Clinical and neurophysiological correlates of upper extremity motor recovery in severely impaired chronic stroke patients

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Bettina Hanna Trunk

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Dekan der Math.-Nat. Fakultät:	Prof. Dr. Thilo Stehle
Dekan der Medizinischen Fakultät:	Prof. Dr. Bernd Pichler
1. Berichterstatter:	Prof. Dr. Alireza Gharabaghi
2. Berichterstatter:	Prof. Dr. Christoph Braun
Prüfungskommission:	Prof. Dr. Alireza Gharabaghi
	Prof. Dr. Christoph Braun
	Prof. Dr. Andreas Bartels
	Prof. Dr. Anna Levina

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Table of contents

Abbreviations

ARAT	Action Research Arm Test
CAHAI	Chedoke Arm and Hand Inventory 13
cMEP	contralateral Motor Evoked Potential
CoG	Center of Gravity
CSE	Corticospinal Excitability
EDC	Extensor Digitorum Communis
EMG	Electromyography
FMLE	Fugl-Meyer Lower Extremity
FMUE	Fugl-Meyer Upper Extremity
FMUE-C	Fugl-Meyer Upper Extremity, part C - hand
iMEP	ipsilateral Motor Evoked Potential
LTP	Long-Term Potentiation
M1	Primary motor cortex
MAS	Modified Ashworth Scale
MCID	Minimal Clinically Important Difference
MEP	Motor Evoked Potential
MoCa	Montreal Cognitive Assessment
MSO	Maximum Stimulator Output
NIBS	Non-invasive Brain Stimulation
NIHSS	National Institute of Stroke Scale
NMES	Neuromuscular Electrical Stimulation
PAS	Paired Associative Stimulation
rTMS	repetitive Transcranial Magnetic Stimulation
SIS	Stroke Impact Scale
tACS	transcranial Alternating Current Stimulation
TMS	Transcranial Magnetic Stimulation

Summary/ Abstract

Introduction Stroke is a leading cause of permanent disabilities worldwide. One third of the patients show only poor recovery of upper-extremity motor functions when reaching the chronic stage of stroke. To improve motor functions in chronic stroke patients, high-dose motor training interventions have been developed. However, the potential has not yet been investigated in patients with severe motor impairment. Additionally, neurostimulation is a widely used tool to facilitate motor recovery. The aim of this thesis was to (1) investigate the potential of a high-dose hand motor training intervention combined with associative neurostimulation in severely affected chronic stroke patients; (2) evaluate and adapt mapping methods for the presented patient cohort; (3) study clinical and neurophysiological effects following the intervention; and (4) evaluate the contributions of the two hemispheres in the recovery process and get insights in underlying recovery mechanisms.

Methods 21 severely impaired chronic stroke patients with hand paralysis took part in a within-subject, standard-of-care controlled clinical trial with high-dose upper limb training. After a 6-months waitlist control period with standard physiotherapy and three evaluations visits (V0, V1, V2), all patients took part in a 6-months intervention period which consisted of two blocks of intensive daily upper-limb training (V2-3, V4-5) lasting 3 weeks each, and two follow-up periods (V3-4, V5-6) lasting 3 month each. During the training blocks, concurrent neuromuscular electrical stimulation (NMES) was applied to the paretic arm. In parallel, patients received ipsi- and contralesional cortical transcranial alternating current stimulation (tACS) during the training, which was applied in double-blind, randomised, cross-over order, i.e., ipsilesional stimulation in block one and contralesional stimulation in block two, or vice versa. The Fugl-Meyer Upper Extremity score (FMUE) was the primary outcome and assessed at all visits (V0-V6), while determining the minimal clinically important difference (MCID) with anchor- and distribution-based methods. From V2-V6, also contra- and ipsilateral corticospinal excitability (CSE) was assessed at the motor hotspot using transcranial magnetic stimulation (TMS). Additionally, extended TMS motor maps were acquired in each hemisphere throughout the study (V0-V6) to estimate both contralateral pathways from the lesioned hemisphere and ipsilateral pathways from the non-lesioned hemisphere to the paralysed hand.

Results The MCID for the investigated patient population was 2 FMUE points. The FMUE (average: 10.84 ± 4.26 at V2) showed no significant changes during the control period. Linear

mixed models revealed a significant, clinically important FMUE improvement over time (on average 2.05 ± 3.21, p = .00022) during the intervention and follow-up periods, i.e., from V2 to V4 (p < .001), V2 to V5 (p = .0033) and V2 and V6 (p < .001), with twelve patients showing a MCID. CSE and motor maps changed in both hemispheres following different patterns, i.e., the excitability of contra- and ipsilateral corticospinal pathways peaked after the first and second training block, respectively. Moreover, both FMUE and CSE of ipsilateral pathways improved significantly more, when tACS was applied to the lesioned hemisphere in the first block, and to the non-lesioned hemisphere in the second block (p = .029, p = .017, respectively). Finally, the excitability of the contralesional motor map predicted the amount of hand motor recovery independent of the clinical baseline status (r = .80, p = .001).

Conclusion This study provides evidence that clinically relevant motor recovery is possible when chronic stroke patients with severe motor impairment undergo high-dose motor training with NMES and tACS. The cortical hemispheres seem to play a complementary role during the recovery process. While contralateral pathways from the lesioned hemisphere are recruited first, ipsilateral pathways from in the non-lesioned hemisphere contribute gradually and peak in parallel to the clinical follow-up effects. Neuromodulation protocols that target both hemispheres in sequential order may enhance the recovery process in severely impaired stroke patients with hand paralysis.

1 Introduction

1.1 Stroke

Stroke is a common disease [1] and one of the leading causes of death and permanent disabilities worldwide [2,3]. Due to population ageing and improved medical care, the prevalence is expected to raise even further within the next years [4–6]. A stroke can cause various deficits in different neurological domains [5]. Persistent disabilities often go along with a severe loss of independency and quality of life [7,8]. To regain independency, recovery of upper extremity motor functions is particularly important [6,9]. The time after stroke is commonly divided in the following stages: the hyperacute (0-24h after stroke), the acute (1-7 days after stroke), the early subacute (7 days-3 months after stroke), late subacute (3-6 months after stroke) and the chronic stage (from six months after stroke onset on) [10]. Within this thesis, the focus is on motor recovery of the upper extremity in chronic stroke patients.

1.2 Motor recovery after stroke

After stroke, there are natural recovery processes known as spontaneous recovery [11]. Motor recovery after stroke is driven by massive neuronal reorganisation of both hemispheres through plastic changes [11–14]. These processes usually occur within three months after stroke [12]. Current research showed a limited time window of heightened motor recovery within the first two-three months after stroke when applying intensive training during this time [15]. There is great interest in predicting motor recovery after stroke.

The amount of spontaneous recovery was proposed to be fixed [16,17]. The proportional recovery rule, a widespread theory, suggests that stroke patients recover around 70% of the initially lost upper extremity motor functions within six months after stroke [17]. However, this rule does not apply to all patients [16–18]. Around one third of the patients are non-fitters, i.e., they show only little spontaneous recovery and suffer from persistent severe motor impairment of the upper extremity [16,17]. These patients are characterised by higher initial impairment, indexed by lower Fugl-Meyer Upper Extremity (FMUE) and Fugl-Meyer Lower extremity (FMLE) scores and absent finger flexion as well as larger strokes and the presence of facial palsy [16]. Furthermore, it has been suggested that these patients lack an intact corticospinal tract early after stroke [19–21].

However, the proportional recovery rule has been criticised for various reasons. First, the concept of proportional recovery suggested the spontaneous recovery to be fixed, independent of factors like therapy, dose or type of stroke [17,22]. Furthermore, the prediction was based on the clinical status after stroke only [23,24]. Additionally, there are methodological limitations, e.g., ceiling effects of the FMUE scale. Consequently, there are ongoing discussions in the literature about the practicality of the proportional recovery rule [23,25–28]. These studies commonly propose recovery not to be proportional [23,26] and an overestimation of the prediction [19,25,26]. It was furthermore concluded that more complex models and factors are necessary to explain and predict recovery after stroke [19,23–25].

However, independent of the exact number of patients, there is a patient cohort that lacks pronounced recovery in the (sub-) acute stage of stroke and remains severely impaired beyond the chronic stage [19].

