F0-values were recorded in phase 1 for the thumb, in phase 2 for the third finger and in phase 3 for the index finger. The lowest F ext- values were measured in phase 1 and 3 for the third finger, in phase 2 for the fourth finger. The highest extension forces were assessed in all three phase 1-3 for the thumb. This indicates that lowest F0-values can be found in the little finger which was expected due to anatomical distance and muscle unit recruitment distance to the thumb. The thumb was assessed with the strongest flexion forces. In sum, this contributes to a stable and strong grasping ability. The reason for these force characteristics of thumb and little finger might result from the training focus which was put on these two fingers.

Single-Case 3:

1) Single-Case 3 showed that the interaction of F ext and F0 was characterized by a strong F0-decrease in phase 1 due to a very high starting value for F0 at T0. In phase 2, a crossing between F0-and F ext values occurred. In phase 3, the F0 starting point is already below the F ext value while F ext increase in this phase most. The crossing of the linear functions from F ext and F0 occurs at 1,9N. Because the value of 1,9N is contained in the suggested F0-range 0-3N as premise for an F ext increase, this indicates that such a value-range might be a premise to increase F ext-values.

The very high F0-value at T0 might be related to a general excitement at the very first session like it was described for the previous discussed single-case 2.

2) The different sound conditions from phase 1 to 3 showed that in the phase without sound a strong F0-decrease was achieved. This might be related to the point of general excitement reflected in an extremely high F0-value recorded at T0. In phase 2 F0-and F ext-values crossed so that F ext resulted in superior values than F0 at the end of phase 2. This might indicate that this patient benefited from polymetric music with game-related sound feedback. In phase 3 this subject already started with an F ext-value above the F0-value and increased F ext strongest, compared to phase 1 and 2. This positive effect might result from a positive motivation during training with music as it was described in single-case 1 and 2.

But this patient reported to not be interested in music especially. Because of that this patient did not bring self-selected music and asked for a suggestion by the therapist. The therapist chose waltz-music which the patient also agreed with. In contrast to the 2 other single-cases, this patient did not talk about personal relations to this music. It seemed as if this patient was not very interested in the music. But instead this patient was highly ambitious in training with a robot. The training motivation was also higher than in single-case1 and 2, even at phase 3. Therefore, the point that music might have been the main reason for the patient`s motivation is discussable. The positive effect might have been rather a result from previous training effects gained in phase 1 and 2. This patient was very motivated when reaching the crossing of F0 and F ext. Following, the general advancement might have been interacting with a general high motivation which even increased more when small positive improvements got visible for the patient.

3) The recordings of the single-finger forces in F0 and F ext displayed that lowest F0-values were achieved in all three phases 1 to 3 for the little finger, while the highest F0-values were seen in all three phases 1 to 3 for the index finger. F ext values were highest in all three phases 1 to 3 for the little finger, and lowest in phase 1 for the third finger, in phase 2 and 3 for the index finger. In general, most activity within all fingers came from the little finger.

The lowest F0-values of all five fingers was expected for the little finger which was this finger in this single-case. The highest F ext-value was recorded for the little finger as well. Together this supports the idea that a very low F0-value is premise to develop finger extension forces. That the little finger achieved highest values in finger extension compared to other fingers might be due to the reason that the training focus on thumb and little finger showed functional effects. Moreover, the highest F0-values in all three phases and the lowest F ext-values for two phases were seen for the index finger. It was discussed before that thumb and index finger usually show a strong muscle synergy which limits the ability to extend the fingers in pinch-tip grasping tasks. Therefore, this single-case illustrates that one way to bypass the problem of a strong muscle co-activation pattern between thumb and index, might be to start with thumb and little finger. At a later stage, when extension forces are clearly above F0-values, other fingers could be involved step by step.

Single-Case 1-3:

General limitations of these single-case studies are that all three cases trained with the same order of sound conditions. Because of that, no comparison between these subjects in regards of another sound condition-order can be drawn. Moreover, the wash-out phase of 4 weeks was very short. The training effects gained in each phase might have influenced the effects of the following phase. Whether this would be a therapeutic success, it makes a differentiation of results gained in each phase less effective. The observer and therapist were the same person. This could lead to a biased treatment or analysis of the data on one hand. On the other hand, because of that, the perspective regarding subjective description of the psychological profile of each patient might have been more homogeneous. The positive outcomes with an extremely strong F0-decrease in phase 1 in single-case 2 and 3 have to be considered carefully. The high starting value in F0 might have been occurred, because patients were in general excited in the first session. Beside of that, the patients might have needed some time to get familiar with the technical environment and the new therapist before being able to relax. Therefore phase 1-outcomes are not as valuable as it was intended.In the following section the three main objectives will be discussed for single-case 1-3 in the same structure as in each single-case discussion.

1) The interaction of F0- and F ext-values was characterized on all three single-case studies by a strong F0-decrease in phase 1, followed by a crossing of F0- and F ext-values in phase 2, and a clear F ext-increase with F ext- starting values above F0. Furthermore, in phase 2 and 3 a stable F0-value range was seen independently of the F ext-increase in phase 3.

All three subjects show a positive development with a F0-decrease from phase 1 to phase 3, which can be interpreted as a reduction of involuntary muscle tension. Furthermore, for all three cases from phase 1 to 3, extension forces of the hand increased. Together, these two effects gained in all three cases over three phases of robotic hand function training under different sound conditions indicate, that prolonged training for patients suffering from a severe grade of a hand paresis post-stroke (> 12 months post-stroke) can improve. As mentioned before, this supports the statement of Krakauer 2005 that chronic patients (more than six months post-stroke), need a longer training time to gain enhancements compared to other cases.

The value-range of 0-3N which was suggested as possible threshold up from which finger extension forces can occur is supported by all three single-case studies. Considering the mean values of the hand of F0 and F ext of all three cases, the crossing of F0- and F ext linear function occurs at 1,6N. 1,6N is contained within the suggested range of 0-3N. Because of that, it might be relevant for further investigations to use a bigger sample size and to refine the boarder values of this F0 value-range.

2) Here the impact of sound on F0 and F ext- values are discussed. In all three cases the best outcomes in manners of a clear F ext-increase and a stable F0-value-range between 0-3N was seen in phase 3. This could be regarded as a positive effect caused by self-selected music which was applied to robotic training in this phase. But this effect might as well be a result from prolonged training over total three training phases. Further investigations with longer wash-out phases than 4 weeks would be needed, to ensure that the music was the reason for this positive effect rather than a general

training effect.

Furthermore, the second training phase in which polymetric music was applied, is the phase in which the crossing of F0- and F ext-values occurs in all three cases. In the single-case 1, the crossing occurs twice, in phase 1 and once more in phase 2. The crossing of F0- and F ext values at phase 2 could be interpreted as an effect which was caused by the application of polymetric music. Then, polymetric music could be considered as stimulation that enables to advance in F ext while reducing F0. Moreover, this result might indicate, that phase 2 with a stabilizing character is premise to improve in the following phase 3.

Together, all three single-cases show a similar course of development which can be subdivided in three steps: First, a strong F0-decrease in the phase without sound occurs. Second, a crossing of F0- and F ext-values in phase 2 with polymetric music is given. Third, a clear distinction of F0- and F ext-values is visible in phase 3 with self-selected music. Here, the F ext- values start with a higher level than F0 and F ext-increases more than in phase 1 and 2. Furthermore, a stable low F0-value-range is seen.

Aluru et al. 2014 studied effects of auditory constraints (no sound, metronome, non-musical happy sounds, and self-selected music) on motor performance during a bimanual wrist extension task in patients suffering from an arm paresis post-stroke. These authors found that patients from the spastic co-contraction-group were able to increase the ability to extend the wrist while reducing muscle co-action without any sound stimulation. This result is similar in one point with the here presented single-cases: F0 was decreased strongest in phase 1 without sound like it was described by Aluru et al. 2014 for the spastic co-contraction group assessed without sound. This result could be considered as a comparable effect with a reduction of muscle co-activation. But in the single-case studies no F ext-increase was found during training without sound like it was shown by Aluru et al 2014. This might be due to the reason that the single-cases were not suffering from spastic co-contraction or because the wrist is in general less complex affected by spasticity than the hand with five fingers. Furthermore, performance measures which were carried out in the study by Aluru et al. 2014, differ from training effect measures used in the single-case studies. The difference of performance and function measures was discussed already more detailed in 4.4..

Regarding the different sound conditions, two of the three cases were especially motivated in phase 3 with self-selected music. This was indicated by their spontaneous positive self-report about their personal relation to the selected piece. Single-case 3 did not choose a song on her own. Independently, in phase 3 in all three cases a positive effect with a strong F ext-increase was seen. This might be related to the perception of being more involved in the therapeutic intervention design by getting an offer to choose the sound environment. Moreover, positive memories related to the music which was chosen, and also for the well-known waltz-music, might have modulated the mood during the training in phase 3. Another reason for single-case 1 and 2 being specifically more motivated in phase 3 compared to phase 1 and 2, might stem from the fact that the patients seemed to enjoy the introduction of the self-selected piece to the therapist. This might have improved the patient-therapist relation.

3) Lowest F0-values were recorded most often for the little finger. Highest F0-values were documented most often for the index finger. Highest F ext-values were assessed most often for the thumb. Lowest F ext-values were measured most often for the third finger. Together, this shows that the little finger was most probably least affected by involuntary muscle tension in all three patients over three training periods. The index finger was expected to show high muscle tension which is reflected in highest F0-values assessed most often for this finger. A possible reason for that might be that the close connection in muscle recruitment between thumb and index finger post-stroke increased spastic symptoms in this finger while the thumb was trained in active extension.

The reason for most often highest F ext- values for the thumb and lowest F0-values for the little finger in all phases 1-3 furthermore implies two aspects: First, that active training of thumb and little finger showed a positive effect on these two fingers, and second, that the little finger is least affected by involuntary muscle tension.

5.5 Outlook

Three single-case studies were presented. All three participants in the single case studies were suffering from a severe grade of a hand paresis post-stroke and the timespan between insult and study participation was longer than 12 months. All cases underwent three training phases each consisting of nine sessions robotic hand therapy with different sound conditions in each phase (phase 1: no sound, phase 2: polymetric music + game-related sound feedback, phase 3: self-selected music + game-related sound feedback). Between each training phase a wash-out phase of 4 weeks without any training was applied. Assessments were carried out on hand forces in rest in a predefined position (F0) and of hand extension forces (F ext) as well as F0 and F ext of all single fingers at each start and end of a training phase (T0,T1,T2,T3,T4,T5).

One goal of these single-case studies was to explore whether the measure of the hand force in a predefined position in rest (F0) ranging between 0-3N could be regarded as a premise for an increase of finger extension forces (F ext). In all three single-cases, F ext increased up from F0-values above a level of 1,6N. Accordingly, it might be beneficial to observe whether a 1,6N value of F0 could serve as starting point up from which sound could be evaluated applied to robotic hand therapy also for this specific patient group. In the previous clinical study results showed that patients suffering from a severe grade of a hand paresis did not benefit from sound. In contrast, the single-case studies reveal that, as soon as F0-values are at a level of 1,6N, F ext can increase while F0 stays at a stable value-range below F ext. These characteristics for F0 and F ext values were fulfilled in phase 2 with polymetric music. Because of that, it could be possible that up from a F0-value of 1,6N, sound could be beneficial also for patients suffering from a severe grade of a hand paresis post-stroke. For future evaluations a comparison of two groups, one that trains with sound up from a level of 1,6N for F0, and one that trains without sound could be observed. Therefore, a bigger sample size needs to be investigated which allows to compute the F0-value range around 1,6N up from which F ext increases more particularly. Furthermore, the single-case studies explored the impact of an additional sound environment, self-selected favorite music, which was not used in the clinical study presented in chapter 4. Three training phases were compared to see whether, each phase with a different sound environment (no sound, polymetric music and self-selected music + game-related sound feedback) had an effect on F0 and F ext- interaction in patients suffering from a severe grade of a hand paresis syndrome. The crossing of F ext and F0-values occurred most often in phase 2 with polymetric music and game-related sound feedback, while the strongest F0-decrease was achieved in phase 1 without sound. In the single-case studies, polymetric music did not boost effects like it was seen in the previous presented clinical study in the patient groups that were affected by a moderate or mild grade of a hand paresis. It rather showed to be the stimulation design compared to no sound and self-selected favorite music, which led to the point in which extension forces overcame forces recorded in rest. Moreover F0-values stayed on a stable level in this phase. The strongest increase of F ext was assessed in the phase with self-selected music. According, it might be beneficial to subdivide treatment in three periods with different sound conditions. First, training without sound could be evaluated in regards of whether this sound condition enables a F0-decrease to at least 1,6N. Than a phase with polymetric music and game-related sound feedback could be investigated to explore whether this stimulus is useful to stabilize the low F0-value and to push the development of extension forces to a level that is above F0-values. Up from then, also effects of self-selected favorite music could be examined. It is likely that self-selected favorite music could increase motivation and in turn promote function.

In summary, it might be possible, that severe cases could benefit from sound up from another threshold of ability than the assessment of BBT used in chapter 4., shows. Therefore, also F0 and F ext-linear functions might be relevant in further investigations. In order to observe the concrete threshold value which could indicate the time-point up from which the application of sound is beneficial, the crossing of F ext and F0-linear function could be taken into account.

Single-finger-force recordings of the hand in rest (F0) and active extension (F ext) revealed that most often the little finger was least affected of involuntary muscle tension. The finger showing strongest F ext-values was most often the thumb. This supports the idea that these fingers could serve as an alternative starting point for hand therapy that commonly focusses on training with the finger combination thumb and index. The single-case-study results indicate that the combination of thumb and little finger gains positive results in both fingers without affecting F0-values of the thumb. The effect of active extension training of thumb and index might increase F0-values compared to thumb-little finger training, because thumb and index finger are closely connected in manners of muscle co-activation patterns (Bhardwaj and Sabapathy 2011). Together, this means that active training of thumb and little finger showed a positive effect on these two fingers, and second, that the little finger is least affected by involuntary muscle tension. Furthermore, active extension training of thumb and index can result in an increase of extension forces for thumb and little finger without affecting involuntary muscle tension patterns counteracting active hand extension. The therapeutic approach focusing on the finger combination thumb and little finger could be investigated by comparing a group training with thumb and index finger and one group training with thumb and little finger.

In the clinical study presented in chapter 4, the Box and Block Test was concluded as possible screening tool that determines patients that can benefit from sound applied to robotic hand training and patients for which sound is counterproductive. Such a grouping is needed as the clinical study showed that some patients do not benefit from sound and therefor need to be prevented from negative effects of sound-extended training. To develop an additional screening tool, data on F0 and F ext are recommended for future research.

OUTCOMES

6. SUMMARY OF OUTCOMES

6.1. Research approach

6.2 Summary of results

6.2.1 Results- literature review

6.2.2 Results- experiment series

6.2.3 Results- clinical study

6.2.4 Results- single case studies

6.1 Research approach

In this chapter a brief summary of the thesis structure is given. Afterwards, an overview on all results gained in this thesis will be summarized. Finally, the impact of these results on clinical usage of robots and sound in the context of post-stroke hand rehabilitation is presented.

In this thesis an investigation on the role of sound in robotic hand rehabilitation post-stroke was performed. The structure of this observation was divided into the following steps: First, a literature review was used to determine music- and sound-components showing potential benefit for robotic hand function training post-stroke. Second, these promising music- and sound-components were composed into sound prototypes for robotic hand function training post-stroke. Third, these sound prototypes were evaluated throughout an experiment series with healthy subjects and stroke patients performing a fine motor task. Effects of different sound-conditions including a condition without sound on performance and mood were assessed and ranked. Following, the strongest designs were explored throughout a practical test phase applied to robotic hand function training with healthy subjects and stroke patients. The goal here was to modify the sound environment in relation to the needs of robotic training and to conclude a sound design for a clinical study design. The auditory environment for the clinical study resulted in a combination of polymetric music and game-related sound feedback. In a next step, a clinical study was carried out which examined effects of this specified sound applied to robotic hand function training post-stroke compared to training without sound on function and motivation. In the clinical study, 34 patients were assigned either to the control-group (n=14) or the sound-group (n=20) and received 9 therapy sessions robotic hand function training over three weeks. Assessments on function and motivation were carried out before, during, after the last intervention and 2 months follow-up. Primary outcome measures, the Box and Block Test (BBT) and the Intrinsic Motivation Inventory (IMI), secondary outcome measures on function and motivation, and two subgroup analysis dividing the patients into three grades of severity (subgroup A) and different time-spans between insult and study participation (subgroup B) were compared between sound- and control-group. The main goal was to observe whether polymetric music and game-related sound feedback applied to robotic hand function training would show significant effects on function and motivation compared to training without sound. Furthermore, it was an aim to answer whether sound or no-sound is effective for patients with different pathological characteristics (grade of severity/ timespan between insult and study participation). In addition to this clinical study, three single-case studies were carried out. In the single-case studies, robotic hand function training was performed over three training phases, each phase consisting of 9 therapy sessions and each with another sound condition (phase 1- no sound, phase 2- polymetric music and game-related sound feedback, phase 3- self-selected favorite music). Between the training phases 1 to 3, 2 months wash-out phase were applied. The goal of these single-case studies was to extend knowledge gained from results of the clinical study with a special focus on an additional sound environment (self-selected favorite music), effects of prolonged training consisting of three training cycles each with 9 sessions, and the effect of different sound environments on the development of single finger forces in rest and active extension. Moreover, single finger force profiles were observed to examine whether training with the finger combination of thumb and little finger is effective or not.

In the following section, the main findings of this thesis are summarized by outlining results of the 1) the literature review, 2) the experiment series, 3) the clinical study, 4) the single-case studies, and 5) the impact of these results for clinical usage of sound in robotic therapies.

6.2.1 Results- literature review

The literature review on effects of sound and music on motor performance, motor learning, motor and cognitive rehabilitation showed that a huge body of research indicates that sound and music can influence motivation, attention, motor performance, motor function and motor rehabilitation positively, dependent upon its design, context of application and recipient (Gebauer, Vuust 2014; Bradt et al. 2010; Amengual et al. 2013; Schneider et al. 2007; Särkämö, Soto 2012).

For the context of robotic hand function training, sound and music were outlined as stimuli with a potential to cause ambivalent effects either by improving or distracting rehabilitation. RAS, pleasant rhythmical music and acoustic real-time feedback were concluded as most promising auditory environments to promote function and motivation in robotic hand function training post-stroke.

This conclusion was based on the following assumptions: RAS, a music therapeutic technique using metronome and march-music applied to gait- and arm training, was shown to promote function, temporal regularity, velocity, and smoothness of movements in stroke patients (Bradt et al. 2010). Moreover RAS was shown to increase the level of attention during movement performance (Thaut et al. 2015; Bradt et al. 2010). Pleasant rhythmical music was shown to increase motivation, the perceived size of enjoyment and its influence on the attitude towards a machine during interaction (Sammler et al. 2007; Dautenhahn 2007; Salimpoor et al. 2014). Acoustic real-time feedback was concluded as sound environment that could impact movement coordination, increase motivation, lower the perceived size of effort and perceived size of time during training (Scholz et al. 2014; Rosati et al. 2012; Effenberg et al. 2011; Fritz et al. 2013; Dubus, Bresin 2013).

The need for a specification of these sound environments for the context of robotic hand function training was emphasized due to the complexity of the technical environment consisting of a robot, a virtual environment and a therapist beside, the complexity of hand and single finger movements, and pathological characteristics of a hand paresis syndrome. In summary, RAS, pleasant rhythmical music and acoustic real-time feedback were determined as sound environments with a potential to improve rehabilitation of the paretic hand, still needing modifications to meet the needs of this specific context. Moreover it was concluded that empirical investigation are needed to provide effective sound extensions for the specific context of robotic hand rehabilitation training post-stroke.

6.2.2 Results- experiment series

Based on results of the literature review, sound design prototypes were composed to be furthermore evaluated empirically throughout an experiment series E1-3 with 20 healthy subjects and in E4 with 8 stroke patients. The sound design prototypes included a metronome-beat and rhythmic sound designs that differed from a common RAS-design like a metronome. Therefore, speech samples embedded in a rhythmic 2/ 2- meter grid (a spearcon-beat), a rhythmic multisensorial display (metronome combined with a rhythmic hit on the foot), and waltz-music with another meter than 2/2, more specifically a 3/ 4 meter was explored. All sound designs were presented in the tempo of 200bpm.

In E1-3 these stimuli were applied during the performance of a fine motor task, the Nine Hole Peg Test (NHPT), and effects on performance and mood on 20 healthy subjects were compared to a condition without sound. E1-3 differed in level of difficulty to simulate limitations of a hand paresis syndrome. Results showed that sound has an effect on mood and performance during performance of a fine motor task when it is compared to a condition without sound. An auditory rhythmical display outperformed not just the condition without sound but also the multisensorial rhythmic display. Performance qualities were generally better with sound than without sound in all levels of difficulty. Best performance was achieved in an easy condition with waltz-music, whereby in more difficult levels metronome gained best results. Mood was rated highest with waltz-music, independently of the level of difficulty.