Beyond the window of heightened plasticity in the (sub-) acute stage after stroke [12,29], there is accumulating evidence that recovery in the chronic stage of stroke is still possible [30,31]. While there is increasing interest in research focusing on the growing population of chronic stroke patients [30,32], there is only a small amount of trials focusing on the sub-group of chronic stroke patients with persistent severe motor impairment [33,34]. As new rehabilitation approaches as well as insights in the underlying physiological mechanisms in this understudied population are highly required, this thesis focuses on severely affected chronic stroke patients. There are multiple approaches to target motor recovery in chronic stroke patients [32].

1.3 High-dose rehabilitation trials

As current rehabilitative standard care is often not leading to relevant improvements in chronic stroke patients [35], one recent approach is to relevantly increase the therapy dose [36,37]. This could be shown to have a positive influence on the amount of clinically meaningful improvements in stroke patients which were on average one year post-stroke [37]. Doses of current standard rehabilitation is reported to be low (minutes per day) [38] of which patients are usually not physically active for a large amount of time during the sessions [39]. However, the exact dose-response relationship remains unclear and requires further

consideration [40]. In rats, it could be shown that even severely injured rats in the acute phase after stroke could significantly recover if rehabilitation intensity was sufficient (up to 600-700 repetitions/day) [41]. In a feasibility study, Birkenmeier et al. 2010 demonstrated the feasibility of translating high doses as shown in animal research to chronic stroke patients. In their study, chronic stroke patients took part in a training with 300 repetitions in one hour (three one-hour sessions per week for six weeks; 18 hours in total), which would be possible to integrate into standard rehabilitative care [42]. However, the patients had only mild-moderate motor impairment (measured in mean Action Research Arm Test (ARAT) at baseline > 20). Further studies, measuring doses in hours of total training (ranging from 24-36 hours) did not lead to improvements in motor functions beyond usual care in sub-acute [43] or chronic stroke patients [44–46]. In contrast, a study with 300 hours of training in 12 weeks led to a significant improvement of motor functions in chronic stroke patients independent of the intervention type (with a mean baseline FMUE score in all intervention groups > 22) [47]. Using the same treatment protocol, Daly et al. 2019 could replicate previous results. Furthermore, they investigated the clinical status during the intervention period, i.e., after 150 hours of training. They showed that there was no mid-term plateau but a similar effect in the first and second half of the training period [48]. In another recent study, a high-dose physical training including 90 hours of training in three weeks could improve upper extremity motor functions in chronic stroke patients relevantly [30]. The patient cohort was mildly to moderately affected (median FMUE at baseline: 26, exclusion of patients with absent limb movements). The findings of high-dose studies in the range of 90-300 hours open new perspectives in the context of motor recovery in chronic stroke patients. However, to our knowledge, the effectiveness of a similar high-dose training has not yet been investigated in a group of severely impaired stroke patients (with a FMUE score < 20) with absent finger extension.

1.4 Neurostimulation as a key to induce plasticity

1.4.1 Background

In addition to physical training, non-invasive brain stimulation (NIBS) is a powerful tool to facilitate motor rehabilitation after stroke [5,49,50]. Pairing NIBS with motor training was shown to be more effective than both techniques alone [51]. NIBS can increase plasticity in the brain, i.e., the ability to adapt to changes for example due to brain damage [52].

Depending on the stimulation parameters, it can have excitatory or inhibitory effects [50,53]. In the context of this thesis, faciliatory stimulation is in the focus. Specifically, the goal is to alter synaptic connections, i.e., strengthen synaptic connections by Long-Term Potentiation (LTP), and consequently improve motor recovery [52–54].

The corticospinal tract is a key target for neuromodulation as it connects the motor cortex with the spinal cord and is the principle pathway for skilled voluntary movement, especially of distal muscles [55]. The goal is to alter the connections between specific circuits [55]. However, responses to NIBS protocols are highly variable between and within patients [53,56]. In this context, there is growing interest in making neurostimulation protocols more efficient.

1.4.2 Combined Stimulation

One approach to increase the efficiency of neurostimulation protocols, is the combination of multiple neurostimulation protocols [6,32,55]. The underlying idea is to maximise the effects by complementing and augmenting the effects of each single therapy [53] by concurrently activating both afferent and efferent pathways [57].

However, combining two effective protocols does not automatically lead to increased effects [32]. When combining protocols, it is essential to take into account factors such as intensity, frequency or relative timing of paired stimulation [55]. Especially the latter is of great importance [53,58]. One key paper in this context is by Stefan et al. 2000. Here, the authors introduced a protocol named Paired-Associative Stimulation (PAS) [59]. It was based on principles of Hebbian learning. The protocol consisted of 90 trials of paired Transcranial Magnetic Stimulation (TMS) and electrical stimulation to the median nerve. The timing was chosen such that the authors expected the effects of both stimulations to arrive approximately synchronously in the motor cortex. They addressed the question if this protocol can induce long-lasting changes in cortical excitability. They showed a plasticity induction that was dependent on the timing of the two stimulation modalities [59]. On this basis, a large number of modified protocols have been developed that follow the principles of PAS [60], e.g., in chronic stroke patients [61]. For example, the combined application of TMS and peripheral electrical stimulation could be shown to lead to increased CSE when applied brain-state dependently. Specifically, when the brain was found to be in an optimal brain state, i.e., detected via event-related desynchronisation in the beta band during motor imagery, the

peripheral electrical stimulation was initiated and followed by a TMS pulse [62]. Furthermore, it could be shown that pairing cortical and peripheral stimulation by TMS and a robotic orthosis led to increased CSE when applying the cortical stimulation in the optimal brain-state and synchronously to the peripheral input [63]. The increased excitability could be found even beyond the motor hotspot, indexed by an extended motor map [64].

In this context, Transcranial Alternating Current Stimulation (tACS) is a promising tool to non-invasively stimulate the cortex [65]. While the exact mechanisms are not completely understood yet [66,67], the current assumption is that tACS entrains cortical oscillations [65]. Oscillatory activity has been proposed to have an impact on neural communication [68]. In the human motor systems, beta oscillations of around 20 Hz have been found to be of particular relevance [65,67,69,70]. However, in stroke patients, these oscillations were shown to be altered, especially in patients with more severe impairment [71]. In contrast, in well-recovered stroke patients, oscillatory beta activity was not significantly different from healthy controls before training, indicating a normalisation of oscillatory activity in the course of motor rehabilitation [72]. In this context, oscillations can be modulated externally, e.g., by beta-tACS [73]. It could be shown that the application of 20Hz tACS leads to an increase of motor evoked potentials (MEP) when measuring during tACS stimulation, indicating increased corticospinal excitability (CSE) [66,67,74]. This increase was higher compared to 10Hz and sham [66] as well as 5 and 40 Hz tACS stimulation [75], indicating frequency-dependent online effects. Additionally, single-pulse TMS during 20Hz tACS was shown to lead to intensity-specific cumulative increases of CSE at 120% of the resting motor threshold [74]. Besides that, targeting specific phases of the tACS cycle with TMS was also shown to increase the effects [58]. This suggests that combining tACS with other stimulation techniques while considering specific parameters can facilitate CSE. In another study, the effects of tACS on the motor network were studied during resting state MRI. Therefore, tACS was applied in different frequencies: 5Hz, 20Hz and sham. The goal was to evaluate the role of M1 beta oscillations in functional connectivity in this region. It was found that 20 Hz stimulation of M1 directly affected the connectivity pattern of M1, but not local or network connectivity. Thus, entraining beta oscillations in M1 modulated the connectivity within that region without changing its connectivity strength to other regions [76]. Taken together, stimulating the motor cortex with 20Hz via tACS offers great potential in facilitating motor recovery after stroke.

Furthermore, combining tACS approaches with other neurorehabilitation approaches was suggested to lead to synergistic effects [77].

Additionally, there are various approaches to non-invasively stimulate the paretic muscle, e.g., electrical stimulation or robotics [47]. However, in severely affected patients, it remains unclear which method is superior [47]. Peripheral electrical stimulation, i.e., Neuromuscular Electrical Stimulation (NMES), is a promising tool in the context of motor rehabilitation [6,78,79]. NMES-based interventions have been recommended as upper extremity motor therapies especially for patients with only minimal active movement [80]. Combined with different techniques, it could be shown to have promising effects [6]. Furthermore, combined with bilateral motor training, the effects could be shown to be enhanced [81]. When electrically stimulating the paretic arm, movements can be induced and afferents of the somatosensory system which are involved in the motor control loop can be activated [32,81]. Finally, peripheral NMES stimulation is especially promising when coupled to the current brain-state [56,57,82].

Taken together, neurostimulation is a promising tool to promotor motor recovery in chronic stroke patients [5]. Combining several techniques in a specific timing was shown to be even more powerful than applying stimulation separately [32,83]. In this context, pairing peripheral and cortical stimulation [59], e.g., by NMES and tACS, may be particularly promising to induce associative plasticity [55].

1.5 Cortical imbalance after stroke as a target for neurostimulation

After stroke, patients typically experience a cortical imbalance: while the contralesional M1 experiences an abnormal over-excitation, the ipsilesional M1 is inhibited via an abnormally high interhemispheric inhibition from the healthy to the affected hemisphere [50,84,85]. In well recovered patients, it could be shown that recovery of motor functions relies predominantly on the reorganisation of activities in the affected hemisphere [86]. Thus, current approaches in stroke recovery focus on restoring interhemispheric balance [85–87]. This can be realised by both facilitating and inhibiting cortical excitability [29,85,86]. Facilitating excitability of the ipsilesional cortex can be done by faciliatory high frequency stimulation [86,88], e.g., by high-frequency repetitive TMS (rTMS). However, the effectiveness

of this approach was shown to be somewhat mixed [86]. Another approach in the context of rebalancing the hemispheres is to suppress inhibitory activity from the contralesional M1 [86,89,90]. This can for example be realised by low-frequency rTMS [87,91]. While this protocol was shown to be accompanied by improvements in motor functions, most studies focused on relatively well recovered patients [92]. In late subacute-chronic stroke patients, this approach was not shown to be superior compared to a sham stimulation in a current multicentre study. The authors applied 18 one-hour sessions of inhibitory 1Hz rTMS (or sham TMS in the control group) to the contralesional hemisphere combined with motor training over a period of six weeks. Both intervention groups showed significant improvements of the FMUE higher than expected for patients 3-12 months after stroke but with no difference between the groups [93]. As a consequence of these findings, recommendations to apply inhibitory stimulation to the contralesional hemisphere in chronic stroke patients are significantly weakened [29].

1.6 The role of the contralesional hemisphere in severely affected stroke patients

In contrast to the above mentioned protocols, in stroke patients with severe damage to the corticospinal tract, the overactive contralesional hemisphere has been repeatedly suggested to be a key to promote motor recovery [6,52,86,90,92].

While in mild to moderately affected patients, crossed corticospinal pathways may still be preserved, in patients with severe hemiparesis, contralateral pathways are often relevantly damaged [52,86,92]. This often leads to the absence of MEPs at the motor hotspot [94]. Additionally, it has been shown that contralesional activity is higher in patients with high motor impairment [95]. Furthermore, it could be shown that contralesional hemisphere excitability increased during recovery in severely affected patients [96].

Consequently, for this patient cohort, it has been suggested to target the contralesional M1 and make use of the over-excitation of the healthy hemisphere [92]. Hence, ipsilateral pathways could support the recovery of lost motor functions [14,85,86,90]. However, the exact pathways and mechanisms are not fully understood yet [86,92,97,98]. While the human corticospinal tract is mostly crossed, there is a small number of ipsilateral pathways (~10 - 15%) [92,99]. These pathways can be probed with TMS to the motor cortex and measuring

ipsilateral motor evoked potentials (iMEPs) on the same limb [100]. While in children until the age of ten, iMEPs can be easily measured [101], in healthy adults, muscle pre-activation is necessary [100]. This is probably related to the increased transcallosal inhibition during development [101]. However, in stroke patients, iMEPs can be measured more easily without pre-activation again suggesting reorganisation mechanisms via ipsilateral pathways [102]. This was suggested to be due to disinhibition of the ipsilateral motor cortex [102,103]. While the exact mechanisms and pathways remain poorly understood, the reticulospinal and rubrospinal pathways have been suggested as candidate pathways [98,100].

Taken together, there are different recovery mechanisms and approaches for motor rehabilitation after stroke. However, none of the approaches was shown to be effective for all patient cohorts [86,92]. Thus, the parameters of the target patient cohort have to be carefully considered. In severely affected chronic stroke patients, both facilitating the ipsilesional or facilitating the contralesional hemisphere and consequently target ipsilateral pathways were suggested to be effective approaches [52,86,90,92,104].

1.7 Clinical and physiological markers of recovery

To study the effectiveness of interventions and understand the underlying physiological mechanisms, it is furthermore essential to have reliable measures that may track plastic reorganisation. However, the standard methods applied in the field are not necessarily applicable to severely affected patients. In this context, the main methods of this thesis and potential limitations within the presented patient cohort will shortly be described in the following.

1.7.1 Clinical measures

As a direct read-out of changes in motor impairment and function, various clinical evaluations were undertaken. In this context, the Fugl-Meyer Upper Extremity (FMUE) [105] is a well-established and reliable tool to assess motor impairment in the context of stroke rehabilitation [106]. Within this thesis, the FMUE served as the primary outcome. Most studies in the field report effects based on FMUE outcomes which again makes it possible to compare the results to other studies. Commonly, the clinical relevance of interventions is furthermore judged by

comparing the amount of change in FMUE scores to a pre-defined critical value, i.e., the minimal clinically important difference (MCID). The most commonly applied MCID values in chronic stroke patients are a change of 4.25-7.25 [107] FMUE points. However, it was calculated based on mild to moderately affected chronic stroke patients. To our knowledge, there is no MCID available in the literature that was specified for the cohort of severely affected chronic stroke patients. Therefore, within this thesis, we first calculated the MCID for the presented patient cohort.

1.7.2 TMS measures

TMS is an established non-invasive and safe tool to study the motor system [108,109]. Mostly, corticospinal excitability (CSE) is studied over the motor cortex. This can be done for both ipsi- and contralateral connections [100]. Additionally, TMS measurements can be performed over a broader area beyond the motor cortex, i.e., by assessing the cortical representation of the affected muscles indexed by motor evoked potentials (MEP) following TMS (TMS-Maps) [108]. TMS-Maps are a reliable [110,111] and promising tool to understand neural background of motor recovery after stroke [108]. Common map parameters, such as the size and location of cortical motor representation serve as indicators of reorganisation processes [108]. However, severely motor impaired patients with extended damage of the corticospinal tract often show no MEP when applying standard TMS procedures [94,112,113]. Mapping the motor area with refined techniques [110,114,115] may allow identifying corticospinal reorganisation [63,64] and detecting residual connections beyond the primary motor cortex even in severely impaired stroke patients [114]. Furthermore, TMS-Maps are commonly assessed solely regarding contralateral pathways from both the ipsi- and contralesional hemisphere [108,116]. However, to our knowledge, there is no literature describing ipsilateral TMS-Maps derived from the contralesional hemisphere. Additionally, it remains unclear whether the size of the investigated area influence the detection of connections to paralysed muscles. In this context, within this thesis, first the potential of bilateral TMS-Maps was investigated before applying it as a measure of cortical reorganisation within the study.

1.8 Summary

In summary, motor recovery in chronic stroke is still challenging [6,32]. While there have been promising recent developments in chronic stroke patients, to our knowledge they mostly focus on mildly to moderately affected patients [30,47,48]. However, it is essential to develop targeted therapies for the subgroup of severely impaired chronic stroke patients [86,92]. Furthermore, the mechanisms that promote motor recovery in this patient cohort remain poorly understood and require further consideration [86]. While a high-dose training program recently showed to result in clinically meaningful improvements in upper extremity motor functions [30], to our knowledge, it has not been tested yet in severely impaired chronic stroke patients. Additionally, applying neurostimulation was shown to be a promising tool to promote plastic changes [56,63,64]. In the context of severely impaired chronic stroke patients, both faciliatory stimulation of the ipsilesional as well as of the contralesional hemisphere could support recovery [52,86,90,92].