In experiment E4 with 8 stroke patients, the two strongest sound designs seen in E1-3, waltz-music and metronome-beat, were furthermore evaluated. Effects on function of these auditory environments were compared to a condition without sound during performance of the Box and Block Test (BBT). In this experiment, stroke patients gained best outcomes with waltz-music, followed by metronome. Also in this experiment, a sounding environment increased functional outcome compared to the no-sound condition. Best results were gained with waltz-music. As waltz-music and the metronome-beat gained better outcomes than no-sound in all four experiments, these two sound-stimulation designs were concluded as test material for further investigations applied to robotic hand function training while the spearcon-beat and multisensorial beat were excluded. Interestingly, less complex sound material like the metronome-beat which is commonly used in RAS was outperformed by the more complex material of waltz-music in E1 and E4. Waltz-music with a 3/ 4 meter, differs from the commonly used metrical structure of RAS (2/ 2 meter). For the purpose of gait training or gross cyclic movements of the whole upper extremity, a meter of 2/ 2 offers to synchronize movements to the beat intuitively and by that improvements of movement execution and planning can be achieved (Bradt et al. 2010; Thaut et al. 2015). In the presented experiments E1-4, subjects did not synchronize their movements to the rhythm but performed better with sound (especially with waltz-music and metronome) than without sound. This led to the conclusion that the design concept of RAS could potentially be extended effectively for fine motor tasks by including music with another meter than 2/ 2. An extended version of RAS that involves other meters would imply that an additional effect mechanisms beside of synchronization would need to be investigated and defined. A possible effect-mechanism induced by an alternative metric structure might lie in anticipation of an accent structure as well as on the process in which a subjective construction of accents on a structure takes place. The construction process might be modulated by accents within a specific movement. This would mean the movement rhythm modulates the perception of musical accent structures.

The aim of E1-4 was to provide information on effects of sound and music on performance of a fine motor task to conclude potentially effective sound-designs for the context of robotic hand function training post-stroke. Because a metronome-beat and metric alternatives to commonly used RAS in form of 3/ 4- meter based waltz-music showed promising results, another metric structure was developed to be explored throughout a practical test phase within robotic hand function training. This was a polymetric structure embedded in music. Throughout a practical test phase with healthy subjects and stroke patients, waltz-music, polymetric music, metronome and game-related sound feedback were applied to robotic hand function training with the commercial system "Amadeo". The goal here was to ensure that the selected sound design would meet the needs of the patient population of stroke patients suffering from a hand paresis and of the context of robotic hand rehabilitation training. Furthermore, technical limitations of the robotic system were taken into account.

A combination of polymetric music and game-related sound feedback was concluded as most promising design for the clinical study. Polymetric music was seen as stimulus with a structure providing a stable pulse on one hand, and on the other hand, as stimulus with a metric structure that would allow to construct and perceive an accent structure suiting any movement rhythm. This was interpreted as very important aspect because of the rhythmic complexity of hand- and single-finger movements. Moreover, the test subjects reported that the polymetric music piece was perceived as "cultural neutral" compared to waltz-music. This aspect was considered as very important because robotic systems are used internationally with patients of different cultural derivations. Beside of that, test subjects were able to accept polymetric music in repeated exposure in contrast to metronome which was described as stressful by all participants. This was concluded as important factor as well, because patients receiving robot-therapies commonly need to train prolonged with this tool. In addition to polymetric music, game-related sound feedback was concluded as useful sound providing information on task performance, an easy access to the game mechanics and as motivating stimulus.

6.2.3 Results- clinical study

A clinical study was performed with 34 stroke patients suffering from a hand paresis post-stroke. All subjects took part in a three week treatment cycle with 9 therapy sessions of robotic hand function training. The study population was assigned either to the control-group (n=14) or the sound-group (n=20) which received polymetric music and game-related sound feedback applied during the robotic training. All subjects underwent a test battery that assessed function and motivation.

The results of the clinical study showed that functional outcomes of the primary outcome measure, the Box and Block Test (BBT), on all 34 study participants did not differ between the sound-group and the control-group. In the primary outcome measure of the Intrinsic Motivation Inventory (IMI), a significant difference was found between the two groups: The sound-group rated the subitems interest/ enjoyment, perceived competence, relaxation and perceived choice significantly higher than the control-group (sound-group: interest/ enjoyment: $p = 0{,}009677$ at $p < 0{,}05$; perceived competence: $p = 0{,}02065$ at $p < 0{,}05$; relaxation: $p = 0{,}040048$ at $p < 0{,}05$; perceived choice: $p = 0{,}00798$ at $p < 0{,}01$).

In addition to the evaluation of primary outcome measures (BBT, IMI), secondary outcome measures (NHPT, GF, F0, F ext, ES, PSE, GAS) and two subgroup analysis (subgroup A: grades of severity/ subgroup B: timespan between insult and study participation) were computed.

According to the subgroup analysis A (severe, moderate mild), sound had a significant influence on outcomes of BBT (severe: sound-group (n=12) vs. control-group (n=5), moderate: sound-group (n=4) vs. control-group (n=4), mild: sound-group (n=4) vs. control-group (n=5)): Mildly and moderately affected cases of the sound-group gained significant better results in the BBT than the control-group (moderate: $p = 0{,}060187$ at $p= 0{,}01$; mild: $p = 0{,}097544$ at $p <0{,}01$). In contrast, severely affected cases of the control-group gained significant better results in the BBT than the sound-group (severe: p = 0,029704 at p < 0,05). Moreover, a significant higher value for hand extension force was found for severe cases in the control-group compared to the sound-group (severe: p = 0,027491 at p < 0,05). Concluding, the combination of polymetric music and game-related sound feedback caused ambivalent effects depending upon the grade of severity: For cases suffering from a severe grade of the hand paresis syndrome post-stroke, the application of sound deteriorated the therapeutic effect significantly compared to subjects training without sound. In this group, sound lowered the outcome of BBT significantly compared to the group training without sound. In addition, severe cases of the sound group showed a significant lower development of hand extension forces than the control-group. This negative effect of sound on function in patients suffering from a severe grade of a hand paresis was independent of significant higher motivation ratings in the same group (see below). In contrast, for moderately and mildly affected cases, therapy effects were boosted with sound significantly compared the control-group. The control-group gained significant higher results in the BBT, and significant higher results in development of hand extension forces.

To prevent the severely affected patient-group from negative sound-induced effects, a screening before treatment is recommended which allows to determine patients that do not and that do benefit from sound. In this study, the grouping of subgroup A was based on results achieved in the BBT at baseline. This test could serve as starting point to develop a more refined screening tool. The current landmark dividing patients into subjects that benefit or do not benefit from sound is the achievement of 16 blocks in the BBT at baseline. Patients gaining less than 16 blocks in the BBT at baseline should not receive sound displays while for patients reaching more than 16 blocks, it is highly recommended to apply sound.

Furthermore, the subgroup analysis A showed that the sound-group with severly affected patients rated three items of the IMI, interest/ enjoyment, relaxation and perceived choice significantly higher than the control-group (severe: "interest/ enjoyment": p = 0,090086 at p < 0,10; "relaxation": p = 0,070526 at p < 0,01; "perceived choice": p = 0,024738 at p < 0,05), while the control-group rated one item of the IMI, Man-machine-relation, higher with significance compared to the sound-group ("Man-machine-relation": p = 0,008155 at p < 0,01). This outlines that motivation was increased in the sound-group also in subjects showing negative functional outcomes. Moreover, these results indicate that for patients suffering from a severe grade of a hand paresis, training without sound led to a better relation to the machine than sound-extended training.

In the subgroup analysis B, no significant differences between sound- and control-group were found for the BBT or other secondary outcome measures in the domain function. In the domain motivation, a significant difference within one subitem of IMI for the subgroup B3 (> 12 months post-stroke) was computed, in which the sound-group rated "value/ usefulness" significantly higher than the control-group (sound-group B3: p = 0,008155 at p < 0,05). Moreover, the same group rated the subitem of ES "motivation" higher with significance (sound-group B3: p = 0,036939 at p < 0,05). Taken together, these results shows that sound might promote the feeling of performing a valuable and useful trainings task and it might influence motivation positively in patients that are commonly receiving therapies already more than one year. Especially for this patient group motivational aspects are important due to the prolonged training phase that is needed to advance after the first three months post-stroke in which strongest functional improvement can be achieved (Krakauer 2005). The main finding of this thesis is presented in the following Figure 37:

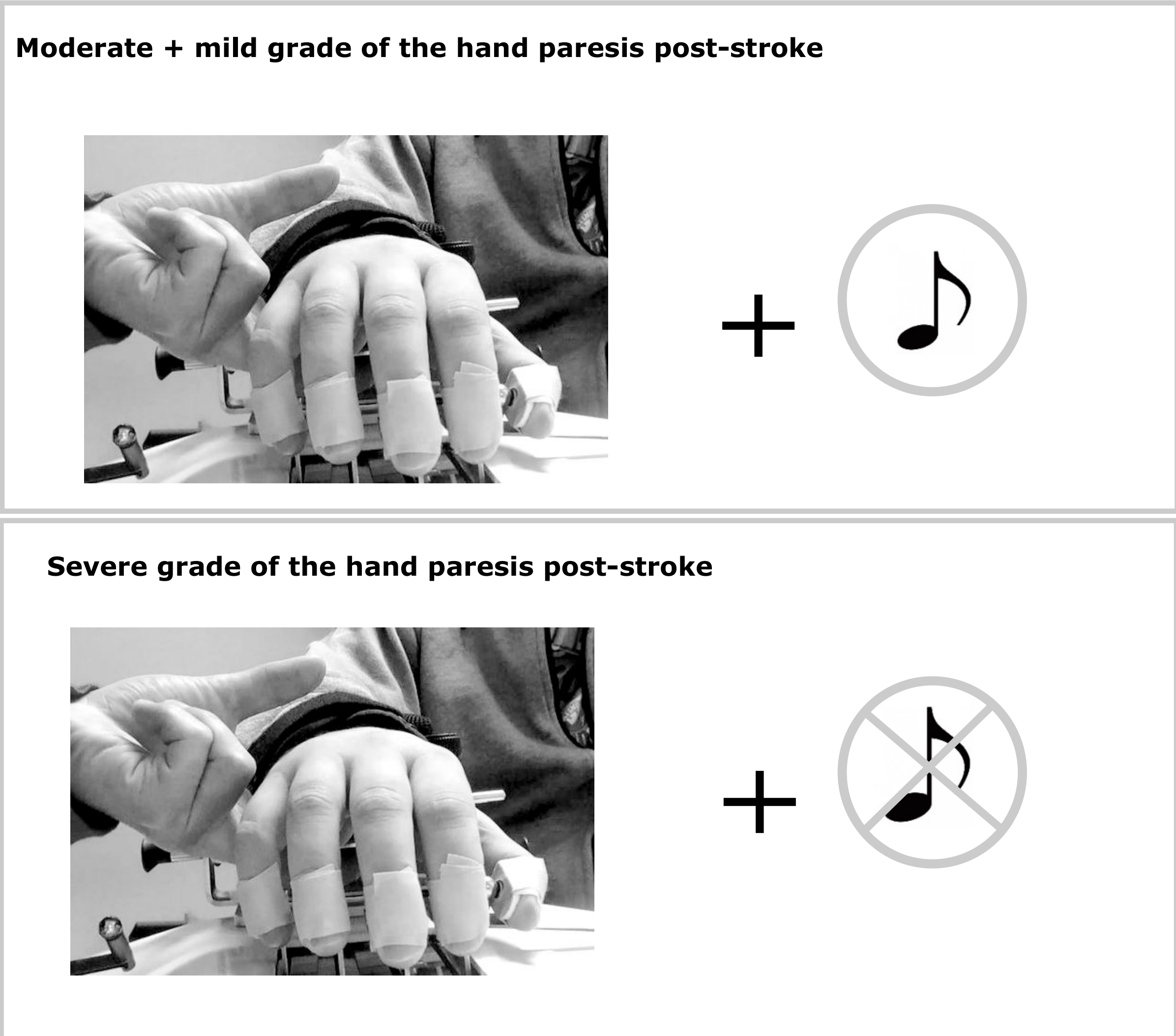


Fig. 37: Subgroup Analysis A showed that patients suffering from moderate to mild grades of a hand paresis post-stroke significantly benefit from sound (marked green). In contrast, for patients suffering from a severe grade of the hand paresis post-stroke

6.2.4 Results- single case studies

To investigate effects of sound applied to robotic hand function training post-stroke on severely affected patients that were at least 12 months post-stroke more detailed, three single-case studies were performed. The main foci of these case-studies were a) to explore whether there was an interaction between hand forces in a rest position (F0) and hand extension forces (F ext) showing a plateau-value of F0 between 0-3N as a premise for an increase of hand extension force, b) whether the different sound conditions had an influence on the development of hand forces in rest and active extension, c) whether the little finger compared to index, third and fourth finger would show lower hand forces in rest (F0). a) The recorded data of finger forces in rest and active extension of three single-case studies indicate that a threshold value of 1,6N for hand forces in rest could serve as landmark dividing patients into patients gaining benefit from sound (F0 > 1,6N) and patients for which sound might be counterproductive (F0 < 1,6N). This value was concluded because the hand extension forces started to increase up from a F0-level of 1,6N. Following, a recording of hand forces in rest at baseline is recommended as starting point for further investigations with a bigger sample size to refine an adequate F0-threshold around 1,6N, probably not higher than 3N.

b) The three sound conditions led to different effects on hand forces in rest and extension: The strongest decrease of hand force in rest was assessed in phase 1 without sound. In phase 2, polymetric music and game-related sound feedback was applied. Hand forces recorded in rest and extension showed a cross-over in this phase, whereby F ext exceeded F0. In phase 2 with polymetric music, the effect of a F0-decrase and F ext- increase was not as strong as seen in phase 1 (with a strong F0-decrease) and in phase 3 (with a strong F ext- increase). In phase 3, patients trained with self-selected favorite music. In this phase, the strongest F ext- increase was observed. According to this, a training course was concluded for further empirical investigations that could subdivide treatment in three periods with different sound conditions in the following order: First, training without sound (to induce a F0-decrease to at least 1,6N), second with polymetric music and game-related sound feedback (to examine whether this stimulus stabilizes the achieved F0-value and induces extension forces exceeding hand forces in rest). In a third phase, self-selected favorite music could be used to investigate whether this stimulation increases motivation and in turn promote functions, compared to another sound condition.

c) In general, all three single-cases benefited from the prolonged training and therefore, three training phases are recommendable. Moreover the finger combination thumb and little finger were indicated as an effective alternative to hand training with thumb and index only. This assumption was based on data showing lowest F0-values for the little finger under all fingers, while the thumb showed strongest forces for an active extension.

7. GENERAL OUTLOOK

7. GENERAL OUTLOOK

Currently sound and music are widely used in robotic technologies. In the future, the amount of robotic tools in modern neurorehabilitation settings will increase (Poli et al. 2013). This will go along with improvements of the robotic design towards soft robotics, a higher grade of perceived transparency of wearable robotics, new virtual environments with adaptive training algorithms, advances in more refined control strategies, and new technological combinations such as robots with brain computer interfaces, new sensors, or displays like 3D glasses (Bianchi et al. 2003; Laschi, Cianchetti 2014). New training environments will contain sonic elements as one part within the virtual scenarios. In this thesis, the role of sound in robotic hand function training post-stroke was investigated within a very specific context of application and sound design. Whether the empirical studies focused on this frame only, this work outlined that sound and music do cause effects on function and motivation with clinical relevance. Beside of stroke patients, rehabilitation robotics are dedicated to a wider range of patient populations including patients suffering from Multiple Sclerosis, Parkinson`s Disease, paraplegia, cerebral palsy, focal dystonia, amputees or other movement related disorders. Because of that, effects of sound and music in robotic therapies would always need to be investigated respectively to the specific patient population (Quinn et al. 2014; Chen, Howard 2014). Accordingly, a systematic investigation on effects of sound- and music applications in machine-based neuro rehabilitation systems is needed that prevents from negative side effects, amplifies therapy effects and provides information on effective sound extensions for robots. Expert perspectives from neurology, engineering, musicology, music therapy, movement science and psychology could collaborate to generate such a knowledge base.

Regarding the musical and sound component within robotic movement therapy for stroke patients, this thesis discussed promising functions of music and sound for motor rehabilitation in which it could influence motoric, cognitive, emotional and social domains positively. Different roles of music and sound could be considered in future studies: On one hand, sound could be observed in the role of a stimulation tool, on the other hand in the role of an additional feedback modality, or both in combination. According to van Vugt 2013, the term stimulation refers to an external stimulus that is presented during an activity but which is not directly connected to an action. In contrast, feedback can be defined as signal which is directly related to a performed movement (van Vugt 2013). Accordingly, music and sound could be explored as stimulation tool extending robotic training with different background music, RAS or speech. Feedback could be explored in directions such as error feedback, adaptive, corrective, continuous or short feedback to provide additional information on a movement, to enable interactive sound experiences and to promote perception, coordination, movement performance and to increase the effectiveness of motor learning. Moreover, a combination of stimulation and feedback could be observed.

Music is very often described as motivating environment and applied to robotic therapies with the same intention. Accordingly, it would be important to gain a better understanding why and which music is motivating and how it could be provided to increase motivation levels effectively. This could be examined in settings in which music is played back in the background (stimulation) or in which a robotic system is used to play music actively (feedback). In the case of playing music actively, the robot could serve as controller for virtual instruments, to create music via a moderated interaction platforms or to conduct music. This active approach could extend current motivation strategies which aim to motivate patients with gaming in single player settings and in competitive or cooperative modes in multiplayer settings (Novak et al. 2014). In contrast to a gaming experience in which the patient wins or loses a game (extrinsic motivation), the creation or modulation of music might stimulate intrinsic drives. Creating music could offer a pleasurable experience during the creation process and could result in e.g. a musical piece, which might be rewarding (Prahalad, Ramaswamy 2004). Music could also be created together with another patient or a therapist in a multiplayer setting. A musical interaction platform controlled by the robot could promote motivation, social interaction as well as function. Furthermore, an intuitive mapping of action and sound might enable robotic training without a graphical user interface. An auditory display only could potentially induce a "focus shift": Commonly the focus is given on a graphical user interface guiding tasks. In the case of an auditory display only, the focus could be given on own body movements or on other co-players allowing direct eye contact as well as movement observation of others. Those auditory displays could be extended by intelligent speech-based audio guides to moderate the tasks. Taken together, this might deepen and expand interaction with the rehabilitation robots in neuro rehabilitative settings.

This short list of possible potential roles of music and sound for robotic training outlines that a huge number of studies could investigate effects of sonic applications to enhance robotic rehabilitation training. The expected effects of music and sound might be found in performance qualities, motor learning, in functional outcomes as well as in domains such as motivation (intrinsic and extrinsic motivation) and cognition. Because robotic tools allow the continuous and precise assessment of movement qualities, the studies on music applied to robots could generate valued data on effects of music and sound on motor performance and function. As a long term goal of this field of research, the development of a tool box defining sound and music environments for specific populations and their effects on function, motivation, cognition and on social aspects could contribute to arising robotic rehabilitation technologies.

8. BIBLIOGRAPHY

8.1 Literature

8.2 Internet resources

8.3 List of Figures

8.4 List of Tables

8.1 Literature

Altenmüller, E.; Schlaug, G. (2015): Apollo's gift: new aspects of neurologic music therapy. In: *Progress in Brain Research* 217, pp. 237–252.

Aluru, V.; Lu, Ying; L., Alan; V., J.; Raghavan, P. (2014): Effect of auditory constraints on motor performance depends on stage of recovery post-stroke. In: *Frontiers in Neurology* 5, pp. 1-13.

Amengual, J. L.; Rojo, N.; Veciana de las Heras, M.; Marco-Pallarés, J.; Grau-Sánchez, J.; Schneider, S. et al. (2013): Sensorimotor Plasticity after Music-Supported Therapy in Chronic Stroke Patients Revealed by Transcranial Magnetic Stimulation. In: *PLoS ONE* 8 (4), pp. 1-10.

Balasubramanian, S.; Klein, J.; Burdet, E. (2010): Robot-assisted rehabilitation of hand function. In: *Current Opinion in Neurology* 23 (6), pp. 661–670.

Bangert, M.; Schlaug, G. (2006): Specialization of the specialized in features of external human brain morphology. In: *The European Journal of Neuroscience* 24 (6), pp. 1832–1834.

Baumgartner, T.; Lutz, K.; Schmidt, C. F.; Jäncke, L. (2006): The emotional power of music: how music enhances the feeling of affective pictures. In: *Brain Research* 1075 (1), pp. 151–164.

Bernardi, N. F.; Buglio, M. de; Trimarchi, P. D.; Chielli, A.; Bricolo, E. (2013): Mental practice promotes motor anticipation: evidence from skilled music performance. In: *Frontiers in Human Neuroscience* 7 (451), pp. 2-36.

Bianchi, L.; Babiloni, F.; Cincotti, F.; Arrivas, M.; Bollero, P.; Marciani, M. G. (2003): Developing wearable bio-feedback systems: a general-purpose platform. In: *IEEE Transactions on Neural Systems and Rehabilitation Engineering* 11, pp. 117–119.