1.9 Aim of doctoral thesis

The aim of the current study was to explore the potential of a high-dose training combined with cortical and peripheral neurostimulation in a cohort of chronic stroke patients with severe upper extremity motor impairment (baseline FMUE < 20). Furthermore, we aimed to better understand the neurophysiological mechanisms underlying motor recovery in this patient cohort. In this context, first methodological improvements and considerations, i.e., MCID of FMUE and potential of bilateral TMS-Maps in the presented patient cohort, were undertaken in order to be able to draw conclusion from the intervention.

Specifically, this thesis is sought to answer the following questions:

1) How can bilateral TMS-Maps be applied to study the ipsi- and contralesional cortical representation of a paretic forearm muscle?
2) What improvements are considered clinically relevant in severely affected chronic stroke patients?
3) Can a high-dose motor training in combination with neurostimulation improve motor functions in chronic stroke patients with severe paresis of the upper extremity?

4) Are changes related to the stimulation order, i.e., ipsi-/contralesional or contra-/ipsilesional stimulation?
5) Does the high-dose intervention lead to changes of the cortical representation of the paretic hand within the ipsi- and contralesional hemisphere?
6) Can recovery be predicted based on clinical and/or neurophysiological markers?

To answer these questions, we performed a clinical trial for chronic stroke patients with severe motor impairment consisting of a high-dose training program combined with transcranial and peripheral electrical stimulation (IN-TENS study). The study was registered with the ClinicalTrials.gov Identifier: NCT03947645.

2 Methods

2.1 Participants

The study was conducted at the University Hospital Tübingen in 2019/2020. All patients gave their written informed consent prior to study participation. The study has been approved by the local Ethics Committee of the University Hospital Tübingen (approval number: 198/2019BO2), was conducted in accordance with the declaration of Helsinki and registered at ClinicalTrials.gov (Identifier: NCT03947645).

Inclusion criteria for participation in the study were 1) age between 18-80 years; 2) chronic stage of stroke (> 6 months since stroke); and 3) no active hand opening/ finger extension on the paretic side. Patients were excluded if 1) they were pregnant; 2) had epilepsy; 3) had seizures less than 6 months before study onset and/or were using any anticonvulsant medication; 4) had any metal implants; 5) had a pacemaker or 6) had no sensation in the paretic arm/hand, indexed by less than 2 out 4 points in the Fugl-Meyer Upper Extremity Item *Light Touch* (H. Sensation).

To ensure that all patients met the inclusion and exclusion criteria of the study, medical records were assessed for eligibility (n=95) followed by an in-house screening (n=42; Fig. 1). This resulted in the final enrolment of 21 chronic stroke patients in this single-centre randomised controlled clinical trial. Two patients discontinued their participation after the first training block: one patient due to illness unrelated to the experiment and one patient due to personal reasons. This resulted in a total of 19 patients that took part in both training blocks and were included in statistical analyses of the reported clinical effects (age: 63.33 ± 9.44 years (mean ± SD), range: 45-78 years, 5 female). Baseline characteristics of the 19 patients that completed the study are shown in Tab. 1.

However, for the TMS analyses, data was not available for all patients. For the TMS-Maps at V0 and V1, data was evaluated only for the patients that participated in both sessions. This resulted in 18 patients (age: 62.28 ± 9.50 years, 5 female, 15 ischemic, time since stroke: 60.39 ± 56.57 months).

For the TMS-Maps at V2 to V6, the grid parameters were changed after the first four patients to capture more extended maps. Hence, this analysis focused on the TMS-Maps in the subsequent 15 patients (age: 63.47 ± 9.21 years, range: 45-78 years).

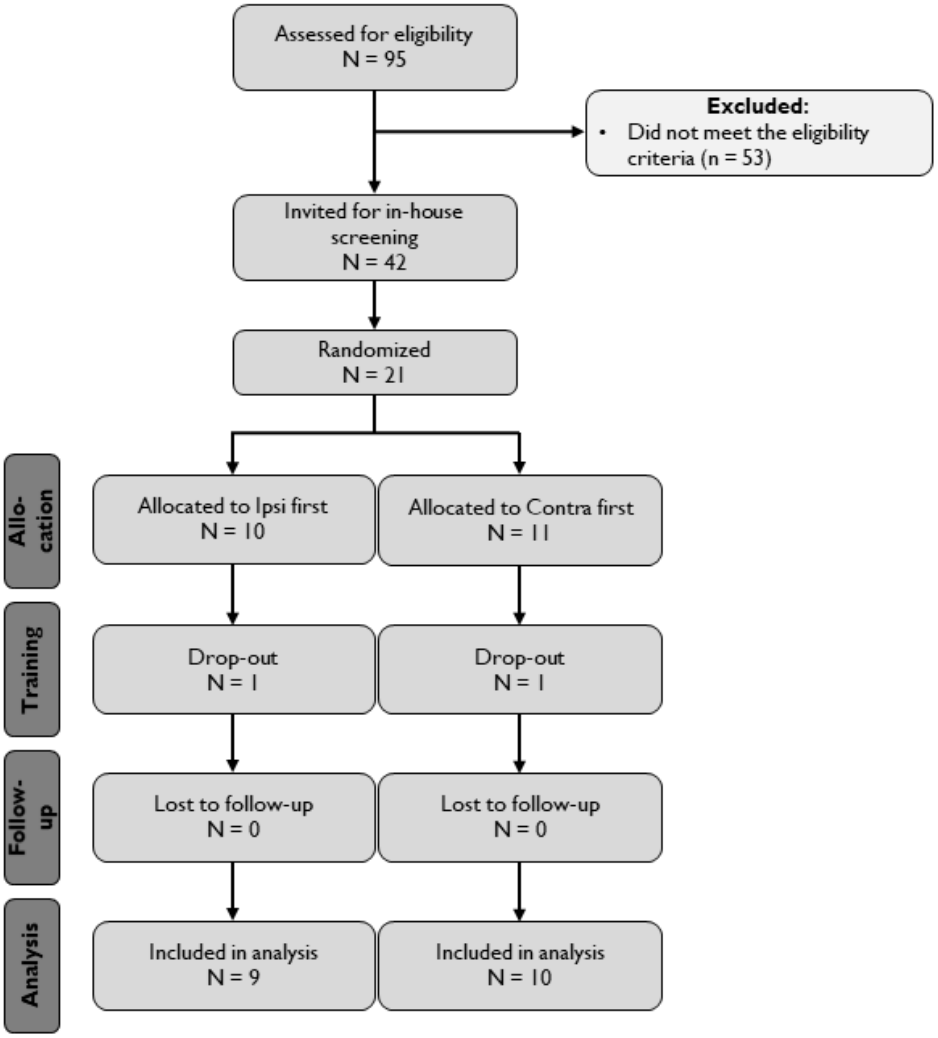

Figure 1. CONSORT diagram of enrolment, allocation, drop-outs, follow-up and analysis of the study.

Table 1. Overview of patients' demographics and clinical details at V2. Abbreviations: m = male, f = female, L = left, R = right.

ID	sex	age	time since stroke [rounded to months]	lesion side	lesion type	lesion location	FMUE at V2
Patient 1	m	65	18	L	ischemic	caput nuclei caudati and capsula interna	10
Patient 2	m	67	153	R	ischemic	basal ganglia	15
Patient 3	m	69	45	L	ischemic	striatum	4
Patient 4	m	56	13	R	ischemic	basal ganglia	19
Patient 5	f	75	27	R	ischemic	n.a.	7
Patient 6	m	65	20	R	ischemic	middle cerebral artery	11
Patient 7	f	63	65	R	ischemic	middle cerebral artery	3
Patient 8	f	57	51	R	hemmorhagic	middle cerebral artery	13
Patient 9	m	75	68	R	ischemic	n.a.	16
Patient 10	f	52	100	L	hemmorhagic	basal ganglia	8
Patient 11	m	58	69	R	hemmorhagic	basal ganglia	13
Patient 12	m	78	216	R	ischemic	middle cerebral artery	9
Patient 13	m	45	44	R	ischemic	middle cerebral artery	15
Patient 14	m	74	106	R	ischemic	middle cerebral artery	7
Patient 15	f	56	18	R	ischemic	middle cerebral artery	9
Patient 16	m	68	121	L	ischemic	middle cerebral artery	9
Patient 17	m	60	162	R	ischemic	middle cerebral artery	13
Patient 18	m	68	40	L	ischemic	middle cerebral artery	8
Patient 19	m	58	84	R	ischemic	middle cerebral artery	17

2.2 Experimental Design

We conducted a within-subject, standard-of-care controlled clinical trial (Fig. 2). After a 6-months waitlist control period with standard physiotherapy (60-90 min/week) and three evaluations (V0, V1, V2), all patients took part in a 6-months intervention period which consisted of two blocks of intensive daily upper-limb training (V2-3, V4-5) lasting 3 weeks each, and two follow-up periods (V3-4, V5-6) lasting 3 month each. During the training blocks, concurrent NMES was applied to the paretic arm. In parallel, patients received ipsi- and contralesional tACS during the training, which was applied in double-blind, randomised, cross-over order, i.e., ipsilesional stimulation in block one and contralesional stimulation in block two, or vice versa.

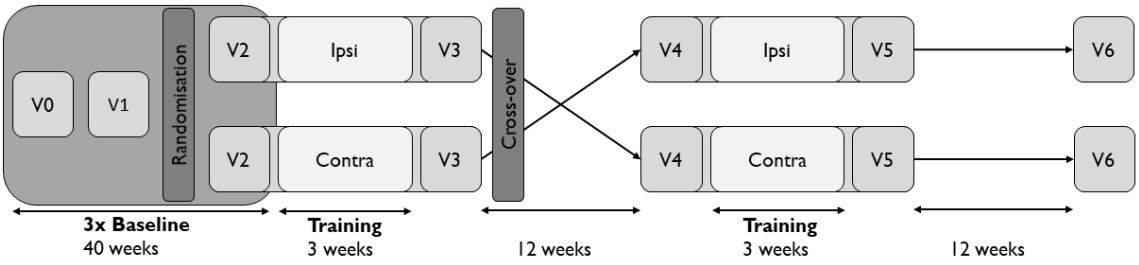

Figure 2. Overview of the experimental design of the presented study. V0, V1 and V2 refer to three assessments during the waitlist control period within on average 10 months prior to the intervention. At V2, patients were randomly assigned to one of the conditions (ipsi- vs. contralesional stimulation) for the first three-week training block. Then, the patients were crossed-over to the other condition and took part in a second training block. Assessments took place directly before (V2 and V4), directly after (V3 and V5) and 12 weeks after each block (V4 and V6). Note that the V4 measurement before training block 2 serves as the follow-up measurement for training block 1.

The Fugl-Meyer Upper Extremity score (FMUE) [105] was the primary outcome and assessed at all visits (V0-V6), while determining the minimal clinically important difference (MCID) with anchor- and distribution-based methods. At all visits, also contra- and ipsilateral corticospinal excitability (CSE) was assessed at the motor hotspot using transcranial magnetic stimulation (TMS). Additionally, extended TMS motor maps were acquired in each hemisphere throughout

the study (V0-V6) to estimate both contralateral pathways from the lesioned hemisphere and ipsilateral pathway from the non-lesioned hemisphere to the paralysed hand.

Patients, caregivers, experimenters, and data analysts were unaware of the tACS condition (ipsi- vs contralesional) that the patients received in each training block. Block-Randomisation was undertaken by a person who was not involved in the training and assessments. Before and after each training block, patients underwent pre- and post-assessments, as well as a 12-week follow-up measurement. For the first training block, the pre-measurements of block 2 served as the follow-up measurement.

To ensure blinding of patients, caregivers, experimenters, and data analysts towards the stimulation condition, an additional experimenter who was not involved in supporting the patients during the daily training was responsible for the tACS preparation on each training day while ensuring that each patient received the randomly assigned stimulation condition for each block. Electrodes with attached cables were always placed over both the ipsi- and contralesional hemisphere to ensure that the patient was not aware of the stimulation condition and to keep the procedure constant for both training blocks. To ensure that the experimenters were also blinded to the stimulation condition, the unblinded experimenter marked the cable to be used for the stimulation (from either the ipsi- or contralesional electrode) and covered the tACS electrodes with an electroencephalography (EEG) cap before the other experimenters entered the training room. The cables of all transcranial stimulation electrodes were furthermore tied together, to ensure that the other experimenters were not able to tell from which scalp location the cable that was used for stimulation originated.

2.3 Intervention

2.3.1 Intensive upper limb training

The study consisted of two 3-week blocks of a high-dose upper limb training. Each 3-week training block comprised 15 training days (5 days per week) with training tasks of one hour each assigned for training each day, i.e., 90 hours for each 3-week block, in line with the intense training program applied by Ward et al. 2019 [30] (Fig. 2). All training tasks were repeated 100 times in the first week, 140 times in the second week, and 180 times in the third week to adapt to improving physical endurance. Thus, the respective active training periods

were less that the respective 1 hour assigned per task. The exact timing of each task and trial can be found in Appendix A. Except for the neurostimulation condition (ipsi- versus contralesional tACS), the training program was identical for each block.

The daily training focused on finger, wrist and elbow movements. Each day consisted of the same training tasks (3 in the morning and 2 in the afternoon), i.e., exercises focusing on finger extension (task 1, 3 and 4), wrist extension (task 2), and elbow extension (task 5), which were all supported by electrical stimulation (see below). In the end of each training day, a transfer task (task 6) was conducted which consisted of activities of daily living (~30 min) and robot-assisted hand movements (~30 min). The latter was performed with a hand robot (AMADEO, Tyromotion GmbH, Graz, Austria) focusing on finger extension. During three different runs, patients were encouraged to actively open their fingers. Muscle activity of extensor and flexor muscles of the arm were measured by electromyography (EMG). In case of detected EMG activity of the extensor digitorum communis (EDC) above a certain threshold, this was rewarded with a movement of the attached robot which passively opened the patients' hands.

For a detailed description of the tasks, please see Appendix A. The training tasks 1-5 were designed to induce bilateral upper limb movements, i.e., passive movements of the paretic side were linked to active movements of the healthy side, as there is growing evidence that bilateral training may be more effective than unilateral movements for motor recovery [81,117–120].

In order to prevent fatigue, patients were allowed to take breaks according to their individual needs.

In addition to the six tasks, two 15-minute periods of aerobic exercises were carried out to facilitate motor learning via a mechanism of motor-based priming [121,122]; one before the first series of training tasks in the morning, and one after the lunch break before the second series of training tasks in the afternoon. The aerobic exercises consisted of the following tasks: (1) cycling on a bicycle ergometer (MOTOmed letto2, RECK-Technik GmbH & Co. KG, Betzenweiler, Germany); (2) stretching the arms with a resistance band (attached in front of the patients); (3) repeatedly standing up and sitting down; (4) repeatedly lifting the heels and (5) abduction and extension of the shoulder. If necessary, these exercises were slightly modified to the patients' movement capabilities.

In the 12-week periods between training blocks 1 and 2 and between training block 2 and the final follow-up assessment, patients were encouraged to continue practicing the tasks at home.

2.3.2 Electrical stimulation protocol

To enhance the effects of the intensive upper limb training, tACS and NMES was applied during each training task.

We applied tACS at 20Hz over the primary motor cortex (M1) [77]. In randomised order, tACS was applied to the ipsi- and then contralesional hemisphere or to the contra- and then ipsilesional hemisphere in the first and second training block, respectively. Stimulation sites were determined using the C3 and C4 location of a 10-20 designed EEG cap as the centre of the doughnut-shaped tACS electrodes (outer diameter: 7.5cm, inner diameter: 2cm, thickness: 2mm). A rectangular return electrode (shape: 5cm x 7cm; thickness: 2mm) was placed over the Pz electrode location. 1-1.5s after the onset of the extension phase of each trial, 3s (60 cycles at full amplitude plus one fade-in and one fade-out cycle) tACS stimulation (neuroConn DC PLUS stimulator, neuroCare, Ilmenau, Germany) was started. A uniform random jitter was applied to reduce habituation. The intensity was set to 1mA (peak-to-peak).