Bidelman, G. M.; Claude, A. (2015): Musical training orchestrates coordinated neuroplasticity in auditory brainstem and cortex to counteract age-related declines in categorical vowel perception. In: *Journal of Neuroscience* 35 (3), pp. 1240–1249.

Birenbaum, D.; Bancroft, L. W.; Felsberg, G. J. (2010): Imaging in Acute Stroke. In: *Western Journal of Emergency Medicine* 12 (1), pp. 67–76.

Blank, A. A.; French, J. A.; Pehlivan, A. U.; O'Malley, M. K. (2014): Current Trends in Robot-Assisted Upper-Limb Stroke Rehabilitation: Promoting Patient Engagement in Therapy. In: *Current Physical Medicine and Rehabilitation Reports* 2 (3), pp. 184–195.

Blefari, M. L.; Sulzer, J.; Hepp-Reymond, M.; Kollias, S.; Gassert, R. (2015): Improvement in precision grip force control with self-modulation of primary motor cortex during motor imagery. In: *Frontiers in Behavioral Neuroscience* 9 (18), pp. 1-11.

Blood, A. J.; Zatorre, R. J. (2001): Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. In: *Proceedings of the National Academy of Science USA* 98 (20), pp. 11818–11823.

Bradt, J.; Dileo, C.; Shim, M. (2013): Music interventions for preoperative anxiety. In: *The Cochrane Database of Systematic Reviews* 6, pp. 1-81.

Bradt, J.; Magee, W. L.; Dileo, C.; Wheeler, B. L.; Mc Gilloway, E. (2010): Music therapy for acquired brain injury. In: *The Cochrane Database of Systematic Reviews* 7, pp. 1-44.

Bütefisch, C. M. (2015): Role of the contralesional hemisphere in post-stroke recovery of upper extremity motor function. In: *Frontiers in Neurology* 6, pp. 1-10.

Burger, B.; Thompson, M. R.; Luck, G.; Saarikallio, S.; Toiviainen, P. (2013): Influences of rhythm- and timbre-related musical features on characteristics of music-induced movement. In: *Frontiers in Psychology* 4 (183), pp. 1-10.

Burger, B.; Thompson, M. R.; Luck, G.; Saarikallio, S. H.; Toiviainen, P. (2014): Hunting for the beat in the body: on period and phase locking in music-induced movement. In: *Frontiers in Human Neuroscience* 8 (903), pp. 1-16.

Cassidy, G. G.; Macdonald, R. A. (2010): The effects of music on time perception and performance of a driving game. In: *Scandinavian journal of psychology* 51 (6), pp. 455–464.

Chanda, M. L.; Levitin, D. J. (2013): The neurochemistry of music. In: *Trends in Cognitive Sciences* 17 (4), pp. 179–193.

Chen, J. L.; Penhune, V. B.; Zatorre, R. J. (2009): The role of auditory and premotor cortex in sensorimotor transformations. In: *Annals of the New York Academy of Science* 1169, pp. 15–34.

Chen, Y.; Howard, A. M. (2014): Effects of robotic therapy on upper-extremity function in children with cerebral palsy: A systematic review. In: *Developmental Neurorehabilitation,* pp. 64-71.

Collins, K. (2013): Playing with Sound: A Theory of Interacting with Sound and Music in Video Games. London: MIT Press.

Colombo, R.; Pisano, F.; Micera, S.; Mazzone, A.; Delconte, C.; Carrozza, M. C. et al. (2005): Robotic techniques for upper limb evaluation and rehabilitation of stroke patients. In: *IEEE Transactions on Meural systems and Rehabilitation Engineering: a Publication of the IEEE Engineering in Medicine and Biology Society* 13 (3), pp. 311–324.

Connelly, L.; Jia, Y.; Toro, M. L.; Stoykov, M. E.; Kenyon, R. V.; Kamper, D. G. (2010): A pneumatic glove and immersive virtual reality environment for hand rehabilitative training after stroke. In: *IEEE Transactions on Neural Systems and Rehabilitation*

Engineering: a Publication of the IEEE Engineering in Medicine and Biology Society 18 (5), pp. 551–559.

Corbetta, D.; Sirtori, V.; Castellini, G.; Moja, L.; Gatti, R. (2015): Constraint-induced movement therapy for upper extremities in people with stroke. In: *The Cochrane Database of Systematic Reviews* 10, pp. 1-118.

Cramer, S. C.; Riley, J. D. (2008): Neuroplasticity and brain repair after stroke. In: *Current Opinion in Neurology* 21 (1), pp. 76–82.

Cross, I. (2003): Music as a Biocultural Phenomenon. In: *Annals of the New York Academy of Sciences* 999 (1), pp. 106–111.

Csikszentmihalyi, M.; Abuhamdeh, S.; Nakamura, J. (2014): Flow. In: *Flow and the Foundations of Positive Psychology*, pp. 227–238.

D'Ausilio, A.; Brunetti, R.; Delogu, F.; Santonico, C.; Belardinelli, M. O. (2010): How and when auditory action effects impair motor performance. In: *Experimental Brain Research* 201 (2), pp. 323–330.

Dautenhahn, K. (2007): Methodology and themes of human-robot interaction: a growing research field. In: *International Journal of Advanced Robotic Systems* 4 (1), pp. 103-108.

Dean, C. (2012): Group task-specific circuit training for patients discharged home after stroke may be as effective as individualised physiotherapy in improving mobility. In: *Journal of physiotherapy* 58 (4), p. 269.

Desrosiers, J.; Bravo, G.; Hebert, R.; Dutil, E.; Mercier, L. (1994): Validation of the Box and Block Test as a measure of dexterity of elderly people: reliability, validity, and norms studies. In: *Archives of Physical Medicine and Rehabilitation* 75 (7), pp. 751–755.

Dietz, V.; Macauda, G.; Schrafl-Altermatt, M.; Wirz, M.; Kloter, E.; Michels, L. (2013): Neural Coupling of Cooperative Hand Movements: A Reflex and fMRI Study. In: *Cerebral Cortex.* 25 (4), pp. 948-58

Dovat, L.; Lambercy, O.; Gassert, R.; Maeder, T.; Milner, T.; Leong, T. C.; Burdet, E. (2008): HandCARE: a cable-actuated rehabilitation system to train hand function after stroke. In: *IEEE Transactions on Neural Systems and Rehabilitation Engineering: a Publication of the IEEE Engineering in Medicine and Biology Society* 16 (6), pp. 582–591.

Dubus, G.; Bresin, R. (2013): A Systematic Review of Mapping Strategies for the Sonification of Physical Quantities. In: *PLoS ONE* 8 (12), pp.1-28.

Duncan, P. W.; Zorowitz, R.; Bates, B.; Choi, J. Y.; Glasberg, J. J.; Graham, G. D. et al. (2005): Management of Adult Stroke Rehabilitation Care: a clinical practice guideline. In: *Stroke; a Journal of Cerebral Circulation* 36 (9), pp. 1-53.

Effenberg, A.; Fehse, U.; Weber, A. (2011): Movement Sonification: Audiovisual benefits on motor learning. In: *BIO Web of Conferences* 1, pp. 1-5.

Elnady, A. M.; Zhang, Xin; X., Zhen Gang; Yong, X.; Randhawa, B. K.; Boyd, L.; Menon, C. (2015): A Single-Session Preliminary Evaluation of an Affordable BCI-Controlled Arm Exoskeleton and Motor-Proprioception Platform. In: *Frontiers in Human Neuroscience* 9 (168), pp. 1-14.

Eschrich, S.; Münte, T. F.; Altenmüller, E. O. (2008): Unforgettable film music: the role of emotion in episodic long-term memory for music. In: *BioMed Central Neuroscience* 9, pp. 1-7.

Evans, D. (2002): The effectiveness of music as an intervention for hospital patients: a systematic review. In: *Journal of Advanced Nursing* 37 (1), pp. 8–18.

Frackowiak, W. (2006): The functional anatomy of cerebral reorganisation after focal brain injury. In: *Journal of Physiology* 99 (4-6), pp. 425–436.

French, B.; Thomas, L. H.; Leathley, M. J.; Sutton, C. J.; McAdam, J.; Forster, A. et al. (2007): Repetitive task training for improving functional ability after stroke. In: *The Cochrane Database of Systematic Reviews* 4, pp. 1-66.

Friedman, N.; Chan, V.; Reinkensmeyer, A. N.; Beroukhim, A.; Zambrano, G. J.; Bachman, M.; Reinkensmeyer, D. J. (2014): Retraining and assessing hand movement after stroke using the MusicGlove: comparison with conventional hand therapy and isometric grip training. In: *Journal of NeuroEngineering and Rehabilitation* 11, pp. 1-14.

Fritz, T. H.; Hardikar, S.; Demoucron, M.; Niessen, M.; Demey, M.; Giot, O. et al. (2013): Musical agency reduces perceived exertion during strenuous physical performance. In: *Proceedings of the National Academy of Sciences* 110 (44), pp. 17784–17789.

Gaillard, V.; Destrebecqz, A.; Michiels, S.; Cleeremans, A. (2009): Effects of age and practice in sequence learning: A graded account of ageing, learning, and control. In: *European Journal of Cognitive Psychology* 21 (2-3), pp. 255–282.

Gärtner, H.; Minnerop, M.; Pieperhoff, P.; Schleicher, A.; Zilles, K.; Altenmüller, E. O.; Amunts, K. (2013): Brain morphometry shows effects of long-term musical practice in middle-aged keyboard players. In: *Frontiers in Psychology* 4, pp. 1-13.

Gebauer, L.; Vuust, P. (2014): Music Interventions in Healthcare. White Paper, pp. 1-66.

Gentilucci, M.; Castiello, U.; Corradini, M. L.; Scarpa, M.; Umilta, C.; Rizzolatti, G. (1991): Influence of different types of grasping on the transport component of prehension movements. In: *Neuropsychologia* 29, pp. 361–378.

Go, A. S.; Mozaffarian, D.; Roger, V. L.; Benjamin, E. J.; Berry, J. D.; Blaha, M. J. et al. (2014): Heart disease and stroke statistics--2014 update: a report from the American Heart Association. In: *Circulation* 129 (3), pp. 1-268.

Goldstein, L. B.; Bertels, C.; Davis, J. N. (1989): Interrater reliability of the NIH stroke scale. In: *Archives of Neurology* 46 (6), pp. 660–662.

Gourlay, D.; Lun, K. C.; Liya, G. (2000): Virtual reality and telemedicine for home health care. In: *Computer & Graphics* 24, pp. 695–699.

Gresham, G. E.; Duncan, P. W.; Stason, W. B. (1996): American Heart Association Prevention Conference. IV. Prevention and Rehabilitation of Stroke. Rehabilitation. In: *Stroke* (28), pp. 1522-1526.

Guidali, M.; Duschau-Wicke, A.; Broggi, S.; Klamroth-Marganska, V.; NEf, T. Riener, R. (2011): A robotic system to train activities of daily living in a virtual environment. In: *Medical & Biological Engineering & Computing* 49 (10), pp. 1213–1223.

Hafsteinsdottir, T. B.; Kappelle, J. Grypdonck, M. F; Algra, A. (2007): Effects of Bobath-based therapy on depression, shoulder pain and health-related quality of life in patients after stroke. In: *Journal of Rehabilitation Medicine* 39 (8), pp. 627–632.

Hammer, A., Lindmark, B. (2003): Test-retest intra-rater reliability of grip force in patients with stroke. In: *Journal of Rehabilitation Medicine* 35 (4), pp. 189–194.

Hankey, G. J.; Jamrozik, K. Broadhurst, R. J.; Forbes, S.; Anderson, C. (2002): Long-term disability after first-ever stroke and related prognostic factors in the Perth Community Stroke Study, 1989-1990. In: *Stroke; a Journal of Cerebral Circulation* 33 (4), pp. 1034–1040.

Hesse, S.; Hess, A.; Werner, C.; Kabbert, N.; Buschfort, R. (2014): 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. In: *Clinical Rehabilitation* 28 (7), pp. 637–647.

Hesse, S.; Schmidt, H.; Werner, C.; Bardeleben, A. (2003): Upper and lower extremity robotic devices for rehabilitation and for studying motor control. In: *Current Opinion in Neurology* 16, pp. 705–710.

Hesse, S.; Werner, C.; Pohl, M.; Mehrholz, J.; Puzich, U.; Krebs, H. I. (2008): Mechanical arm trainer for the treatment of the severely affected arm after a stroke: a single-blinded randomized trial in two centers. In: *American Journal of Physical Medicine & Rehabilitation/ Association of Academic Physiatrists* 87 (10), pp. 779–788.

Heuschmann, P. U.; Busse, O.; Wagner, M., Endres, A.; Villringer, J. et al. (2010): Schlaganfallhäufigkeit und Versorgung von Schlaganfallpatienten in Deutschland. In: *Aktuelle Neurologie* 37, pp. 333–340.

Higgins, J.; Mayo, N. E.; Derorsiers, J.; Salbach, N. M.; Ahmed, S. (2005): Upper-limb function and recovery in the acute phase post stroke. In: *Journal of Rehabilitation Research & Development* 42 (1), pp. 65–76.

Holmqvist, L. W.; von Koch, L. (2001): Environmental factors in stroke rehabilitation. Being in hospital itself demotivates patients. In: *BioMed Journal* 322 (7301), pp. 1501–1502.

Hove, M. J.; Fairhurst, M. T.; Kotz, S. A.; Keller, P. E. (2013): Synchronizing with auditory and visual rhythms: an fMRI assessment of modality differences and modality appropriateness. In: *NeuroImage* 67, pp. 313–321.

Hwang, C. H. Seong, J. W.; Son, D. (2012): Individual finger synchronized robot-assisted hand rehabilitation in subacute to chronic stroke: a prospective randomized clinical trial of efficacy. In: *Clinical Rehabilitation* 26 (8), pp. 696–704.

Hyde, K. L.; Lerch, J.; Norton, A.; Foregard, M.; Winner, E. Evans, A. C.; Schlaug, G. (2009a): The effects of musical training on structural brain development: a longitudinal study. In: *Annals of the New York Academy of Sciences* 1169, pp. 182–186.

Hyde, K. L.; Lerch, J.; Norton, A.; Forgeard, M.; Winner, E.; Evans, A. C.; Schlaug, G. (2009b): Musical training shapes structural brain development. In: *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 29 (10), pp. 3019–3025.

Israely, S.; Carmeli, E. (2015): Error augmentation as a possible technique for improving upper extremity motor performance after a stroke - a systematic review. In: *Topics in Stroke Rehabilitation*, pp. 1-10.

Ivanhoe, C. B.; Reistetter, T. A. (2004): Spasticity: the misunderstood part of the upper motor neuron syndrome. In: *American Journal of Physical Medicine & Rehabilitation* 83 (10), pp. 3-9.

Iversen, J. R.; Repp, B. H.; Patel, A. D. (2009): Top-Down Control of Rhythm Perception Modulates Early Auditory Responses. In: *Annals of the New York Academy of Sciences* 1169 (1), pp. 58–73.

Jacobsen, J.; Stelzer, J.; Fritz, T. H.; Chetelat, G.; La Joie, R.; Turner, R. (2015): Why musical memory can be preserved in advanced Alzheimer's disease. In: *Brain* 2015, pp.1-13.

Jäncke, L. (2008): Music, memory and emotion. In: *Journal of Biology* 7 (6), pp. 7-21.

Juslin, P. N. (2013a): From everyday emotions to aesthetic emotions: towards a unified theory of musical emotions. In: *Physics of Life Reviews* 10 (3), pp. 235–266.

Juslin, P. N. (2013b): What does music express? Basic emotions and beyond. In: *Frontiers in Psychology* 4 (596), pp. 1-15.

Kamioka, H.; Tsutani, K.; Yamada, M.; Park, H.; Okuizumi, H.; Tsuruoka, K. et al. (2014): Effectiveness of music therapy: a summary of systematic reviews based on randomized controlled trials of music interventions. In: *Patient Prefer Adherence* 8, pp. 727–754.

Kamper, D. G.; Fischer, H. C.; Cruz, E.G.; Rymer, W. Z. (2006): Weakness is the primary contributor to finger impairment in chronic stroke. In: *Archives of Physical Medicine and Rehabilitation* 87 (9), pp. 1262–1269.

Kashdan, T. B.; Gallagher, M. W.; Silvia, P. J.; Winterstein, B. P.; Breen, W. E.; Therhar, D.; Steger, M. F. (2009): The Curiosity and Exploration Inventory-II: Development, Factor Structure, and Psychometrics. In: *Journal of Research in Personality* 43 (6), pp. 987–998.

Kattenstroth, J.; Kalisch, T.; Peters, S.; Tegenthoff, M.; Dinse, H. R. (2012): Long-term sensory stimulation therapy improves hand function and restores cortical responsiveness in patients with chronic cerebral lesions. Three single case studies. In: *Frontiers in Human Neuroscience* 6 (244), pp. 1-13.

Keller, P. E.; Rieger, M. (2009): Special Issue—Musical Movement and Synchronization. In: *Music Perception: An Interdisciplinary Journal* 26 (5), pp. 397–400.

Kenyon, R. V.; Leigh, J.; Keshner, E. A. (2004): Considerations for the future development of virtual technology as a rehabilitation tool. In: *Journal of NeuroEngineering and Rehabilitation* 1, pp. 1-13.

King, H.; Pastel, R.; Ward, P.; Wallace, C. (2013): Extrinsic Motivation and User Performance. In: *Proceedings of the Human Factors and Ergonomics Annual Meeting*, pp. 1017-1021

Kirschner, S.; Tomasello, M. (2010): Joint music making promotes prosocial behavior in 4-year-old children. In: *Evolution and Human Behavior* 31 (5), pp. 354–364.

Klamroth-Marganska, V.; Blanco, J.; Campen, K.; Curt, A.; Dietz, V.; Ettlin, T. et al. (2014): Three-dimensional, task-specific robot therapy of the arm after stroke: a multicentred, parallel-group randomised trial. In: *The Lancet. Neurology* 13 (2), pp. 159–166.

Klassen, J. A.; Liang, Y. T. L.; Klassen, T. P.; Hartling, L. (2008): Music for pain and anxiety in children undergoing medical procedures: a systematic review of randomized controlled trials. In: *Ambulatory Pediatrics: The Official Journal of the Ambulatory Pediatric Association* 8 (2), pp. 117–128.

Knecht, S.; Hesse, S.; Oster, P. (2011): Rehabilitation After Stroke. In: *Deutsches Ärzteblatt International* 108 (36), pp. 600–606.

Koelsch, S. (2011): Towards a neural basis of music perception -- A review and updated model. In: *Frontiers in Psychology* 2 (110), pp. 1-20.

Koelsch, S.; Fuermetz, J.; Sack, U.; Bauer, K.; Hohenadel, M.; Wiegel, M. et al. (2011): Effects of music listening on Cortisol levels and Propofol consumption during spinal anaesthesia. In: *Frontiers in Psychology* 2 (58), pp. 1-9.

Koelsch, S. (2012): *Brain and music.* John Wiley & Sons, Ltd., West Sussex.

Koeneman, E. J.; Schultz, R. S.; Wolf, S. L.; Herring, D. E.; Koeneman, J. B. (2004): A pneumatic muscle hand therapy device. In: *Conference Proceedings IEEE Engineering in Medicine and Biology Society 2004*, pp. 2711 - 2713

Koh, C.; Pan, S.; Jeng, J.; Chen, B.; Wang, Y.; Hsueh, I.; Hsieh, C. (2015): Predicting Recovery of Voluntary Upper Extremity Movement in Subacute Stroke Patients with Severe Upper Extremity Paresis. In: *PLoS ONE* 10 (5), pp. 2711- 2713.

Krakauer, J. W. (2005): Arm function after stroke: from physiology to recovery. In: *Seminars in Neurology* 25 (4), pp. 384–395.

Krakauer, J. W. (2006): Motor learning: its relevance to stroke recovery and neurorehabilitation. In: *Current Opinion in Neurology* 19 (1), pp. 84–90.

Krebs, H. I.; Hogan, N.; Aisen, M. L.; Volpe, B. T. (1998): Robot-aided neurorehabilitation. In: *IEEE* Transactions on Neural Systems and *Rehabilitation Engineering* 6, pp. 75–87.

Kwakkel, G.; Kollen, B. J.; Krebs, H. I. (2008): Effects of robot-assisted therapy on upper limb recovery after stroke: a systematic review. In: *Neurorehabilitation and Neural Repair* 22 (2), pp. 111–121.

Ladda, A. M.; Pfannmoeller,, J. P.; Kalisch,, T.; Roschka, S.; Platz,, T.; Dinse,, H. R.; Lotze, M. (2014): Effects of Combining 2 Weeks of Passive Sensory Stimulation with Active Hand Motor Training in Healthy Adults. In: *PLoS ONE* 9 (1), pp. 1-8.

Lambercy, O.; Kim, Y.; Gassert, R. (2013): Robot-assisted assessment of vibration perception and localization on the hand. In: *Disability and Rehabilitation. Assistive Technology* 8 (2), pp. 129–135.

Langhorne, P.; Pollock, A.; Baer, G.; Campbell, P.; Choo, P. L. et al. (2014): Physical Rehabilitation Approaches for the Recovery of Function and Mobility After Stroke: Major Update. In: *Stroke* (45), pp. 1-2.

Langhorne, P.; Bernhardt, J.; Kwakkel, G. (2011): Stroke rehabilitation. In: *Lancet* 377 (9778), pp. 1693–1702.

Langhorne, P.; Coupar, F.; Pollock, A. (2009): Motor recovery after stroke: a systematic review. In: *The Lancet. Neurology* 8 (8), pp. 741–754.

Large, E. W.; Snyder, J. S. (2009): Pulse and meter as neural resonance. In: *Annals of the New York Academy of Science* 1169, pp. 46–57.

Laschi, C.; Cianchetti, M. (2014): Soft Robotics: New Perspectives for Robot Bodyware and Control. In: *Frontiers in Bioengineering and Biotechnology* 2, pp. 1-5.

Laver, K. E.; George, S.; Thomas, S.; Deutsch, J. E.; Crotty, M. (2015): Virtual reality for stroke rehabilitation. In: *The Cochrane Database of Systematic Reviews* 2, pp. 1-53.

Lawrence, E. L.; Fassola, I.; Werner, I.; Leclercq, C.; Valero-Cuevas, F. J. (2014): Quantification of dexterity as the dynamical regulation of instabilities: comparisons across gender, age, and disease. In: *Frontiers in Neurology* 5, pp. 1-13.

Liao, K.; Xiao, R.; Gonzalez, J.; Ding, L. (2014): Decoding individual finger movements from one hand using human EEG signals. In: *PLoS ONE* 9 (1), pp. 1-12.

Loureiro, R. C. V.; Harwin, W. S.; Nagai, K.; Johnson, M. (2011): Advances in upper limb stroke rehabilitation: a technology push. In: *Medical & Biological Engineering & Computing* 49 (10), pp. 1103-1118.

Lum, P. S.; Burgar, C. G.; Shor, P. C.; Majmundar, M.; Van der Loos, M (2002): Robot-assisted movement training compared with conventional therapy techniques for the rehabilitation of upper-limb motor function after stroke. In: *Archives of Physical Medicine and Rehabilitation* 83*,* pp. 952–959.

Lum, P. S.; Godfrey, S. B.; Brokaw, E. B.; Holley, R. J.; Nichols, D. (2012): Robotic approaches for rehabilitation of hand function after stroke. In: *American Journal of Physical Medicine & Rehabilitation/ Association of Academic Physiatrists* 91 (11-3), pp. 242-254.

Lundstrom, E.; Smits, A.; Terent, A.; Borg, J. (2010): Time-course and determinants of spasticity during the first six months following first-ever stroke. In: *Journal of rehabilitation medicine* 42 (4), pp. 296–301.

MacDonald, R. (2013): Music, health, and well-being: A review. In: *International Journal of Qualitative Studies on Health and Well-being* 8, pp. 1-13.

Maciejasz, P.; Eschweiler, J.; Gerlach-Hahn, K.Jansen-Troy, A.; Leonhardt, S. (2014): A survey on robotic devices for upper limb rehabilitation. In: *Journal of NeuroEngineering and Rehabilitation* 11, pp. 1-29.

Maclean, N.; Pound, P. (2000): A critical review of the concept of patient motivation in the literature on physical rehabilitation. In: *Social Science & Medicine* 50 (4), pp. 495–506.

Maclean, N.; Pound, P.; Wolfe, C.; Rudd, A. (2000): Qualitative analysis of stroke patients' motivation for rehabilitation. In: *BioMed Journal* 321 (7268), pp. 1051–1054.

Maes, P.; Wanderley, M. M.; Palmer, C. (2014): The role of working memory in the temporal control of discrete and continuous movements. In: *Experimental Brain Research* 233, pp. 263–273.

Mainka, S. (2015): Music stimulates muscles, mind and feelings in one go. In: *Frontiers in Psychology* 6 (1547), pp. 1-3.

Malcolm, M. P.; Massie, C.; Thaut, M. (2009): Rhythmic auditory-motor entrainment improves hemiparetic arm kinematics during reaching movements: a pilot study. In: *Topics in Stroke Rehabilitation* 16 (1), pp. 69–79.

Margulis, E. H. (2014): *On Repeat: How Music Plays the Mind.* Oxford University Press, New York.

Masiero, S.; Celia, A.; Rosati, G.; Armani, M. (2007): Robotic-assisted rehabilitation of the upper limb after acute stroke. In: *Archives of Physical Medicine and Rehabilitation* 88 (2), pp. 142–149.

Masiero, S.; Poli, P., Rosati, G.; Zanotto, D.; Iosa, M.; Paolucci, S.; Morone, G. (2014): The value of robotic systems in stroke rehabilitation. In: *Expert Review of Medical Devices* 11 (2), pp. 187–198.

Mathiowetz, V.; Volland, G.; Kashman, N.; Weber, K. (1985): Adult norms for the Box and Block Test of manual dexterity. In: *The American Journal of Occupational Therapy: Official Publication of the American Occupational Therapy Association* 39 (6), pp. 386–391.

Maulucci, R. A.; Eckhouse, R. H. (2001): Retraining reaching in chronic stroke with real-time auditory feedback. In: *NeuroRehabilitation* 16 (3), pp. 171–182.

McAuley, E.; Duncan, T.; Tammen, V. V. (1989): Psychometric properties of the Intrinsic Motivation Inventory in a competitive sport setting: a confirmatory factor analysis. In: *Research Quarterly for Exercise and Sport* 60 (1), pp. 48–58.

Mehrholz, J.; Elsner, B.; Werner, C.; Kugler, J.; Pohl, M. (2013): Electromechanical-assisted training for walking after stroke. In: *The Cochrane Database of Systematic Reviews* 7, pp. 1-71.

Mehrholz, J.; Hadrich, A.; Platz, T.; Kugler, J.; Pohl, M. (2012): Electromechanical and robot-assisted arm training for improving generic activities of daily living, arm function, and arm muscle strength after stroke. In: *The Cochrane Database of Systematic Reviews* 6, pp. 1-64.

Mehrholz, J.; Platz, T.; Kugler, J.; Pohl, M. (2008): Electromechanical and robot-assisted arm training for improving arm function and activities of daily living after stroke. In: *The Cochrane Database of Systematic Reviews* 4, pp. 1-34.

Meilink, A.; Hemmen, B.; Seelen, H. A. M.; Kwakkel, G. (2008): Impact of EMG-triggered neuromuscular stimulation of the wrist and finger extensors of the paretic hand after stroke: a systematic review of the literature. In: *Clinical Rehabilitation* 22 (4), pp. 291–305.

Merker, B. H.; Madison, G. S.; Eckerdal, P. (2009): On the role and origin of isochrony in human rhythmic entrainment. In: *Cortex* 45 (1), pp. 4–17.

Metcalf, C. D.; Irvine, T. A.; Sims, J. L.; Wang, Y. L.; Su, A. W.; Norris, D. O. (2014): Complex hand dexterity: a review of biomechanical methods for measuring musical performance. In: *Frontiers in Psychology* 5 (414), pp. 1-12.

Morales, R.; Badesa, F. J.; Garcia-Aracil, N.; Sabater, J. M.; Perez-Vidal, C. (2011): Pneumatic robotic systems for upper limb rehabilitation. In: *Medical & Biological Engineering & Computing* 49 (10), pp. 1145–1156.

Münte, T. F.; Altenmüller, E. O.; Jäncke, L. (2002): The musician's brain as a model of neuroplasticity. In: *Nature Reviews Neuroscience* 3 (6), pp. 473–478.

Nakayama, H.; Jorgensen, H. S.; Raaschou, H. O.; Olsen, T. S. (1994): Compensation in recovery of upper extremity function after stroke: the Copenhagen Stroke Study. In: *Archives of Physical Medicine and Rehabilitation* 75 (8), pp. 852–857.

Nieminen, S.; Istok, E.; Brattico, E.; Tervaniemi, M.; Huotilainen, M. (2011): The development of aesthetic responses to music and their underlying neural and psychological mechanisms. In: *Cortex* 47 (9), pp. 1138–1146.

Nordin, N.; Xie, S. Q.; Wunsche, B. (2014): Assessment of movement quality in robot-assisted upper limb rehabilitation after stroke: a review. In: *Journal of NeuroEngineering and Rehabilitation* 11 (137), pp. 1-23.

Norman, G. (2010): Likert scales, levels of measurement and the "laws" of statistics. In: *Advances in Health Sciences Education: Theory and Practice* 15 (5), pp. 625–632.

Norouzi-Gheidari, N.; Archambault, P. S.; Fung, J. (2012): Effects of robot-assisted therapy on stroke rehabilitation in upper limbs: systematic review and meta-analysis of the literature. In: *Journal of Rehabilitation Research & Development* 49 (4), pp. 479–496.

Novak, D.; Nagle, A.; Keller, U.; Riener, R. (2014): Increasing motivation in robot-aided arm rehabilitation with competitive and cooperative gameplay. In: *Journal of NeuroEngineering and Rehabilitation* 11 (64), pp. 1-15.

Novak, D.; Riener, R. (2013): Enhancing patient freedom in rehabilitation robotics using gaze-based intention detection. In: *IEEE International Conference on Rehabilitation Robotics:* 2013, Seattle, USA, pp. 1-6.

Nudo, R. J. (2013): Recovery after brain injury: mechanisms and principles. In: *Frontiers in Human Neuroscience* 7 (887), pp. 1-14.

Oscari, F.; Secoli, R.; Avanzini, F.; Rosati, G.; Reinkensmeyer, D. J. (2012): Substituting auditory for visual feedback to adapt to altered dynamic and kinematic environments during reaching. In: *Experimental Brain Research* 221 (1), pp. 33–41.

Oujamaa, L.; Relave, I.; Froger, J.; Mottet, D.; Pelissier, J-Y (2009): Rehabilitation of arm function after stroke. Literature review. In: *Annals of Physical and Rehabilitation Medicine* 52 (3), pp. 269–293.

Oxford Grice, K.; Vogel, K. A.; Le, V.; Mitchell, A.; Muniz, S.; Vollmer, M. A. (2003): Adult norms for a commercially available Nine Hole Peg Test for finger dexterity. In: *The American Journal of Occupational Therapy: Official Publication of the American Occupational Therapy Association* 57 (5), pp. 570–573.

Page, S. J.; Gater, D. R.; Bach-Y-Rita, P. (2004): Reconsidering the motor recovery plateau in stroke rehabilitation. In: *Archives of Physical Medicine and Rehabilitation* 85 (8), pp. 1377–1381.

Paltsev, E. I.; Elner, A. M. (1967): Change in the functional role of spinal segments subjected to acoustic stimulation and its role in involuntary movement. In: *Biofizika* 12 (6), pp. 1064–1070.

Park, J.; Lee, N.; Cho, M.; Kim, D.; Yang, Y. (2015): Effects of mental practice on stroke patients' upper extremity function and daily activity performance. In: *Journal of Physical Therapy Science* 27 (4), pp. 1075–1077.

Patel, A. D. (2014): The Evolutionary Biology of Musical Rhythm: Was Darwin Wrong? In: *PLoS Biology* 12 (3), pp. 1-6.

Patel, A. D.; Iversen, J. R.; Chen, Y.; Repp, B. H. (2005): The influence of metricality and modality on synchronization with a beat. In: *Experimental Brain Research* 163 (2), pp. 226–238.

Paul, S.; Ramsey, D. (1998): The effects of electronic music-making as a therapeutic activity for improving upper extremity active range of motion. In: *Occupational Therapy International* 5 (3), pp. 223–237.

Pereira, C. S.; Teixeira, J.; Figueiredo, P.; Xavier, J.; Castro, S. L.; Brattico, E. (2011): Music and emotions in the brain: familiarity matters. In: *PLoS ONE* 6 (11), pp. 1-9.

Phillips-Silver, J.; Aktipis, C. A.; Bryant, G. A. (2010): The ecology of entrainment: Foundations of coordinated rhythmic movement. In: *Music perception* 28 (1), pp. 3–14.

Piron, L.; Cenni, F.; Tonin, P.; Dam, M. (2001): Virtual Reality as an assessment tool for arm motor deficits after brain lesions. In: *Studies in Health Technology & Informatics* 81, pp. 386–392.

Platz, T.; Roschka, S. (2011): *Rehabilitative Therapie bei Armlähmungen nach einem Schlaganfall - Patientenversion der Leitlinie der Deutschen Gesellschaft für Neurorehabilitation.* Hippocampus-Verlag, Bad Honnef.

Platz, T.; van Kaick, S.; Mehrholz, J.; Leidner, O.; Eickhof, C.; Pohl, M. (2009): Best conventional therapy versus modular impairment-oriented training for arm paresis after stroke: a single-blind, multicenter randomized controlled trial. In: *Neurorehabilitation and Neural Repair* 23 (7), pp. 706–716.

Poli, P.; Morone, G.; Rosati, G.; Masiero, S. (2013): Robotic technologies and rehabilitation: new tools for stroke patients' therapy. In: *BioMedical Research International* 2013, pp. 1-9.

Pollock, A., Farmer, S. E.; Brady, M. C.; Langhorne, P.; Mead, G. E.; Mehrholz, J.; van Wijck, F. (2014): Interventions for improving upper limb function after stroke. In: The *Cochrane Database of Systematic Reviews* 11, pp. 1-169.

Prahalad, C. K.; Ramaswamy, V. (2004): Co-Creation Experiences: The Next Practice in Value Creation. In: *Journal of Interactive Marketing* (18-3), pp. 5-14.

Prange, G. B.; Jannink, M. J. A.; Groothuis-Oudshoorn, C. G. M.; Hermens, H. J.; Ijzerman, M. J. (2006): Systematic review of the effect of robot-aided therapy on recovery of the hemiparetic arm after stroke. In: *Journal of Rehabilitation Research & Development* 43 (2), pp. 171–184.

Quandt, F.; Hummel, F. C. (2014): The influence of functional electrical stimulation on hand motor recovery in stroke patients: a review. In: *Experimental & Translational Stroke Medicine* 6, pp. 6-9.

Quinn, L.; Busse, M.; Dal Bello-Haas, V. (2014): Management of upper extremity dysfunction in people with Parkinson disease and Huntington disease: facilitating outcomes across the disease lifespan. In: *Journal of hand therapy: Official Journal of the American Society of Hand Therapists* 26 (2), pp. 148-154.

Raglio, A.; Attardo, L.; Gontero, G.; Rollino, S.; Groppo, E.; Granieri, E. (2015): Effects of music and music therapy on mood in neurological patients. In: *World Journal of Psychiatry* 5 (1), pp. 68–78.

Ramasubramania, R. N. A.; Arumugam, N. (2006): Role of Music on Muscle Recruitment. In: *Journal of Exercise Science and Physiotherapy* 2, pp. 84–86.

Raymond, J. (2009): Interactions of attention, emotion and motivation. In: *Progress in Brain Research* 176, pp. 293–308.

Repp, B. H.; Penel, A. (2004): Rhythmic movement is attracted more strongly to auditory than to visual rhythms. In: *Psychological Research* 68, pp. 252–270.

Riener, R. (2007): Robot-aided rehabilitation of neural function in the upper extremities. In: *Acta Neurochirurgica* 97 (1), pp. 465–471.

Riener, R.; Nef, T.; Colombo, G. (2005): Robot-aided neurorehabilitation of the upper extremities. In: *Medical & Biological Engineering & Computing* 43 (1), pp. 2–10.

Rodriguez-Fornells, A.; Rojo, N.; Amengual, J. L.; Ripolles, P.; Altenmüller, E. O.; Münte, T. F. (2012): The involvement of audio-motor coupling in the music-supported therapy applied to stroke patients. In: *Annals of the New York Academy of Science* 1252, pp. 282–293.

Ronsse, R.; Puttemans, V.; Coxon, J. P.; Goble, D. J.; Wagemans, J.; Wenderoth, N.; Swinnen, S. P. (2011): Motor Learning with Augmented Feedback: Modality-Dependent Behavioral and Neural Consequences. In: *Cerebral Cortex* 21 (6), pp. 1283–1294.

Rosati, G.; Oscari, F.; Reinkensmeyer, D. J.; Secoli, R.; Avanzini, F.; Spagnol, S.; Masiero, S. (2011): Improving robotics for neurorehabilitation: enhancing engagement, performance, and learning with auditory feedback. In: Proceedings of *IEEE International Conference of Rehabilitation Robotics* 2011, pp. 1-6.

Rosati, G.; Oscari, F.; Spagnol, S.; Avanzini, F.; Masiero, S. (2012): Effect of task-related continuous auditory feedback during learning of tracking motion exercises. In: *Journal of NeuroEngineering and Rehabilitation* 9 (73), pp. 1-13.

Ross, J. M.; Balasubramaniam, R. (2014): Physical and neural entrainment to rhythm: human sensorimotor coordination across tasks and effector systems. In: *Frontiers in Human Neuroscience* 8, pp. 1-6.

Rossignol, S.; Jones, G. M. (1976): Audio-spinal influence in man studied by the H-reflex and its possible role on rhythmic movements synchronized to sound. In: *Electroencephalography* and *Clinical Neurophysiology* 41 (1), pp. 83–92.

Rosslau, K.; Steinwede, D.; Schröder, C.; Herholz, S.; Lappe, C.; Dobel, C.; Altenmüller, E. O. (2015): Clinical investigations of receptive and expressive musical functions after stroke. In: *Frontiers in Psychology* 6 (768), pp. 1-11.

Ryan, R. M.; Deci, E. L. (2000): Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. In: *The American Psychologist* 55 (1), pp. 68–78.

Sacco, R. L.; Benjamin, E. J.; Broderick, J. P.; Dyken, M.; Easton, J. D.; Feinberg, W. M. et al. (1997): American Heart Association Prevention Conference. IV. Prevention and Rehabilitation of Stroke. Risk factors. In: *Stroke* 28 (7), pp. 1507–1517.

Sale, P.; Franceschini, M.; Mazzoleni, S.; Palma, E.; Agosti, M.; Posteraro, F. (2014): Effects of upper limb robot-assisted therapy on motor recovery in subacute stroke patients. In: *Journal of NeuroEngineering and Rehabilitation* 11, pp. 104.

Sale, P.; Lombardi, V.; Franceschini, M. (2012): Hand robotics rehabilitation: feasibility and preliminary results of a robotic treatment in patients with hemiparesis. In: *Stroke Research and Treatment* 2012, pp. 1-5.

Sale, P.; Mazzoleni, S.; Lombardi, V.; Galafate, D.; Massimiani, M. P.; Posteraro, F.et al. (2014): Recovery of hand function with robot-assisted therapy in acute stroke patients: a randomized-controlled trial. In: *International Journal of Rehabilitation Research* 37 (3), pp. 236–242.

Salimpoor, V. N.; Zald, D. H.; Zatorre, R. J.; Dagher, A.; McIntosh, A. R.: Predictions and the brain: how musical sounds become rewarding. In: *Trends in Cognitive Sciences* 19 (2), pp. 86-91.

Salvanes; M.; Ebbesson; N.; Jensen; B. (2013): Environmental enrichment promotes neural plasticity and cognitive ability in fish. In: *Proceedings of Biological Sciences/ The Royal Society* 280 (1767), pp. 20131-20331.

Sammler, D.; Grigutsch, M.; Fritz, T.; Koelsch, S. (2007): Music and emotion: electrophysiological correlates of the processing of pleasant and unpleasant music. In: *Psychophysiology* 44 (2), pp. 293–304.

Sanger, T. D.; Chen, D.; Fehlings, D. L. et al. (2010): Definition and Classification of Hyperkinetic Movements in Childhood. In: *Movement Disorders* 25 (11), pp. 1538–1549.

Saposnik, G.; Levin, M. (2011): Virtual reality in stroke rehabilitation: a meta-analysis and implications for clinicians. In: *Stroke; a Journal of Cerebral Circulation* 42 (5), pp. 1380–1386.

Särkämö, T.; Tervaniemi, M.; Huotilainen, M. (2013): Music perception and cognition: development, neural basis, and rehabilitative use of music. In: *Wiley Interdisciplinary Reviews: Cognitive Science* 4; pp. 441–451.

Särkämö, T.; Soto, D. (2012): Music listening after stroke: beneficial effects and potential neural mechanisms. In: *Annals of the New York Academy of Science* 1252, pp. 266–281.

Särkämö, T.; Tervaniemi, M.; Laitinen, S.; Forsblom, A.; Soinila, S.; Mikkonen, M. et al. (2008): Music listening enhances cognitive recovery and mood after middle cerebral artery stroke. In: *Brain* 131 (3), pp. 866–876.

Schaffert, N.; Mattes, K. (2015): Effects of acoustic feedback training in elite-standard Para-Rowing. In: *Journal of Sports Science* 33 (4), pp. 411–418.

Schneider, S.; Schönle, P. W.; Altenmüller, E.; Münte, T. F. (2007): Using musical instruments to improve motor skill recovery following a stroke. In: *Journal of Neurology* 254 (10), pp. 1339–1346.