Peripheral NMES stimulation was applied concurrently for 3s at 20Hz as well (STG 4008; Multi Channel Systems GmbH, Reutlingen, Germany). The NMES was timed so that the stimulation pulses hit the rising flank of the tACS cycle on the basis of previous findings on phase-dependent corticospinal excitability [123].

To ensure that the stimulation supported specifically the trained movement, NMES was applied in each task over the paretic muscle of interest, i.e., over the Extensor Digitorum Communis (EDC) in a belly-tendon montage during training sessions focusing on finger extension; over the EDC with both electrodes on the muscle belly (2cm apart from each other) for training sessions focusing on wrist movement, and over the triceps brachii with both electrodes on one side of the muscle belly (2cm apart) for training sessions focusing on elbow extension. Ag/AgCI AmbuNeuroline 720 wet gel surface electrodes (Ambu GmbH, Bad Nauheim, Germany) were used for NMES. NMES was applied at motor threshold intensity, which was defined as just visible movements in (at least three) fingers, wrist and triceps, respectively, depending on the target muscle. The thresholds were defined for each patient

individually on the first day of each training block and remained the same over the three-week training period. To ensure consistent stimulation electrode placement, electrode locations were marked throughout each training block. Impedances of tACS (Ten20 Conductive Neurodiagnostic Electrode Paste; Weaver and Company, Aurora, USA) and NMES electrodes were kept < 10 kΩ.

2.4 Outcome measures

2.4.1 Primary outcome measure

Our primary outcome measure was the upper extremity part of the Fugl-Meyer assessment (FMUE) [105], a well-known and reliable tool to assess impairment after stroke [124]. In line with Ward et al. 2019, a modified version was used excluding section A.I (reflex activity), A.V (normal reflex activity), and section D (coordination/speed). The remaining assessment consists of 18 items that are rated on a scale of 0-2, with 0 meaning not able to perform and 2 meaning full function (compared to the healthy side). This adds up to a total score ranging from 0-54, with 0 representing no motor function and 54 normal motor function compared to the healthy side.

2.4.2 Secondary outcome measures

As recommended by a recent consensus paper [106] and in line with the measures used by Ward et al. 2019, the following clinical assessments served as secondary outcome measures: the Action Research Arm Test (ARAT) [125,126], Modified Ashworth Scale (MAS) [127], Fugl-Meyer Lower Extremity Assessment (FMLE) [105], and Chedoke Arm and Hand Inventory 13 (CAHAI) [128]. In addition, the National Institute of Stroke Scale (NIHSS; only at baseline) [129] served as an indicator for stroke severity, and the Montreal Cognitive Assessment (MoCA) [130] as a measure of cognitive abilities. Besides that, the ArmA and the Stroke Impact Scale (SIS) (questionnaires) served as subjective outcome measures. For a more detailed description of the scales and questionnaires, see Appendix B.

2.4.3 Measures of corticospinal excitability (CSE)

In order to analyse the effects of the training on CSE, measurements with transcranial magnetic stimulation (TMS) were conducted.

Patients reported no contraindications to TMS [91]. During each pre-post-assessment, the patients were seated in a comfortable chair with their elbows semiflexed and their forearms pronated and relaxed as much as possible. Throughout the TMS session, patients were encouraged to stay awake. Biphasic TMS pulses (MagPro-R30 with MagOption, MagVenture, Farum, Denmark) were delivered through a figure-of-eight coil (MCF-B70, MagVenture, Farum, Denmark) at an orientation of 45° compared to the midsagittal plane. A neuro-navigation system (TMS Navigator, Localite GmbH, Germany) was used to ensure accurate TMS-coil positioning using a template MRI (MNI ICBM152 non-linear symmetric T1 Average Brain) that was registered to each patients' head. The system tracked the relative position of the TMS coil to the patients' head.

The motor 'hotspot' was determined by applying 40 stimuli over the contralesional 'handknob' of M1. 45% maximum stimulator output (MSO) was used as the starting intensity and increased in steps of 5% MSO in case no motor evoked potentials (MEP) could be elicited. From these 40 stimuli, the location of the three stimuli with the greatest response, i.e., the largest MEP peak-to-peak amplitude were selected, and an additional three stimuli were applied over each location. The stimulation site which consistently elicited the largest MEPs in the EDC was selected as the hotspot. For the ipsilesional side, the contralesional hotspot was mirrored at the midsagittal plane since not all patients showed reliable MEPs at baseline when stimulating over ipsilesional M1 with 100% MSO. To assess MEPs, EMG was recorded over the paretic EDC using Ag/AgCI AmbuNeuroline 720 wet gel surface electrodes (Ambu GmbH, Bad Nauheim, Germany). One electrode was placed on the muscle belly and a second electrode two centimetres below. In the following we refer to MEPs obtained by stimulating the contralesional hemisphere as *ipsilateral* MEPs (iMEP) and MEPs resulting from the stimulation of the ipsilesional hemisphere as *contralateral* MEPs (cMEP). The EMG was recorded with a sampling rate of 1kHz (BrainAmp ExG Amplifier, BrainProducts GmbH, Gilching, Germany). Impedances were kept below 10kΩ.

TMS over the motor hotspot

To measure contra- and ipsilateral CSE, 40 stimuli were applied on the motor hotspots of both hemispheres with 100% MSO from V2-V6. The order of stimulation was randomised for each session.

TMS-Maps

Furthermore, TMS-Maps were acquired at all visits. However, the grid outlines differed for the first (V0, V1) and later visits (V2-V6).

At V0 and V1, differently sized TMS maps with a 5x5 grid centered around the motor hotspot were acquired (see Fig. 3). The distance between the stimulation points was 0.5cm and 1cm resulting in smaller (i.e., 2.5cmx2.5cm) and larger (i.e., 5cmx5cm) grids, respectively. Each grid-point was stimulated 5 times with an interstimulus interval of 5s and a random jitter of ±1.25s to reduce habituation. All grid-points were stimulated in a snake-like pattern with 100% MSO.

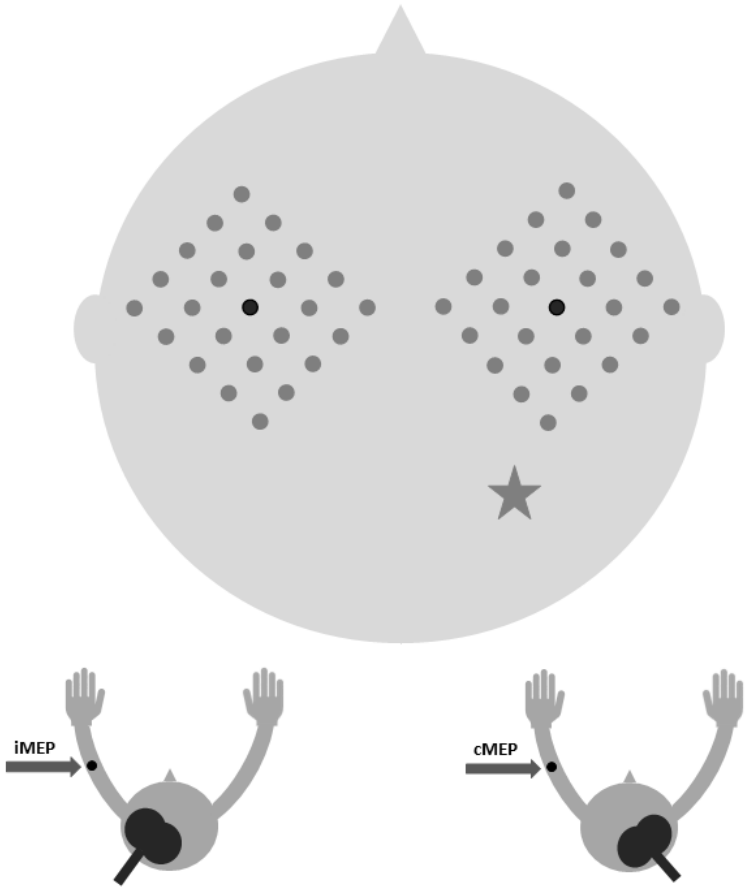

Figure 3. Scheme of TMS-map acquisition at V0 and V1. The lesioned side is marked with a star. The map is centered around the motor hotspot which is marked in black. TMS-maps were obtained bilaterally and analysed regarding ipsi- and contralateral corticospinal excitability (i.e., iMEP and cMEP) regarding the paralysed hand. The distance between the stimulation points was 0.5cm and 1cm resulting in smaller (i.e., 2.5cmx2.5cm) and larger (i.e., 5cmx5cm) grids, respectively. Grid-points were stimulated in a snake-like pattern. At each point, five pulses with an intensity of 100% maximum stimulator output (MSO) were applied.