Scholz, D. S.; Wu, L.; Pirzer, J.; Schneider, J.; Rollnik, J. D.; Grossbach, M.l; Altenmüller, E. O. (2014): Sonification as a possible stroke rehabilitation strategy. In: *Frontiers in Neuroscience* 8 (322), pp. 1-7.

Schulkin; R. (2014): The Evolution of Music and Human Social Capability. In: *Frontiers in Neuroscience* 8 (292), pp. 1-13.

Secoli, R.; Milot, M.; Rosati, G.; Reinkensmeyer, D. J. (2011): Effect of visual distraction and auditory feedback on patient effort during robot-assisted movement training after stroke. In: *Journal of NeuroEngineering and Rehabilitation* 8 (21), pp. 1-10.

Shanahan, J.; Morris, M. E.; Bhriain, O. N.; Saunders, J.; Clifford, A. M. (2015): Dance for people with Parkinson disease: what is the evidence telling us? In: *Archives of Physical Medicine and Rehabilitation* 96 (1), pp. 141–153.

Sharman, M. J.; Cresswell, A. G.; Riek, S. (2006): Proprioceptive neuromuscular facilitation stretching. Mechanisms and clinical implications. In: *Sports Medicine* 36 (11), pp. 929–939.

Sheean, G.; McGuire, J. R. (2009): Spastic Hypertonia and Movement Disorders: Pathophysiology, Clinical Presentation, and Quantification. In: *Physical Medicine & Rehabilitation* 1 (9), pp. 827–833.

Smania, N.; Paolucci, S.; Tinazzi, M.; Borghero, A.; Manganotti, P.; Fiaschi, A. et al. (2007): Active finger extension: a simple movement predicting recovery of arm function in patients with acute stroke. In: *Stroke* 38 (3), pp. 1088–1090.

Staubli, P.; Nef, T.; Klamroth-Marganska, V.; Riener, R. (2009): Effects of intensive arm training with the rehabilitation robot ARMin II in chronic stroke patients: four single-cases. In: *Journal of NeuroEngineering and Rehabilitation* 6 (46), pp. 1-10.

Stein, J.; Bishop, J.; Gillen, G.; Helbok, R. (2011): A pilot study of robotic-assisted exercise for hand weakness after stroke. In: *IEEE International Conference of Rehabilitation Robotics* 2011, pp. 1-4.

Stein, J.; Bishop, L.; Gillen, G.; Helbok, R. (2011): Robot-assisted exercise for hand weakness after stroke: a pilot study. In: *American Journal of Physical Medicine & Rehabilitation/ Association of Academic Physiatrists* 90 (11), pp. 887–894.

Stern, J. (2015): Musicogenic epilepsy. In: *Handbook of Clinical Neurology* 129, pp. 469–477.

Sterr, A.; Freivogel, S. (2004): Intensive training in chronic upper limb hemiparesis does not increase spasticity or synergies. In: *Neurology* 63 (11), pp. 2176–2177.

Street, A. J.; Magee, W. L.; Odell-Miller, H.; Bateman, A.; Fachner, J. C. (2015): Home-based Neurologic Music Therapy for Upper Limb Rehabilitation with Stroke Patients at Community Rehabilitation Stage - a Feasibility Study Protocol. In: *Frontiers in Human Neuroscience* 9 (480), pp. 1-16.

Stupacher, J.; Hove, M. J.; Novembre, G.; Schutz-Bosbach, S.; Keller, P. E. (2013): Musical groove modulates motor cortex excitability: a TMS investigation. In: *Brain and Cognition* 82 (2), pp. 127–136.

Sullivan, G. M.; Artino, A. R. (2013): Analyzing and Interpreting Data From Likert-Type Scales. In: *Journal of Graduate Medical Education* 5 (4), pp. 541–542.

Susanto, E. A.; Tong, R. K.; Ockenfeld, C.; Ho, N. S. (2015): Efficacy of robot-assisted fingers training in chronic stroke survivors: a pilot randomized-controlled trial. In: *Journal of NeuroEngineering and Rehabilitation* 12, pp. 1-9.

Taheri, H.; Rowe, J. B.; Gardner, D.; Chan, V.; Reinkensmeyer, D. J.; Wolbrecht, E. T. (2012): Robot-assisted Guitar Hero for finger rehabilitation after stroke. In: *Conference Proceedings of Engineering in Medicine and Biology Society* 2012, pp. 3911–3917.

Taheri, H.; Rowe, J. B.; Gardner, Da.; Chan, V.; Gray, K.; Bower, C. et al. (2014): Design and preliminary evaluation of the FINGER rehabilitation robot: controlling challenge and quantifying finger individuation during musical computer game play. In: *Journal of NeuroEngineering and Rehabilitation* 11 (10), pp. 1-10.

Takeuchi, N.; Izumi, S. (2013): Rehabilitation with Poststroke Motor Recovery: A Review with a Focus on Neural Plasticity. In: *Stroke Research and Treatment* (2013), pp. 1-13.

Tatla, S. K.; Shirzad, N.; Lohse, K. R.; Virji-Babul, N.; Hoens, A. M.; Holsti, L. et al. (2015): Therapists' perceptions of social media and video game technologies in upper limb rehabilitation. In: *Journal of Medical Internet Research Serious Games* 3 (1), pp. 1-14.

Teasell, R.; Mehta, S.; Pereira, S.; McIntyre, A.; Janzen, S.; Allen, L. et al. (2012): Time to rethink long-term rehabilitation management of stroke patients. In: *Topics in Stroke Rehabilitation* 19 (6), pp. 457–462.

Teassell, R.; Norhayati, H. (2014a): Stroke Rehabilitation Clinician Handbook. Motor Rehabilitation; Rehab of Hemiplegic Upper Extremity Post Stroke." *Ontario, Canada: Evidence-Based Review of Stroke Rehabilitation*, pp. 1-18.

Teasell, R.; Norhayati, H.; Mc Clure, A.; Meyer, M. (2014b): Stroke: More than a 'brain attack'. In: *International Journal of Stroke* 9 (2), pp. 188–190.

Thaut, M. H. (2015): Music as therapy in early history. In: *Progress in Brain Research* 217, pp. 143–158.

Thaut, M. H.; Kenyon, G. P.; Hurt, C. P.; McIntosh, G. C.; Hömberg, V. (2002): Kinematic optimization of spatiotemporal patterns in paretic arm training with stroke patients. In: *Neuropsychologia* 40 (7), pp. 1073–1081.

Thaut, M. H.; McIntosh, G. C.; Hömberg, V. (2015): Neurobiological Foundations of Neurologic Music Therapy: Rhythmic Entrainment and the Motor System. In: *Frontiers in Psychology* 5 (1185), pp. 1-6.

Thaut, M. H.; McIntosh, G. C.; Rice, R. R.; Miller, R. A.; Rathbun, J.; Brault, J. M. (1996): Rhythmic auditory stimulation in gait training for Parkinson's disease patients. In: *Movement Disorders: Official Journal of the Movement Disorder Society* 11 (2), pp. 193–200

Thaut, M. H.; Mc Intosh, G. C.; Prassas, S. G.; Rice, R. R. (1993): Effect of Rhythmic Auditory Cuing on Temporal Stride Parameters and EMG. Patterns in Hemiparetic Gait of Stroke Patients. In: *Neurorehabilitation and Neural Repair* 7 (1), pp. 9–16.

Tong, K. Y.; Ho, S. K.; Pang, P. K.; Hu, X. L.; Tam, W. K.; Fung, K. L. et al. (2010): An intention driven hand functions task training robotic system. In: *Conference Proceedings IEEE Engineering in Medicine and Biology Society* 2010, pp. 3406–3409.

Turner-Stokes, L. (2009): Goal attainment scaling (GAS) in rehabilitation: a practical guide. In: *Clinical Rehabilitation* 23 (4), pp. 362–370.

van Delden, A. E. Q.; Peper, C. E.; Kwakkel, G.; Beek, P. J. (2012): A systematic review of bilateral upper limb training devices for poststroke rehabilitation. In: *Stroke Research and Treatment* 2012 (972069), pp. 1-17.

van den Bosch, I.; Salimpoor, V. N.; Zatorre, R. J. (2013): Familiarity mediates the relationship between emotional arousal and pleasure during music listening. In: *Frontiers in Human Neuroscience* 7 (534), pp. 1-10.

van der Hejden, M.J.; Oliai, A. S.; van Dijk, M.; Jeekel, J.; Hunink, M. G. (2015): The Effects of Perioperative Music Interventions in Pediatric Surgery: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. In: *PLoS ONE* 10 (8), pp. 1-11.

van Vugt, F. T.; Jabusch, H.; Altenmüller, E. O. (2012): Fingers phrase music differently: trial-to-trial variability in piano scale playing and auditory perception reveal motor chunking. In: *Frontiers in Psychology* 3 (495), pp. 1-9.

van Vugt, F. T. (2013): *Sounds on time: auditory feedback in motor learning, re-learning and over-learning of timing regularity*. Neuroscience. Université Claude Bernard - Lyon I.

van Vugt, F. T.; Ritter, J.; Rollnik, J. D.; Altenmüller, E. O. (2014): Music-supported motor training after stroke reveals no superiority of synchronization in group therapy. In: *Frontiers in Human Neuroscience* 8 (315), pp. 1-9.

van Vugt, F. T.; Tillmann, B. (2015): Auditory feedback in error-based learning of motor regularity. In: *Brain Research* 1606, pp. 54- 67.

van Vugt, F. T.; Kafczyk, T.; Kuhn, W.; Rollnik, J. D.; Tillmann, B.; Altenmüller, E. O. (2016): The role of auditory feedback in music-supported stroke rehabilitation: A single-blinded randomised controlled intervention. In: *Restorative Neurology and Neuroscience* 34 (2), pp. 297-311.

Veerbeek, J. M.; van Wegen, E.; van Peppen, R.; van der Wees, P.J.; Hendriks, E.; Rietberg, M.; Kwakkel, G. (2014): What is the evidence for physical therapy poststroke? A systematic review and meta-analysis. In: *PLoS ONE* 9 (2), pp. 1-33.

Vuilleumier, P.; Trost, W. (2015): Music and emotions: from enchantment to entrainment. In: *Annals of the New York Academy of Sciences* 1337, pp. 212–222.

Waddell, K. J.; Birkenmeier, R. L.; Moore, J. L.; Hornby, T. G.; Lang, C. E. (2014): Feasibility of High-Repetition, Task-Specific Training for Individuals With Upper-Extremity Paresis. In: *The American Journal of Occupational Therapy* 68 (4), pp. 444–453.

Walker, B. N.; Lindsay, J.; Nance, A.; Nakano, Y.; Palladino, D. K.; Dingler, T.; Jeon, M. (2013): Spearcons (speech-based earcons) improve navigation performance in advanced auditory menus. In: *Human Factors* 55 (1), pp. 157–182.

Wan, C. Y.; Schlaug, G. (2010): Music making as a tool for promoting brain plasticity across the life span. In: *The Neuroscientist: a Review Journal bringing Neurobiology, Neurology and Psychiatry* 16 (5), pp. 566–577.

Wang, T.; Pen, Y.; Chen, Y.; Lu, T.; Liao, H.; Tang, P.; Shieh, J. (2013): A Home-Based Program Using Patterned Sensory Enhancement Improves Resistance Exercise Effects for Children With Cerebral Palsy: A Randomized Controlled Trial. In: *Neurorehabilitation and Neural Repair* 27 (8), pp. 684–694.

Whitall, J.; Mc Combe Waller, S.; Silver, K. H.; Macko, R. F. (2000): Repetitive bilateral arm training with rhythmic auditory cueing improves motor function in chronic hemiparetic stroke. In: *Stroke* 31 (10), pp. 2390–2395.

Wissel, J.; Manack, A.; Brainin, M. (2013): Toward an epidemiology of poststroke spasticity. In: *Neurology* 80 (3, 2), pp. 13-19.

Wissel, J.; Verrier, M.; Simpson, D. M.; Charles, D.; Guinto, P.; Papapetropoulos, S.; Sunnerhagen, K. S. (2014): Post-stroke Spasticity: Predictors of Early Development and Considerations for Therapeutic Intervention. In: *Physical Medicine & Rehabilitation* 7 (1), pp. 60–67.

Zatorre, R. J.; Chen, J. L.; Penhune, V. B. (2007): When the brain plays music: auditory-motor interactions in music perception and production. In: *Nature Reviews Neuroscience* 8 (7), pp. 547–558.

Zimmermann-Schlatter, A.; Schuster, C.; Puhan, M. A.; Siekierka, E.; Steurer, J. (2008): Efficacy of motor imagery in post-stroke rehabilitation: a systematic review. In: *Journal of NeuroEngineering and Rehabilitation* 5, pp. 1-10.

8.2 Internet resources

www.cyberglovesystems.com/cybergrasp/ (4.04.2016).

www.escience.anu.edu.au/lecture/ivr/exercises/a1/02IVRA1_U3948801/index.en.html (4.04.2016).

www.guppy.mpe.nus.edu.sg/~teocl/rehabilitation/Hand%20Rehabilitation%20Project.html (4.04.2016).

www.humananatomybody.info (4.04.2016).

www.interactive-motion.com/inmotion-arm-the-new-standard-of-care/ (4.04.2016).

www.ksiunited.com/?attachment_id=829 (4.04.16).

www.kompetenznetz-schlaganfall.de/reha-neuro (4.04.2016).

www.rehab-robotics.com (4.04.2016).

www.rehab-robotics.com/hoh_basic.html (4.04.2016).

www.rehabilitationrobotics.eu%2Fsystem%2Ffiles%2Ffiledepot%2F7%2FCOSTTD1006_WG3Rome_2.EtienneRehabilitationSynergies.pdf&bvm=bv.118443451,d.ZWU&psig=AFQjCNF34BcROQ_iTSdCsji-WAnPndNIEQ&ust=1459861708118894&cad=rjt (4.04.2016).

www.reha-stim.de/cms/index.php?id=83 (4.04.2016).

www.strokecenter.org/professionals/stroke-diagnosis/neuropathology-image-library/acute-infarction/ (4.04.2016).

www.stroke.org (4.04.2016).

www.tyromotion.com/en/i-robot-erfahrungsbereicht-uber-therapierobotik/4188 (4.04.2016).

8.3 List of Figures

Fig. 37: Subgroup Analysis A showed that patients suffering from moderate to mild grades of a hand paresis post-stroke significantly benefit from sound (marked green). In contrast, for patients suffering from a severe grade of the hand paresis post-stroke sound deteriorates the therapeutic effect with significance (marked red). (photography by Florina Speth, may 2015).

8.4 List of Tables

9. Appendix

9.1 List of abbreviations

9.2 Secondary outcome measures and additional data

9.2 a) Function/ Secondary Outcome measures- function

9.2 b) Motivation/ Secondary Outcome measures- motivation

9.2 c) Additional data

9.3 Acknowledgments

9.1 List of abbreviations

Tests	
BBT	Box and Block Test
ES	Experience Sampling (items: mood; involvement; motivation; fun)
F0	single finger forces in rest measured with “Amadeo”
F ext	maximum single finger forces measured with “Amadeo”
FM	Fugl-Meyer Test
GAS	Goal Attainment Scale
GF	Grip force measured with dynamometer
IMI	Intrinsic Motivation Inventory (items: Interest/ enjoyment, perceived competence, perceived choice, relaxation, value/ usefulness, Man-machine-relation)
mAS	Modfied Ashworth Scale
Mmr	Subitem of IMI: Man-machine-relation
NHPT	Nine Hole Peg Test
PSE	Perceived Size of Effort

Statistics and data evaluation	
ANCOVA	analysis of covariance
CI	Confidence interval
F- H0	Function- null hypothesis
F- H1	Function-alternative hypothesis
F- µ1	mean n (T3-T0) sound-group
F- µ2	mean n (T3-T0) control-group
M- H0	Motivation- null hypothesis
M- H1	Motivation alternative hypothesis
M- µ1	mean rating on each subitem of IMI (1:7)
M- µ2	mean rating on each subitem of IMI (1:7)
Mmr	Man-machine-relation
p, t	p-value; t-value
sd	Standard deviation

Other terms	
ADL	Activities of daily living
AROM	Active range of motion
BATRAC	bilateral arm-training with rhythmic auditory cueing
BPM	Beats per minute
CIMT	Constrained induced movement therapy
E (E1-3)	Experiment 1-3
ES	Electric stimulation
EMG	Electromyography
FES	Functional electric stimulation
IOT	Impairment Oriented Therapy
MST	Music supported Therapy
NIHSS	National Institute of Health Stroke Scale
NMES	Neuro muscular electric stimulation
PROM	Passive range of motion
PSS	Post-stroke spasticity
tDCS	Transcranial direct current stimulation
RAS	Rhythmic auditory stimulation
RCT	Randomized controlled trial
ROM	Range of motion
rTMS	repetitive transcranial magnetic stimulation
RT	Robot-assisted hand therapy
WHO	World Health Organization

9.2 Secondary outcome measures and additional data

9.2 a) Function/ Secondary Outcome measures- function

Out of 34 study subjects, 16 patients were able to perform the Nine Hole Peg Test. Of those, 9 belonged to the sound-group and 7 to the control-group.

Results from Nine Hole Peg Test (NHPT) 16 subjects (see Fig. 30)

The t-test for 2 independent means of the mean d (T2-T0) gained with the NHPT was performed to compare whether the sound-group or the control-group showed significant differences in NHPT outcomes. The t-value of 0,353443 and the p-value of 0,728674 showed that no significant difference between the groups at $p < 0,1$ was computed. This means that with a probability of 90%, there will be no significant difference in NHPT-outcomes dependent on sound-assisted training or training without sound.

Results from Nine Hole Peg Test- Subgroup A (see Fig. 30)

The t-test for 2 independent means of the mean d (T2-T0) gained with the NHPT was performed to compare whether the sound-group or the control-group showed significant differences in cases suffering from moderate paresis. The t-value of 0,212376 and the p-value of 0,8402 showed that there was no significant difference between the two groups at $p < 0,1$. This means that with a probability of 90%, there will be no significant difference in NHPT-outcomes dependent on sound-assisted training or training without sound in moderate cases of hand paresis.

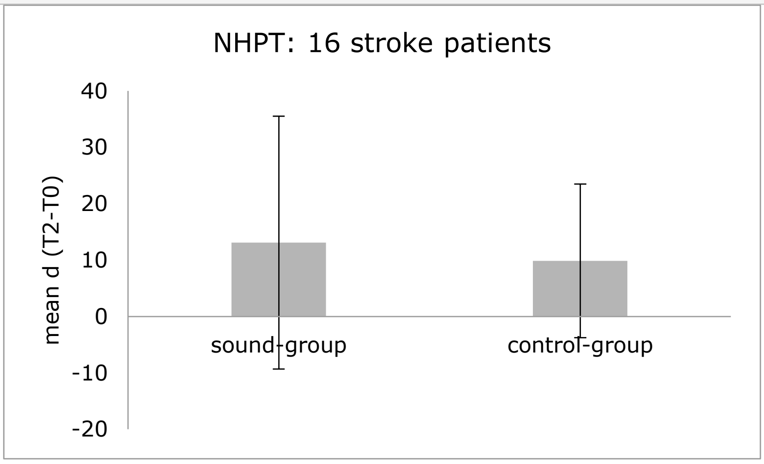
The t-test for 2 independent means of the mean d (T2-T0) gained with the NHPT was performed to compare whether the sound-group or the control-group showed significant differences in cases suffering from moderate paresis. The t-value of 0,010498 and the p-value of 0,991917 showed that there was no significant difference between the two groups at $p < 0,1$. This means that with a probability of 90%, there will be no significant difference in NHPT-outcomes dependent on sound-assisted training or training without sound in mild cases of hand paresis.

Results from Nine Hole Peg Test- Subgroup B- B1, B3 (see Fig. 30)

The t-test for 2 independent means of the mean d (T2-T0) gained with the NHPT was performed to compare whether the sound-group or the control-group showed significant differences in subgroup B1 (2-6 months post-stroke). The t-value of 0,611217 and the p-value of 0,55802 showed that there was no significant difference between the two groups at $p < 0,1$. This means that with a probability of 90%, there will be no significant difference in NHPT-outcomes dependent on sound-assisted or training without sound in cases of 2-6 months post-stroke in NHPT outcomes.