For V2-V6, a 6x6 grid with distances of 1.5cm between grid points was used. The order of the hemispheres for TMS maps was randomised between patients. Each spot was stimulated five times with an interstimulus interval of 4s with a random jitter of ± 0.5s to reduce habituation. The intensity was set to 100% MSO. The grid outline was chosen to cover a large area of the cortex. To capture possible changes in more frontal areas as indicated in previous literature [34], the motor hotspot was not located in the center but rather more posterior/lateral within the grid (see Fig. 4). The grid-points were stimulated in a snake-like pattern.

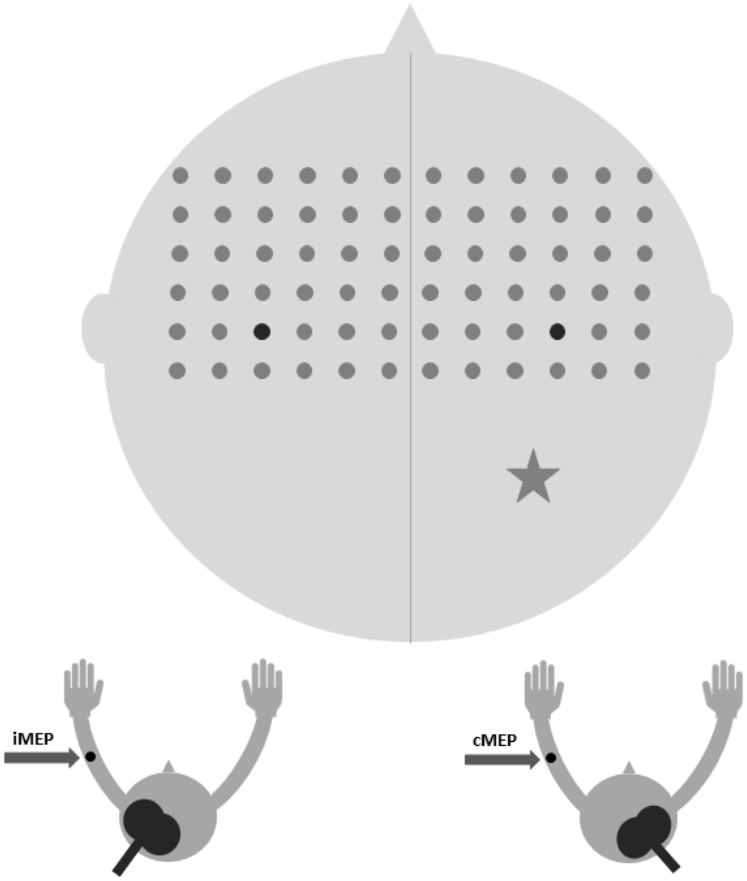

Figure 4. The lesioned hemisphere is displayed on the right side and marked with a star. TMS maps were acquired for both hemispheres. The motor hotspot is marked in black for each hemisphere. Grid-points were stimulated 5 times each in a snake-like pattern. The distance between grid-points was 1.5 cm, and the stimulation intensity was set to 100% MSO. On the bottom, the acquisition of MEPs is shown: all MEPs are obtained from the lesioned (e.g., left) arm. Hence, we estimated contralateral MEPs (cMEP) from the ipsilesional and ipsilateral MEPs (iMEP) from the contralesional hemisphere.

2.5 Data Preprocessing

2.5.1 TMS/EMG analysis

For the analysis of iMEPs and cMEPs, the EMG data of the paretic EDC was cut in epochs of -100-100ms before and after the TMS artifact. All epochs were visually inspected for the presence of MEPs within 15-100ms after the pulse. Trials were rejected in case of artifacts or muscle pre-activation > 20µV within 50ms prior to the pulse. MEPs of any amplitude of the

rectified EMG signal were considered for further analyses. The peak-to-peak amplitudes were calculated and served as a measure for CSE.

TMS at the motor hotspot

Within the patient cohort of severely affected stroke patients, the presence of MEPs is rare for most patients [16,114]. Therefore, only trials that showed a MEP were included in further analyses and served as an indicator for the CSE in case of the presence of MEPs. For each patient and visit, the mean of the individual MEPs was then calculated for further analyses. In addition, the mean occurrence rate of MEPs for each visit was calculated by taking the percentage of MEP+ trials after rejection of artifacted trials.

Cortical TMS-Maps

For the first TMS-Maps (V0, V1), the area of the motor map was determined by assessing the number of active grid-points for each session and calculating it by the size of the grid-point [116]. A grid-point was considered active, if at least one of the five pulses resulted in a MEP of any amplitude.

For the following TMS-Maps (V2-V6), we were first interested in the overall MEP responses, as for this patient population, the MEP occurrence is expected to be low [114,131]. For this purpose, the absolute number of MEPs on each grid-point was summed up for all timepoints and patients, to get a descriptive insight in the question if and where MEPs could be elicited in this patient cohort. Furthermore, for each patient and visit, common TMS Map parameters were calculated for both hemispheres separately. The area of the motor map was determined by assessing the number of active grid-points for each session [116]. A grid-point was considered active, if at least one of the five pulses resulted in a MEP of any amplitude. Furthermore, the map volume was determined as described in Veldema et al. 2017 [116] and was defined as the sum of all peak-to-peak amplitudes of all active grid-points. Lastly, the center of gravity (CoG) was determined. It is the weighted average of all active grid-points. Commonly, the CoG is separately determined for the x-direction (medial-lateral) and y-direction (anterior-posterior). The formula for deriving the x-CoG was: $(\sum(\text{MEP size})i \times (\text{x-coordinate})i)/\text{map volume}$ and for the y-CoG: $(\sum(\text{MEP size})i \times (\text{y-coordinate})i)/\text{map volume}$.

2.5.2 Clinical assessment scoring

All clinical assessments were rated from video recordings by two independent trained assessors who were blinded to the timepoint of the recording. In case the two independent ratings did not match, a third rater decided on the final score for the assessments. For the FMUE scoring, each assessor completed the training material developed by See et al. 2013 [132] to ensure highly consistent and reliable ratings. For the ARAT, the scoring guidelines described by Yozbatiran et al. 2008 were used [133]. As the patients' clinical performance can vary from day to day, e.g., due to changing spasticity, the FM-UE assessment as our primary outcome was performed two times at each visit. For the FMUE analysis, the better score at each visit was used.

2.6 Statistical analysis of clinical and physiological measures

Statistical analyses were carried out using custom-written Python code (Python version 3.8), SPSS (IBM Statistics, Version 25) and R Studio. The tool described in Scherer et al., in prep. using the r-package lme4 was used for linear mixed models. P-values of $< .05$ are considered as significant results. Data was log-transformed in case of a non-normal distribution. For correction for multiple comparisons, the Benjamini-Hochberg [134] correction was applied. In case results did not survive the correction for multiple comparisons, this is specifically marked.

2.6.1 V0 and V2 Maps

Paired t-tests were used to assess the differences in map area for the two grid-sizes for both hemispheres separately. Furthermore, the FMUE was correlated with the motor map in both hemispheres using the Pearson's correlation coefficient.

2.6.2 MCID determination

In this study, we applied both anchor- and distribution-based methods to estimate the MCID for FMUE in severely affected chronic stroke patients. Based on previous studies, the perceived recovery item of the SIS was used as the external anchor [135–137]. The MCID was then calculated as the mean change in FMUE scores of patients reporting a 10-15% change on the SIS-9 perceived recovery score from V2 to V6 [135–137]. For distribution-based approaches, 0.5SD of baseline was suggested to reflect a small but important change [138]

and was applied in other studies calculating MCIDs in the context of stroke patients accordingly [136,139]. Thus, we took half of the standard deviation of the FMUE at V2.