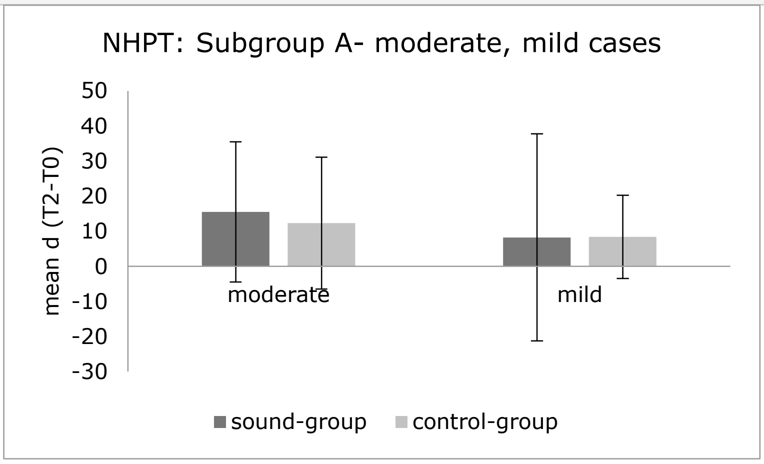
Results Nine Hole Peg Test all subjects/ subgroup A/ subgroup B- Plots

Results from Nine Hole Peg Test (NHPT) 16 subjects:



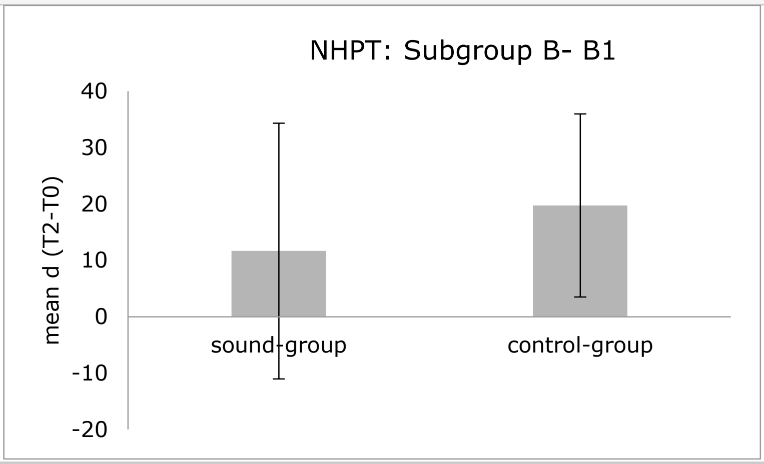
16 subjects: sound-group (n=8) vs. control-group (n=8)	
sound-group: mean d (T2-T0)/ sd	13,11111111
	22,43013846
control-group: mean d (T2-T0)/ sd	9,875
	13,63228835

Results from Nine Hole Peg Test- Subgroup A:



Subgroup A	severe sound-group (n=11) vs. control-group (n=6)	moderate sound-group (n=4) vs. control-group (n=3)	mild sound-group (n=4) vs. control-group (n=9)
sound-group: mean d (T2-T0)/ sd	Severe cases were not able to perform the NHPT.	15,5	8,25
		19,97498436	29,51129727
control-group: mean d (T2-T0)/ sd		12,33333333	8,4
		18,82374387	11,86591758

Results from Nine Hole Peg Test- Subgroup B- B1, B3:



Subgroup B	B1: 2-6 months post-stroke sound-group (n=6) vs. control-group (n=4)	B2: > 6 months < 12 months post-stroke; sound-group (n=1)	B3: >12 months post-stroke sound-group (n=2) vs. control-group (n=2)
sound-group: mean d (T2-T0)/ sd	11,66666667	Only one subject performed the NHPT in group B2, four subjects performed the NHPT in the group B3. Because of that, no computation on group B2 and B3 was performed.	
	22,66862737		
control-group: mean d (T2-T0)/ sd	19,75		
	16,21470526		

Fig. 30: Results from Nine Hole Peg Test (NHPT) all subjects/ subgroup A/ subgroup B

Grip Force measurements with a dynamometer (GF)

Results from grip force measurements- all subjects (see Fig. 31)

The t-test for 2 independent means of the mean force (T2-T0) gained with the GF was performed to compare whether the sound-group or the control-group showed significant differences. The t-value of 0,529397 and the p-value of 0,599385 showed that there was no significant difference between the two groups at $p < 0,1$. This means that with a probability of 90%, there will be no significant difference in force measurements depending on sound- or no-sound- conditions in robotic training.

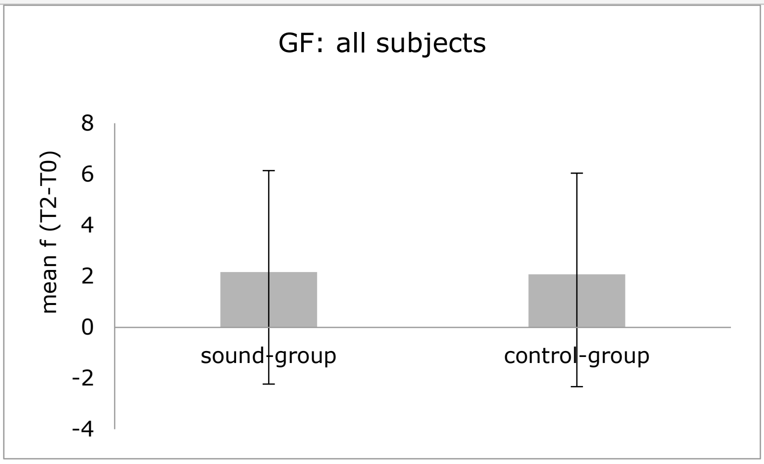
Results from grip force measurements- Subgroup A (see Fig. 31)

The t-test for 2 independent means of the mean force (T2-T0) gained with the GF was performed to compare whether the sound-group or the control-group showed significant differences. The t-value of 1,445221 and the p-value of 0,164688 showed that there was no significant difference between the two groups at $p < 0,05$. This

means that with a probability of 95 %, there will be no significant difference in force measurements depending on sound- or no-sound- conditions in robotic training for patients suffering from severe hand paresis. The t-test for 2 independent means of the mean force (T2-T0) gained with the GF was performed to compare whether the sound-group or the control-group showed significant differences. The t-value of 0,85251and the p-value of 0,41604showed that there was no significant difference between the two groups at p < 0,05. This means that with a probability of 95 %, there will be no significant difference in force measurements depending on sound- or no-sound-conditions in robotic training for patients suffering from moderate hand paresis. The t-test for 2 independent means on the mean force (T2-T0) gained with the GF was performed to compare whether the sound-group or the control-group showed significant differences. The t-value of 0,312143 and the p-value of 0,762912 showed that there was no significant difference between the two groups at p < 0,05. This means that with a probability of 95 % there will be no significant difference in force measurements depending on sound- or no-sound- conditions in robotic training for patients suffering from mild hand paresis.
Results from grip force measurements- Subgroup B: B1, B3 (see Fig. 31)
The t-test for 2 independent means of the mean force (T2-T0) gained with the GF was performed to compare whether the sound-group or the control-group showed significant differences in Subgroup B1 (2-6 months post-stroke). The t-value of 0,01897 and the p-value of 0,985036 showed that there was no significant difference between the two groups at p < 0,05. This means that with a probability of 95 %, there will be no significant difference in force measurements depending on sound- or no-sound- conditions in robotic training for patients suffering from hand paresis 2-6 months post-stroke. The t-test for 2 independent means of the mean force (T2-T0) gained with the GF was performed to compare whether the sound-group or the control-group showed significant differences in Subgroup B3 (> 12 months post-stroke). The t-value of 1,245067 and the p-value of 0,235084 showed that there was no significant difference between the two groups at p < 0,05. This means that with a probability of 95 %, there will be no significant difference in force measurements depending on sound- or no-sound- conditions in robotic training for patients suffering from hand paresis after more than 12 months post-stroke.

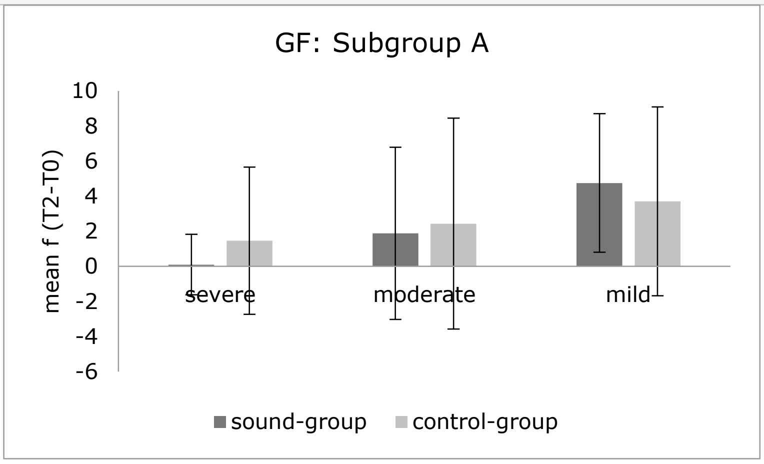
Results Grip Force- all subjects/ subgroup A/ subgroup B- Plots:

Results from grip force measurements- all subjects:



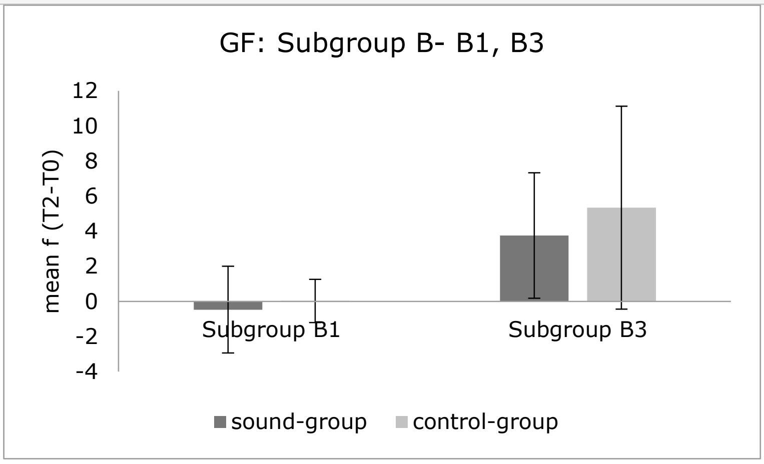
34 subject: sound-group (n=20) vs. control-group (n=14)	
sound-group:	2,17
mean f (T2-T0)/ sd	3,97
control-group:	2,07
mean f (T2-T0)/ sd	4,4

Results from grip force measurements- Subgroup A:



Subgroup A	severe sound-group (n=11) vs. control-group (n=6)	moderate sound-group (n=4) vs. control-group (n=4)	mild sound-group (n=4) vs. control-group (n=5)
sound-group: mean f (T2-T0)/ sd	Severe cases were not able to perform the NHPT.	15,5	8,25
		19,97498436	29,51129727
control-group: mean f (T2-T0)/ sd	Severe cases were not able to perform the NHPT.	12,33333333	8,4
		18,82374387	11,86591758

Results from grip force measurements- Subgroup B:



Subgroup B	B1: 2-6 months post-stroke sound-group (n=8) vs. control-group (n=9)	B2: > 6 months < 12 months post-stroke; sound-group (n=3)	B3: >12 months post-stroke sound-group (n=9) vs. control-group (n=5)
sound-group: mean f (T2-T0)/ sd	0,46875	-	3,75
	2,4656117		3,57571172
control-group: mean f (T2-T0)/ sd	0,02777778	-	5,35
	1,22757666		5,78143581

Fig. 31: Results from grip force measurement (GF) all subjects/ subgroup A/ subgroup B

F0/ F ext

Hand forces were measured in rest (F0) and maximal hand forces in extension (F ext) at T0 and at T2 with "Amadeo" of all 34 subjects.

Results from F0/ F ext of all subjects (see Fig. 32)
The t-test for 2 independent means of the mean F0 and F ext (T2-T0) measured with "Amadeo" were compared to see whether the sound-group or the control-group

showed significant differences. For F0 the t-value of 0,25723 and the p-value of 0,797735 showed that there was no significant difference between the two groups at p < 0,05. This means that with a probability of 95%, there will be no significant difference in F0 measurements depending on sound- or no-sound- conditions in robotic training for patients suffering from a post-stroke hand paresis syndrome. For F ext the t-value of 0,797084 and the p-value of 0,428444 showed that there was no significant difference between the groups at p < 0,05. This means that with a probability of 95%, there will be no significant difference in F ext measurements depending on sound- or no-sound-conditions in robotic training for patients suffering from a post-stroke hand paresis syndrome.

Results from F0/ F ext measurements- Subgroup A (see Fig. 32)

The t-test for 2 independent means of the mean F0 and F ext (T2-T0) measured with "Amadeo" was compared to see whether the sound-group or the control-group within the subgroup of patients suffering from a severe hand paresis showed significant differences. For F0 the t-value of 0,665601 and the p-value of 0,511113 showed that there was no significant difference between the two groups. For F ext the t-value of 2,369159 and the p-value of 0,027491 showed that there was a significant difference between the groups at p < 0,05. This means that with a probability of 95% there will be no significant difference in F ext measurements depending on sound- or no-sound-conditions in robotic training for patients suffering from a severe post-stroke hand paresis syndrome. The t-test for 2 independent means of the mean F0 and F ext (T2-T0) measured with "Amadeo" was compared to see whether the sound-group or the control-group within the subgroup of patients suffering from a moderate hand paresis showed significant differences. For F0 the t-value of 0,514412 and the p-value of 0,615597 showed that there was no significant difference between the two groups at p < 0,05. This means that with a probability of 95%, there will be no significant difference in F0 measurements depending on sound- or no-sound- conditions in robotic training for patients suffering from a moderate post-stroke hand paresis syndrome. For F ext the t-value of 0,659601 and the p-value of 0,521025 showed that there was no significant difference between the groups at p < 0,05. This means that with a probability of 95%, there will be no significant difference in F ext measurements depending on sound- or no-sound-conditions in robotic training for patients suffering from a moderate post-stroke hand paresis syndrome. The t-test for 2 independent means of the mean F0 and F ext (T2-T0) measured with "Amadeo" was compared to see whether the sound-group or the control-group within the subgroup of patients suffering from a mild hand paresis showed significant differences. For F0 the t-value of

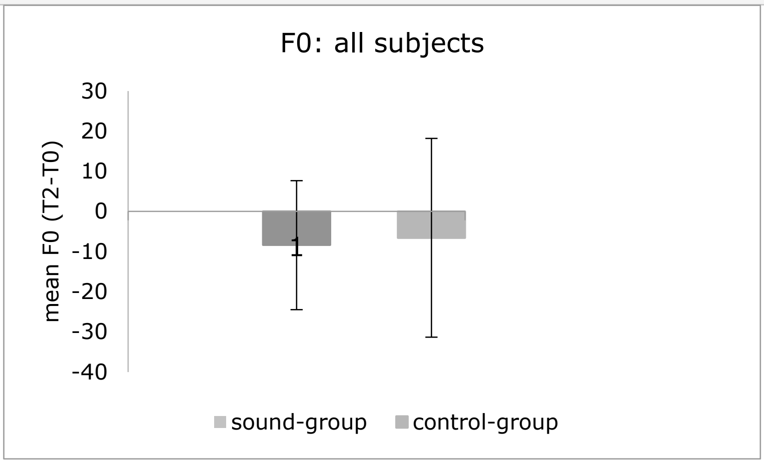
0,132692 and the p-value of 0,896201 showed that there was no significant difference between the two groups at $p < 0,05$. This means that with a probability of 95%, there will be no significant difference in F0 measurements depending on sound- or no-sound-conditions in robotic training for patients suffering from a moderate post-stroke hand paresis syndrome. For F ext the t-value of 0,873757 and the p-value of 0,396991 showed that there was no significant difference between the groups at $p < 0,05$. This means that with a probability of 95%, there will be no significant difference in F ext measurements depending on sound- or no-sound-conditions in robotic training for patients suffering from a mild post-stroke hand paresis syndrome.

Results from F0/ F ext measurements- Subgroup B: B1, B3 (see Fig. 32)

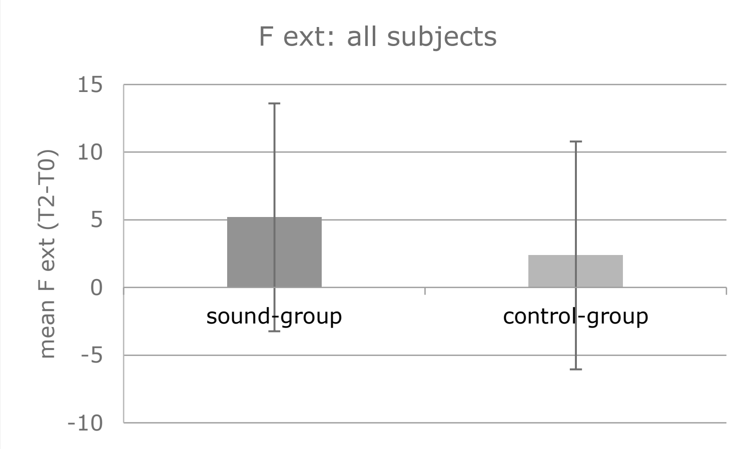
The t-test for 2 independent means of the mean F0 and F ext (T2-T0) measured with “Amadeo” was compared to see whether the sound-group or the control-group showed significant differences in Subgroup B1 (2-6 months post-stroke). The t-value of 0,01897 and the p-value of 0,985036 showed that there was no significant difference between the two groups. The t-test for 2 independent means of the mean F0 and F ext (T2-T0) measured with “Amadeo” was compared to see whether the sound-group or the control-group showed significant differences in Subgroup B3 (> 12 months post-stroke). The t-value of 1,245067 and the p-value of 0,235084 showed that there was no significant difference between the two groups.

Results F0/ F ext- all subjects/ subgroup A/ subgroup B- Plots:

Results from F0/ F ext of all subjects:

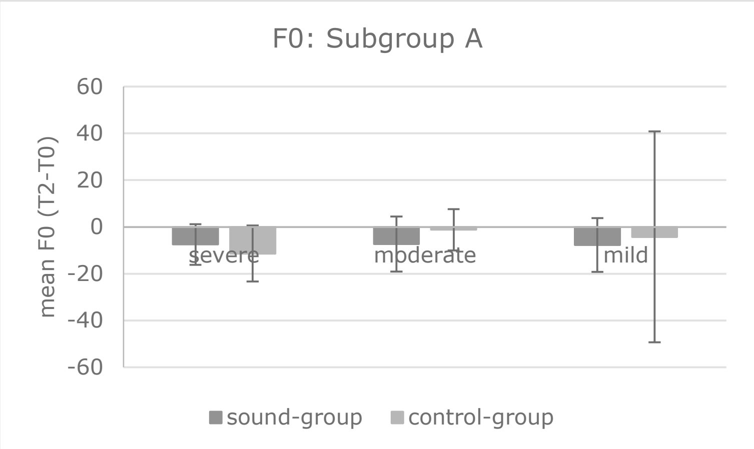


34 subject: sound-group (n=20) vs. control-group (n=14)	
sound-group: mean F0 (T2-T0)/ sd	-8,416666667
	16,04598464
control-group: mean F0 (T2-T0)/ sd	-6,625
	24,75292575

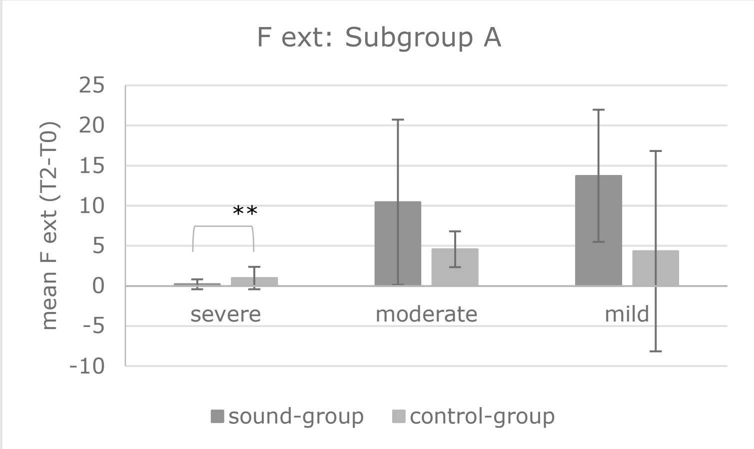


34 subject: sound-group (n=20) vs. control-group (n=14)	
sound-group: mean F ext (T2-T0)/ sd	5,191666667
	8,416490886
control-group: mean F ext (T2-T0)/ sd	2,38125
	6,88991715

Results from F0/ F ext of Subgroup A:

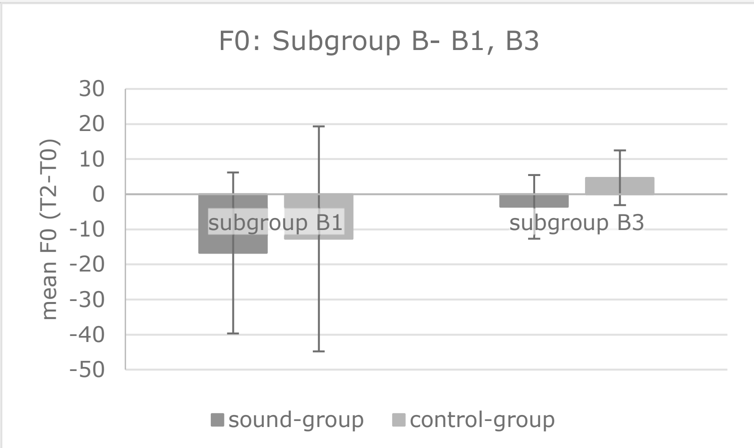


Subgroup A	severe sound-group (n=12) vs. control-group (n=5)	moderate sound-group (n=4) vs. control-group (n=4)	mild sound-group (n=4) vs. control-group (n=4)
sound-group: mean F0 (T2-T0)/ sd	-7,454545455	-7,325	-7,725
	8,684971346	11,71652145	11,55127158
control-group: mean F0 (T2-T0)/ sd	-11,35	-1,175	-4,28
	11,96540848	8,825070821	45,06824825

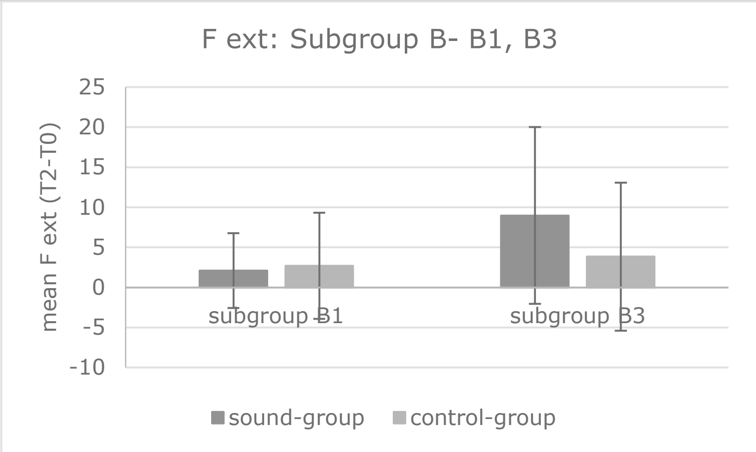


Subgroup A	severe sound-group (n=12) vs. control-group (n=5)	moderate sound-group (n=4) vs. control-group (n=4)	mild sound-group (n=4) vs. control-group (n=4)
sound-group: mean F ext (T2-T0)/ sd	0,209090909	10,425	13,725
	0,628417927	10,30081914	8,243595999
control-group: mean F ext (T2-T0)/ sd	0,983333333	4,575	4,32
	1,394871559	2,226404051	12,49227761
T, P, p	T = 2,369159 P = 0,027491 p < 0,05		

Results from F0/ F ext of Subgroup B- B1, B3:



Subgroup B	B1: 2-6 months post-stroke; sound-group (n=9) vs. control-group (n=5)	B2: > 6 < 12 months post-stroke; sound-group (n=3)	B3: >12 months post-stroke sound-group (n=9) vs. control-group (n=5)
sound-group: mean F0 (T2-T0)/ sd	-16,7375	-	-3,588888889
	22,94290662		9,065379811
control-group: mean F0 (T2-T0)/ sd	-12,72222222	-	4,66
	32,02427898		7,799230731



Subgroup B	B1: 2-6 months post-stroke; sound-group (n=9) vs. control-group (n=5)	B2: > 6 < 12 months post-stroke; sound-group (n=3)	B3:>12 months post-stroke; sound-group (n=9) vs. control-group (n=5)
sound-group: mean F ext (T2-T0)/ sd	2,1	-	8,977777778
	4,68249018		11,04499635
control-group: mean F ext (T2-T0)/ sd	2,688888889	-	3,84
	6,623904522		9,233796619

Fig. 32: Results from F0/ F ext of all subjects/ subgroup A/ subgroup B

9.2 b) Secondary outcome measures- motivation

Experience Samplings (ES)

Results Experience Samplings (ES)- all sub-items- all subjects (see Fig. 34)
The t-test for 2 independent means of all subjects was performed on all sub-items to compare whether the sound-group or the control-group showed significant differences. The results showed that for each sub-item: "mood", "involvement", "motivation", "fun" there was no significant difference between sound-group and control-group at p < 0,05 (t-values and p-values for each sub-item: see below).
Results ES- sub-item "mood"- all subjects (see Fig. 34)
The t-test for 2 independent means of the item "mood" was computed to compare whether the sound-group or the control-group showed significant differences. The t-value of 1,24475 and the p-value of 0,222552 showed that "mood" was not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- or the sound-group concering the item "mood".
Results ES- sub-item "involvement"- all subjects (see Fig. 34)
The t-test for 2 independent means of the item "involvement" was computed to compare whether the sound-group or the control-group showed significant differences. The t-value of 0,07845 and the p-value of 0,937976 showed that "involvement" was not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- and the sound-group concerning the item "involvement".
Results ES- sub-item "motivation"- all subjects (see Fig. 34)
The t-test for 2 independent means of the item "motivation" was computed to compare whether the sound-group or the control-group showed significant differences. The t-value of 1,23805 and the p-value of 0,224991 showed that "motivation" was not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- or the sound-group concering the item "motivation".
Results ES- sub-item "fun"- all subjects (see Fig. 34)
The t-test for 2 independent means of the item "fun" was computed to compare whether the sound-group or the control-group showed significant differences. The t-value of 0,70423 and the p-value of 0,486546 showed that "fun" was not rated

significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- or the sound-group concerning the item "fun".

Results Experience Samplings (ES)- subgroup A (see Fig. 34)

The t-test for 2 independent means of subgroup A was performed on ~~for~~ severe, moderate and mild cases on all sub-items to compare whether the sound-group or the control-group showed significant differences. The results showed that for each sub-item: "mood", "involvement", "motivation", "fun" there was no significant difference between sound-group and control-group at $p < 0,05$ (t-values and p-values for each sub-item: see below).

Results ES- subgroup A -sub-item "mood" (see Fig. 34)

The t-test for 2 independent means of the item "mood" was computed to compare whether the sound-group or the control-group showed significant differences in subgroup A - severe cases. The t-value of 1,30321 and the p-value of 0,210947 showed that "mood" was not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- or the sound-group concerning the item "mood". The t-test for 2 independent means of the item "mood" was computed to compare whether the sound-group or the control-group showed significant differences in subgroup A - moderate cases. The t-value of -0,02704 and the p-value of 0,979475 showed that "mood" was not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- or the sound-group concerning the item "mood". The t-test for 2 independent means of the item "mood" was computed to compare whether the sound-group or the control-group showed significant differences in subgroup A- mild cases. The t-value of 0,37796 and the p-value of 0,720971 showed that "mood" was not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- or the sound-group concerning the item "mood".

Results ES- subgroup A -sub-item "involvement" (see Fig. 34)

The t-test for 2 independent means of the item "involvement" was computed to compare whether the sound-group or the control-group showed significant differences in subgroup A- severe cases. The t-value of -1,36201 and the p-value of 0,192064 showed that "involvement" was not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- or the sound-group concerning the item "involvement". The t-test for 2 independent means of the item "involvement" was computed to compare whether the sound-group or the control-group showed significant differences in subgroup A - moderate cases. The t-value of 0,18898 and the p-value of 0,857538 showed that "involvement" was not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- or the sound-group concerning the item "involvement". The t-test for 2 independent means of the item "involvement" was computed to compare whether the sound-group or the control-group showed significant differences in subgroup A - mild cases. The t-value of 1,05633 and the p-value of 0,339161 showed that "involvement" was not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- or the sound-group concerning the item "involvement".

Results ES- subgroup A -sub-item "motivation" (see Fig. 34)

The t-test for 2 independent means of the item "motivation" was computed to compare whether the sound-group or the control-group showed significant differences in subgroup A - severe cases. The t-value of 0,21053 and the p-value of 0,835915 showed that "motivation" was not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- or the sound-group concerning the item "motivation". The t-test for 2 independent means of the item "motivation" was computed to compare whether the sound-group or the control-group showed significant differences in subgroup A - moderate cases. The t-value of 1,37192 and the p-value of 0,228442 showed that "motivation" was not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- or the sound-group concerning the item "motivation". The t-test for 2 independent means of the item "motivation" was computed to compare whether the sound-group or the control-group showed significant differences in subgroup A - mild cases. The t-value of 0,13199 and the p-value of 0,900138 showed that "motivation" was not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- or the sound-group concerning the item "motivation".

Results ES- subgroup A -sub-item "fun" (see Fig. 34)

The t-test for 2 independent means of the item "fun" was computed to compare whether the sound-group or the control-group showed significant differences in subgroup A - severe cases. The t-value of -0,36515 and the p-value of 0,719783 showed that "fun" was not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- or the sound-group concerning the item "fun". The t-test for 2 independent means of the item "fun" was computed to compare whether the sound-group or the control-group showed significant differences in subgroup A - moderate cases. The t-value of 0,59761 and the p-value of 0,576132 showed that "fun" was not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- or the sound-group concerning the item "fun". The t-test for 2 independent means of the item "fun" was computed to compare whether the sound-group or the control-group showed significant differences in subgroup A - mild cases. The t-value of 0 and the p-value of 1 showed that "fun" was not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- or the sound-group concerning the item "fun".

Results ES- subgroup B 1, 3 (see Fig. 34)

The t-test for 2 independent means of subgroup B 1 (2-6 months post-stroke) and B3 (>12 months post-stroke) was performed to compare whether the sound-group or the control-group showed significant differences depending ~~upo~~n the time-span post-stroke ~~till~~ to treatment. The results showed that in each sub-item "mood", "involvement", "motivation" there was no significant difference between sound-group and control-group at $p < 0,05$. Regarding the sub-item "fun", a difference was found in subgroup B3. The sound-group rated "fun" significantly higher than the control-group at $p < 0,05$. This means that with a probability of 95%, patients > 12 months post-stroke rate "fun" higher in the sound-group than in the control-group (t-values and p-values for each sub-item: see below).

Results ES- subgroup B - sub-item "mood" (see Fig. 34)

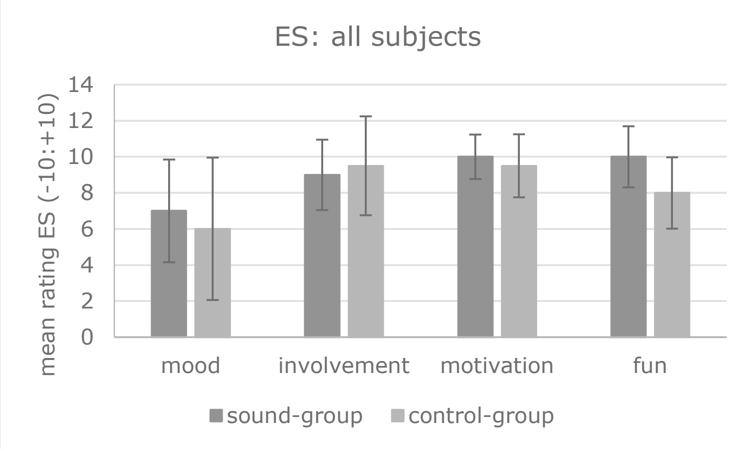
The t-test for 2 independent means of the item "mood" was computed to compare whether the sound-group or the control-group showed significant differences in subgroup B1 (2-6 months post-stroke). The t-value of -0,22292 and the p-value of 0,826416 showed that "mood" was not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- or the sound-group concerning the item "mood". The t-test for 2 independent means of the item "mood" was computed to compare whether the sound-group or the control-group showed significant differences in subgroup B3 (> 12 months post-stroke).The t-value of 0,75984 and the p-value of 0,464886 showed that "mood" was not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- or the sound-group concerning the item "mood".

Results ES- subgroup B - sub-item "involvement" (see Fig. 34)

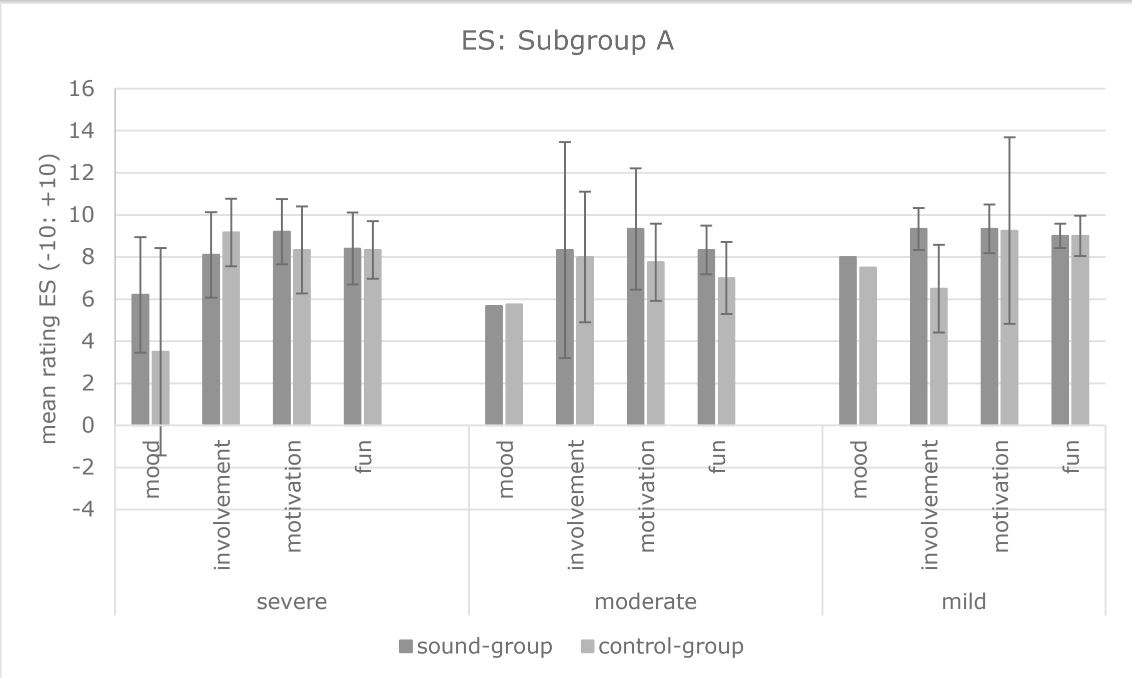
The t-test for 2 independent means of the item “involvement” was computed to compare whether the sound-group or the control-group within subgroup B1 (2-6 months post-stroke) or subgroup B3 (>12 months post-stroke) showed significant differences. The t-value of subgroup B1: -0,16405 or subgroup B3: 2,16431 and the p-value of subgroup B1: 0,87175 or subgroup B3: 0,055702 showed that ratings of “involvement” did not differ significantly between sound-group and control-group.
Results ES- subgroup B - sub-item “motivation” (see Fig. 34)
The t-test for 2 independent means of the item “motivation” was computed to compare whether the sound-group or the control-group within subgroup B1 (2-6 months post-stroke) or subgroup B3 (>12 months post-stroke) showed significant differences. The t-value of subgroup B1: 1,5395 and the p-value of subgroup B1: 0,143224 showed that ratings of “motivation” did not differ significantly between sound-group and control-group in subgroup B1. The t-value of subgroup B3: 2,40594 and the p-value of 0,036939 showed that the sound-group rated “motivation” higher with p < 0,05. This means that with a probability of 95% patients in subgroup B3 (> 12 months post-stroke) rate “motivation” higher in the sound-group than the control-group.
Results ES- subgroup B - sub-item “fun” (see Fig. 34)
The t-test for 2 independent means of the item “fun” was computed to compare whether the sound-group or the control-group within subgroup B1 (2-6 months post-stroke) or subgroup B3 (>12 months post-stroke) showed significant differences. The t-value of subgroup B1 -0,88775: or subgroup B3: 1,5832 and the p-value of subgroup B1: 0,387827 or subgroup B3: 0,144458 showed that ratings of “fun” did not differ significantly between sound-group and control-group.

Results Experience Samplings (ES) - all subjects / subgroup A/B- plots:

Results Experience Sampling Method of all subjects:



Experience Samplings (ES): sound-group (n=20) vs. control-group (n=14)				
	Mood	involvement	motivation	fun
sound-group: mean rating (-10:+10)/ sd	6,684210526	8,421052632	9,210526316	8,736842105
	2,84902774	1,952656011	1,228320776	1,694504361
control-group: mean rating (-10:+10)/ sd	5,214285714	8,35714285	8,571428571	8,285714286
	3,945368686	2,734597224	1,741541568	1,977899874



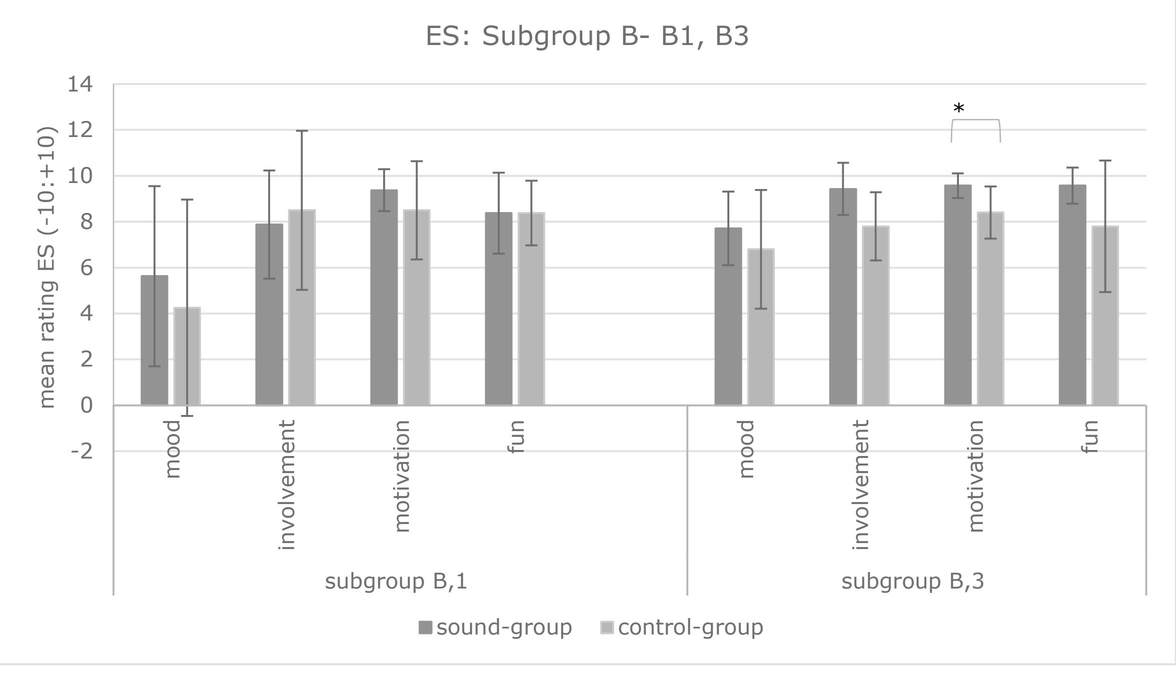
subgroup A- severe: sound-group (n=12) vs. control-group (n=5)				
	mood	involvement	motivation	fun
sound-group: mean rating (-10:+10)/ sd	6,2	8,1	9,2	8,4
	2,740640639	2,024845673	1,549193338	1,712697677

control-group: mean rating (-10:+10)/ sd	3,5	9,166666667	8,333333333	8,333333333
	4,929503018	1,602081979	2,065591118	1,366260102

subgroup A- moderate: sound-group (n=4) vs. control-group (n=4)				
	mood	involvement	motivation	fun
sound-group: mean rating (-10:+10)/ sd	5,666666667	8,333333333	9,333333333	8,333333333
	5,131601439	2,886751346	1,154700538	2,886751346
control-group: mean rating (-10:+10)/ sd	5,75	8	7,75	7
	3,095695937	1,825741858	1,707825128	2,943920289

subgroup A- mild: sound-group (n=4) vs. control-group (n=5)				
	mood	involvement	motivation	fun
sound-group: mean rating (-10:+10)/ sd	8	9,333333333	9,333333333	9
	1	1,154700538	0,577350269	1,732050808
control-group: mean rating (-10:+10)/ sd	7,5	6,5	9,25	9
	2,081665999	4,434711565	0,957427108	1,154700538

Results Experience Sampling- Subgroup B1, 3



subgroup B1: 2-6 months post-stroke: sound-group (n=9) vs. control-group (n=5)				
	mood	involvement	motivation	fun
sound-group: mean rating (-10:+10)/ sd	5,625	7,875	9,375	8,375
	3,925648263	2,356601669	0,916125381	1,767766953
control-group: mean rating (-10:+10)/ sd	4,25	8,5	8,5	8,375
	4,713203339	3,464101615	2,138089935	1,407885953

subgroup B3: >12 months post-stroke: sound-group (n=9) vs. control-group (n=5)				
	mood	involvement	motivation	fun
sound-group: mean rating (-10:+10)/ sd	7,714285714	9,428571429	9,571428571	9,571428571
	1,603567451	1,133893419	0,534522484	0,786795792
control-group: mean rating (-10:+10)/ sd	6,8	7,8	8,4	7,8
	2,588435821	1,483239697	1,140175425	2,863564213
T, P, p			2.40594 0.036939 significant at p <0.05	

Fig. 34: Results Experience Samplings (ES)- all sub-items- all subjects/ subgroup A/ subgroup B

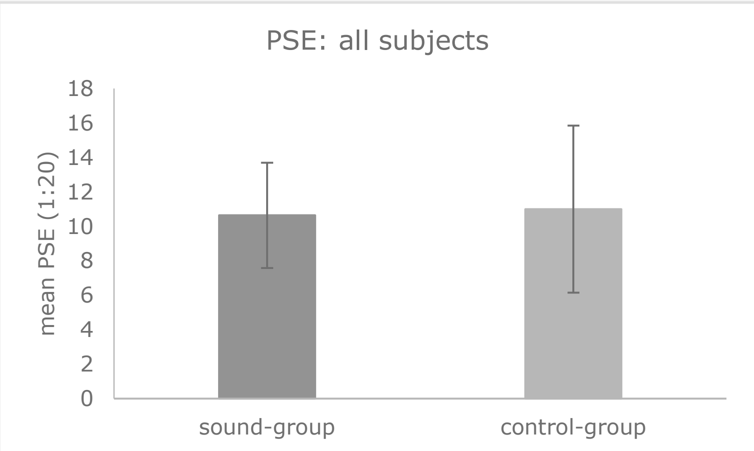
Perceived Size of Effort (PSE)

Results "Perceived Size of Effort" (PSE) - all subjects (see Fig. 35)
The t-test for 2 independent means of "Perceived Size of Effort" was computed to compare whether the sound-group or the control-group showed significant differences. The t-value of 0,03275 and the p-value of 0,974085 showed that the "Perceived Size of Effort" was not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- or the sound-group concerning the item "Perceived Size of Effort".
Results "Perceived Size of Effort" (PSE) – subgroup A (see Fig. 35)
The t-test for 2 independent means of "Perceived Size of Effort" was computed to compare whether the sound-group or the control-group showed significant differences in subgroup A - severe cases. The t-value of -0,99395 and the p-value of 0,335041 showed that the "Perceived Size of Effort" was not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between

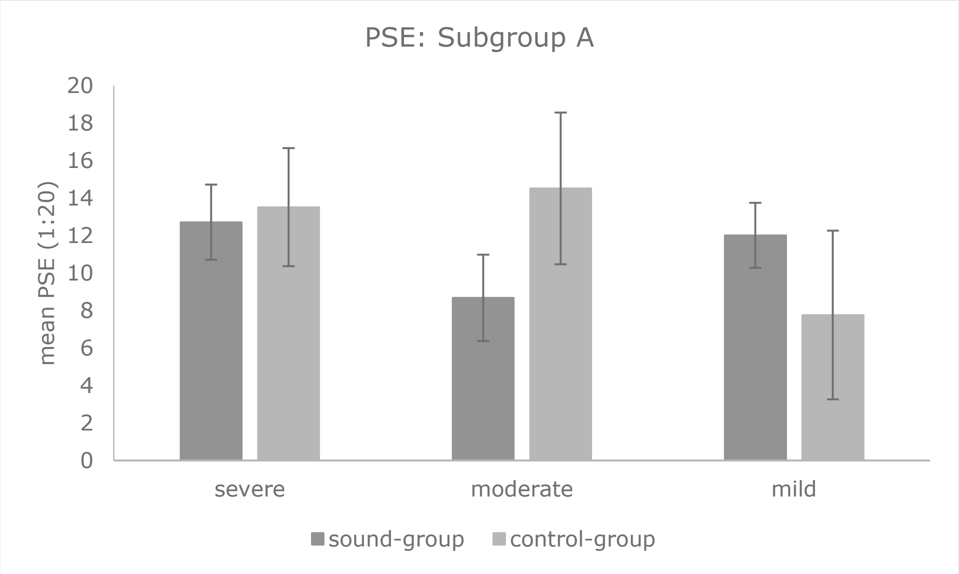
ratings of the control- or the sound-group concerning the item "Perceived Size of Effort". The t-test for 2 independent means of "Perceived Size of Effort" was computed to compare whether the sound-group or the control-group showed significant differences in subgroup A- moderate cases. The t-value of -2,21094 and the p-value of 0,078012 showed that the "Perceived Size of Effort" was not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- or the sound-group concerning the item "Perceived Size of Effort". The t-test for 2 independent means of "Perceived Size of Effort" was computed to compare whether the sound-group or the control-group showed significant differences in subgroup A - mild cases. The t-value of 1,52297 and the p-value of 0,188266 showed that the "Perceived Size of Effort" was not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- or the sound-group concerning the item "Perceived Size of Effort".
Results "Perceived Size of Effort" (PSE) – subgroup B- B1, B3 (see Fig. 35)
The t-test for 2 independent means of the "Perceived Size of Effort" was computed to compare whether the sound-group or the control-group within subgroup B1 (2-6 months post-stroke) or subgroup B3 (>12 months post-stroke) showed significant differences. The t-value of subgroup B1: -0,9447 or subgroup B3: 1,06914 and the p-value of subgroup B1: 0,358861 or subgroup B3: 0,310136 showed that ratings of the "Perceived Size of Effort" did not differ significantly between sound-group and control-group.

Results Perceived Size of Effort (PSE) - all subjects / subgroup A/ B- plots:

Results Perceived Size of Effort (PSE) - all subjects:



Perceived Size of Effort (PSE): sound-group (n=20) vs. control-group (n=14)	
sound-group:	10,6363636
mean PSE/ sd	3,061742805
control-group:	11
mean PSE/ sd	4,847113109

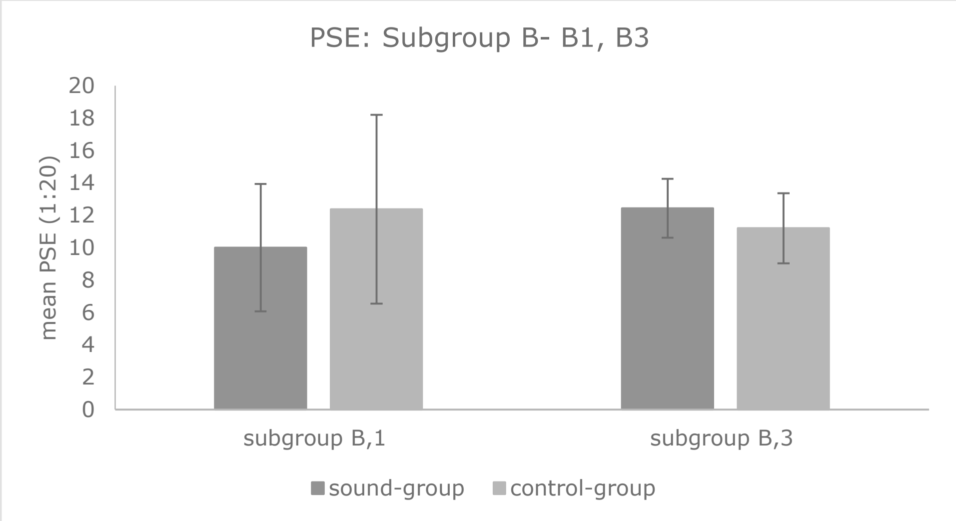


Subgroup A- severe- Perceived Size of Effort (PSE): sound-group (n=12) vs. control-group (n=5)	
sound-group:	12,7
mean PSE/ sd	2,002775851
control-group:	13,5
mean PSE/ sd	3,146426545

Subgroup A- moderate- Perceived Size of Effort (PSE): sound-group (n=4) vs. control-group (n=4)	
sound-group:	8,66666667
mean PSE/ sd	2,309401077
control-group:	14,5
mean PSE/ sd	4,041451884

Subgroup A- mild- Perceived Size of Effort (PSE): sound-group (n=4) vs. control-group (n=5)	
sound-group:	12
mean PSE/ sd	1,732050808
control-group:	7,75
mean PSE/ sd	4,5

Results Perceived Size of Effort (PSE)- Subgroup B: B1, B3



	subgroup B1: 2-6 months post-stroke: sound-group (n=9) vs. control-group (n=5)	subgroup B3: 2-6 months post-stroke: sound-group (n=9) vs. control-group (n=5)
sound-group: mean PSE/ sd	10	12,42857143
	3,927922024	1,812653934
control-group: mean PSE; sd	12,375	11,2
	5,829420456	2,167948339

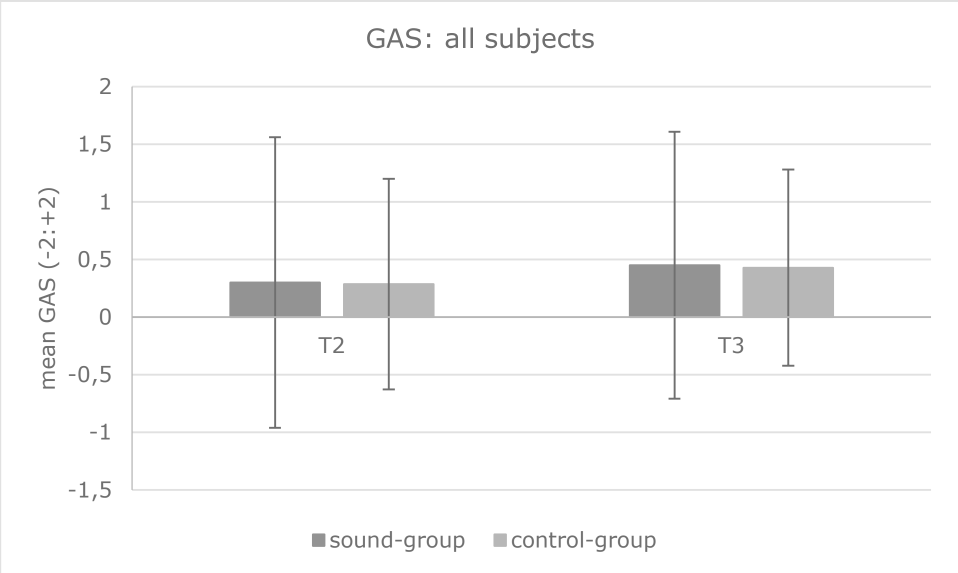
Fig. 35: Results Perceived Size of Effort (PSE) - all subjects/ subgroup A/ subgroup

Goal Attainment Scale (GAS)

Results" Goal Attainment Scale" (GAS) - all subjects (see Fig. 36)
The t-test for 2 independent means of ratings of the "Goal Attainment Scale" was computed to compare whether the sound-group or the control-group showed significant differences. The t-value of T2: 0,03619/ T3: 0,05768 and the p-value of T2: 0,971353/ T3: 0,954366 showed that ratings of the "Goal Attainment Scale" were not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- or the sound-group ratings concerning the "Goal Attainment Scale".
Results" Goal Attainment Scale" (GAS) – subgroup A (see Fig. 36)
The t-test for 2 independent means of ratings on the "Goal Attainment Scale" was computed to compare whether the sound-group or the control-group showed significant differences in subgroup A - severe cases. The t-value of T2: -2,11255/ T3: -1,37288 and the p-value of T2: 0,051816 / T3: 0,189968 showed that ratings on the "Goal Attainment Scale" were not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- or the sound-group ratings concerning the "Goal Attainment Scale" in subgroup A for severe cases.The t-test for 2 independent means of ratings on the "Goal Attainment Scale" was computed to compare whether the sound-group or the control-group showed significant differences in subgroup A - moderate cases. The t-value of T2: 1,89737/ T3: 1,80579 and the p-value of T2: 0,106558 / T3: 0,120979 showed that the ratings on the "Goal Attainment Scale" were not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- or the sound-group ratings concerning the "Goal Attainment Scale" in subgroup A for moderate cases.The t-test for 2 independent means of ratings on the "Goal Attainment Scale" was computed to compare whether the sound-group or the control-group showed significant differences in subgroup A - mild cases. The t-value of T2: 0,33333 / T3: 0,42366 and the p-value of T2: 0,748645 / T3: 0,684528 showed that the ratings on the "Goal Attainment Scale" were not rated significantly higher in the sound-group than in the control-group. This means that there is no difference between ratings of the control- or the sound-group ratings concerning the "Goal Attainment Scale" in subgroup A for mild cases.
Results" Goal Attainment Scale" (GAS) – subgroup B- B1, B3 (see Fig. 36)
The t-test for 2 independent means of ratings on the "Goal Attainment Scale" was computed to compare whether the sound-group or the control-group within subgroup

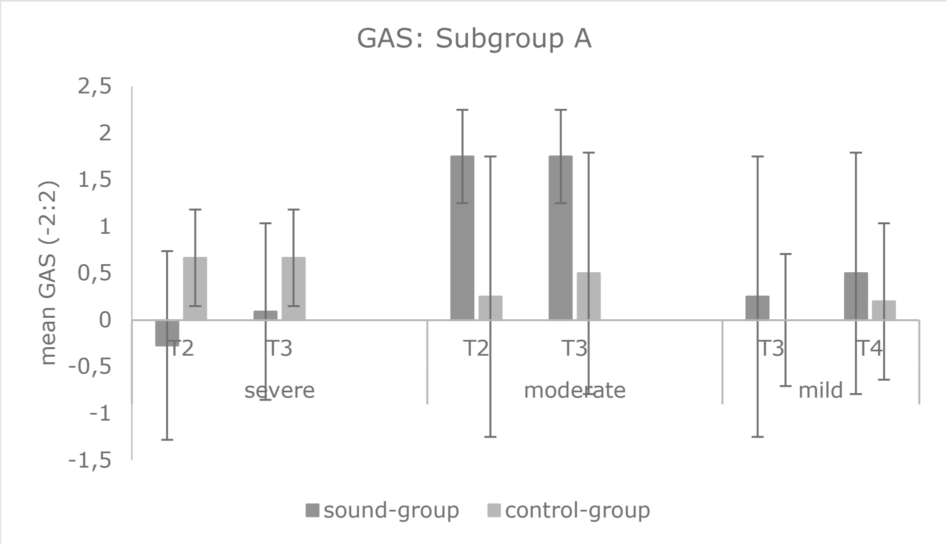
B1 (2-6 months post-stroke) or subgroup B3 (>12 months post-stroke) showed significant differences. The t-value of subgroup B1: T2: -0,5484/ T3: -0,58347 or subgroup B3: T2: 1,39912/ T3: 1,5377 and the p-value of subgroup B1: T2: 0,591485/ T3: 0,568248 or subgroup B3: T2: 0,187091/ T3: 0,150061 showed that ratings on the "Goal Attainment Scale" did not differ significantly between sound-group and control-group.

Results Goal Attainment Scale- all subjects/ subgroup A/ B- Plots:



Goal Attainment Scale (GAS): sound-group (n=20) vs. control-group (n=14)		
	T2	T3
sound-group:	0,3	0,45
mean GAS/ sd	1,260743306	1,157230006
control-group:	0,285714286	0,428571429
mean GAS/ sd	0,913873533	0,851630627

Results “Goal Attainment Scale”- Subgroup A:

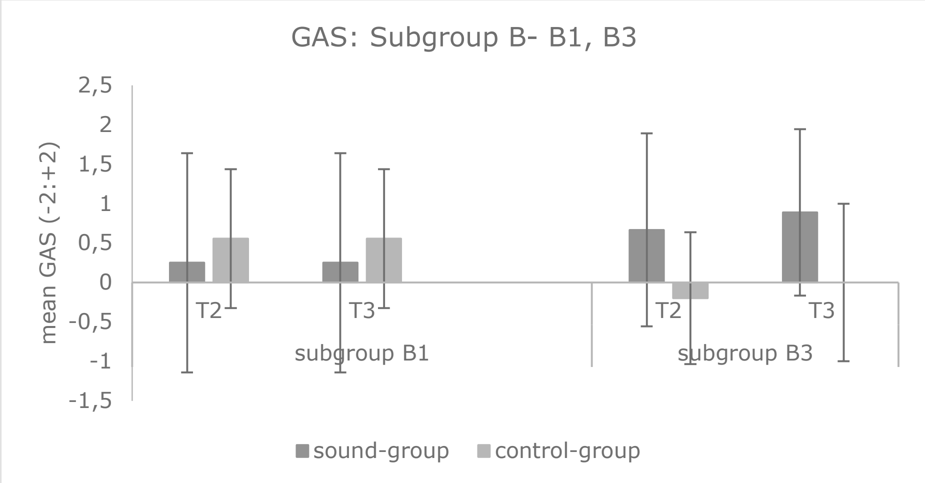


Goal Attainment Scale (GAS) subgroup A- severe: sound-group (n=12) vs. control-group (n=5)		
	T2	T3
sound-group:	-0,272727273	0,090909091
mean GAS/ sd	1,009049958	0,943879807
control-group:	0,666666667	0,666666667
mean GAS/ sd	0,516397779	0,516397779

Goal Attainment Scale (GAS) subgroup A- moderate: sound-group (n=4) vs. control-group (n=4)		
	T2	T3
sound-group:	1,75	1,75
mean GAS/ sd	0,5	0,5
control-group:	0,25	0,5
mean GAS/ sd	1,5	1,290994449

Goal Attainment Scale (GAS) subgroup A- mild: sound-group (n=4) vs. control-group (n=5)		
	T2	T3
sound-group:	0,25	0,5
mean GAS/ sd	1,5	1,290994449
control-group:	0	0,2
mean GAS/ sd	0,707106781	0,83666002

Results “Goal Attainment Scale”- Subgroup B- B1, B3:

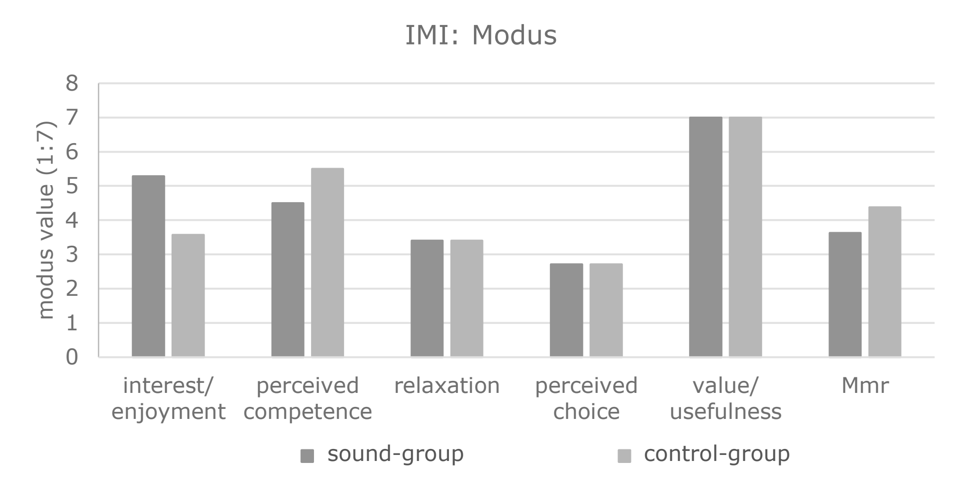


Goal Attainment Scale (GAS) subgroup B1: sound-group (n=9) vs. control-group (n=5)		
	T2	T3
sound-group:	0,25	0,25
mean GAS/ sd	1,38873015	1,38873015
control-group:	0,555555556	0,555555556
mean GAS/ sd	0,881917104	0,881917104
Goal Attainment Scale (GAS) subgroup B3: sound-group (n=9) vs. control-group (n=5)		
	T2	T3
sound-group:	0,666666667	0,888888889
mean GAS/ sd	1,224744871	1,054092553
control-group:	-0,2	0
mean GAS/ sd	0,836660027	1

Fig. 36: Results” Goal Attainment Scale” (GA all subjects, subgroup A/ subgroup B.

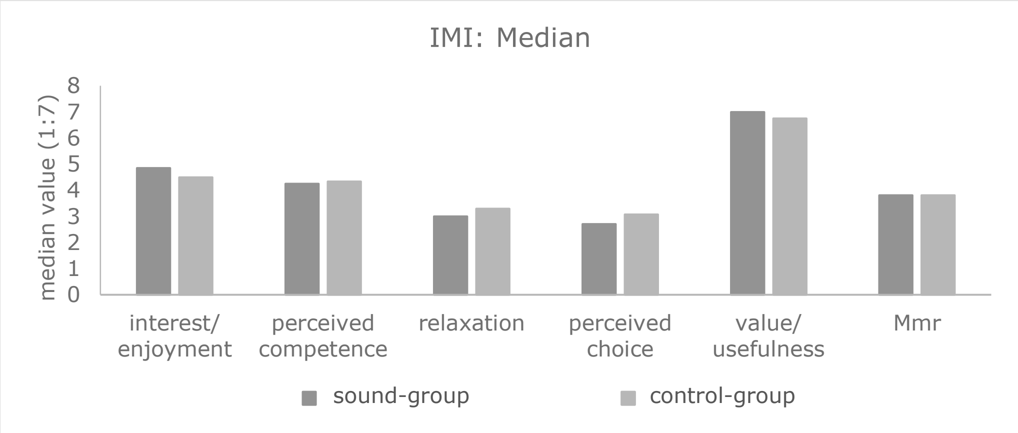
9.2 c) Additional Data

Intrinsic Motivation Inventory- overall study population (n=34)- modus values



Modus	sound-group	control-group
interest/ enjoyment	5,28571429	3,57142857
perceived competence	4,5	5,5
relaxation	3,4	3,4
perceived choice	2,71428571	2,71428571
value/ usefulness	7	7
man-machine relation	3,625	4,375

Intrinsic Motivation Inventory- overall study population (n=34)- median values



Median	sound-group	control-group
interest/ enjoyment	4,85714286	4,5
perceived competence	4,25	4,33333333
relaxation	3	3,3
perceived choice	2,71428571	3,07142857
value/ usefulness	7	6,75
man-machine relation	3,8125	3,8125

9.3 Acknowledgments

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