2.6.3 Assessing changes over time

First, we aimed to control whether improvements in motor functions can be expected in the presented patient cohort during standard-of-care. Therefore, we assessed the patients' FMUE score at three visits prior to the intervention, while they underwent 60-90 min physiotherapy per week in their home environment. A mixed model with the main factor *time* and random variable *patient* was fitted to the data.

Furthermore, we were interested in identifying changes in clinical assessments (FMUE, FMUE-C, ARAT, CAHAI-13, FMLE, MoCA), questionnaires (ArmA-A, ArmA-B, SIS 1-9) and MEPs (ipsi- and contralateral peak-to-peak amplitudes as well as occurrence rates) in the course of the intervention, i.e., from V2-V6. To assess these time-effects, for each outcome measure, a mixed model with the main factor *time* and random variable *patient* was fitted to the data. In case of significant overall time effects, post hoc tests were carried out by comparing the data of each visit individually to V2 (four tests) with paired t-tests as we were interested in changes compared to baseline.

2.6.4 Effects of stimulation sequence

As all patients received tACS in randomised order, i.e., ipsi-/contralesional or contra-/ipsilesional, we evaluated possible order effects of the applied conditions. For the primary outcome (FMUE) and ipsi- and contralateral CSE, changes originating in the order of applied stimulation conditions were assessed using mixed models with main factor *order* (levels: ipsilesional first and contralesional first), the interaction of *time and order* and *patient* as a random variable (outcome ~ time + order + time:order + (1|patient)).

2.6.5 Predictors of the outcome

Lastly, we performed correlation analyses to get more insights in what factors predicted final motor status and the magnitude of motor recovery. In more detail, we were interested if any of the baseline scores (clinical scores, MEPs, TMS-Map parameters) could predict the impairment level of the upper extremity (represented in FMUE scores) at the final visit (V6), and or the amount of motor improvement. As the goal of the study was to improve hand

function, correlations were also calculated for the FMUE-hand subscale (C Hand). In case of significant correlations, we could draw conclusions which patients would benefit most from the presented therapeutic intervention. Correlations were performed using Pearson's correlation coefficients to evaluate relationships between baseline scores and FMUE outcome values (at V6) and the magnitude of change of FMUE scores (from V2 to V6).

3 Results

3.1 Refining the methodology for the investigated patient cohort

3.1.1 Bilateral TMS-Maps

Investigating larger areas improves the detection of corticospinal connectivity

With the smaller grids, MEP could be identified in ten (55.56%) and eleven patients (61.11%) in the lesioned and non-lesioned hemisphere, respectively. Together, in fourteen of eighteen patients (77.78%), MEP could be detected in either hemisphere.

With the larger grids, MEP could be identified in fifteen (83.33%) and twelve patients (67.67%) in the lesioned and non-lesioned hemisphere, respectively. Together, in seventeen of eighteen patients (94.44%), MEP could be detected in either hemisphere.

Investigating larger areas reveals more extended maps of corticospinal connectivity

In both hemispheres, larger motor maps were detected, when investigating more extended areas (lesioned hemisphere: $t = 3.38$, $p = .0036$, non-lesioned hemisphere: $t = 2.86$, $p = .011$). In the lesioned hemisphere, the motor maps were on average 1.58 ± 2.05 cm^2 and 8.11 ± 8.89 cm^2 for the smaller and larger grids, respectively. In the non-lesioned hemisphere, the motor maps were on average 0.81 ± 1.05 cm^2 and 2.67 ± 2.81 cm^2 for the smaller and larger grids, respectively. In Fig. 5, data from an example patient can be seen.

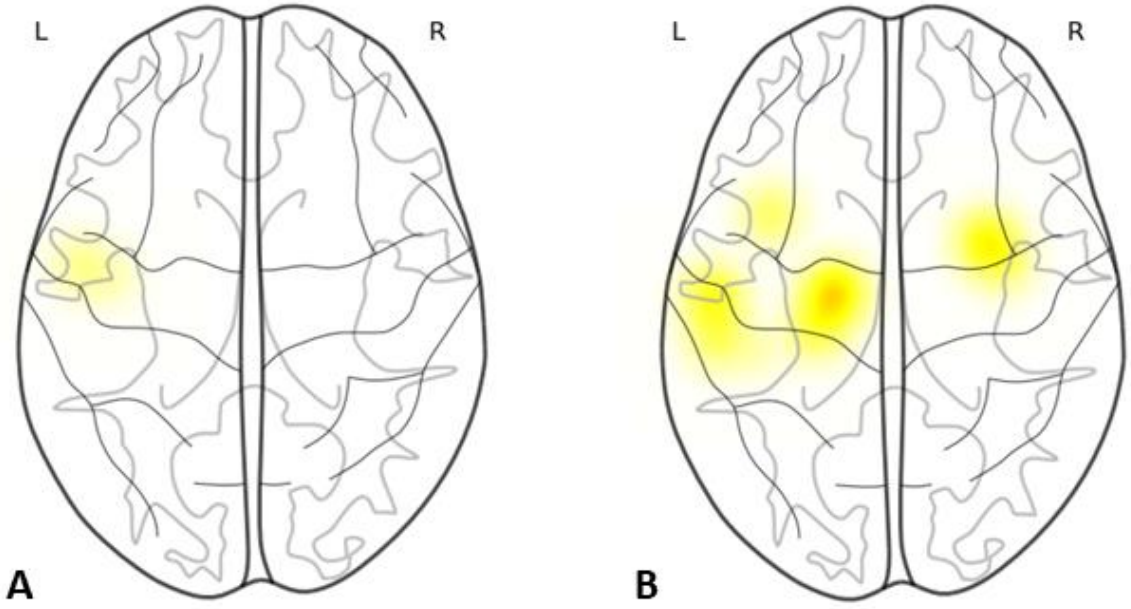

Figure 5. Exemplary data from one patient (FMUE = 9) with a stroke in the right hemisphere. The TMS maps show the MEP obtained from the paralysed extensor digitorum communis muscle projected on the position of the stimulation site using two different grid sizes of (A) 2.5cmx2.5cm and (B) 5cmx5cm.

Corticospinal connectivity from the non-lesioned hemisphere corresponds to motor impairment

In the lesioned hemisphere, there was no correlation of the motor maps acquired with either larger ($r = .12$, $p = .63$) or smaller ($r = .041$, $p = .87$) grids with the motor impairment.

In the non-lesioned hemisphere, there was a correlation of the motor maps acquired with larger ($r = -.52$, $p = .026$) - but not smaller ($r = -.27$, $p = .28$) grids - with the motor impairment.

Specifically, the findings indicate that a higher impairment level (i.e., lower FMUE) was associated with an increased map area in the non-lesioned hemisphere, and that a larger grid size was necessary to detect this relationship.

3.1.2 Determination of MCID for the FMUE in severely impaired stroke patients

Next, we determined the MCID of the FMUE for the investigated patient group with severe upper extremity motor impairment. If the patient's FMUE would improve by at least the resulting MCID after the intervention, this would reflect a clinically meaningful change.

The anchor-based approach revealed a MCID of 1.67 FMUE points based on six patients reporting a change between 10-15% on the SIS perceived recovery item. The distribution-based MCID estimate was 2.13 FMUE points. Considering both anchor- and distribution-based MCID calculation approaches and the fact that the FMUE is an integer scale, we identified a MCID of 2 FMUE points for chronic stroke patients with severe motor impairment (FMUE < 20).

3.2 Clinical assessments

3.2.1 Stable motor impairment level prior to intervention

For the 16 patients who participated in all 7 visits (V0-V6), the FMUE scores over time prior to the study were evaluated. On average, 114 ± 39 days (mean ± SD) passed between V0 and V1, and 195 ± 36 days (mean ± SD) between V1 and V2. Thus, the patients' FMUE was assessed three times within a waitlist control period of about 309 days. The absence of a significant time effect of the FMUE ($F(2.0005, 30) = 2.02$, $p = .39$) indicates an unchanged motor status despite standard physiotherapy.

3.2.2 Significant improvement in clinical status over time

The clinical status of the whole patient cohort of 19 patients improved from V2 to V6 with significant time effects for the FMUE ($F(4,70.99) = 6.27$, $p = .00022$); FMUE-C ($F(4,71.051) = 3.054$, $p = .022$); FMLE ($F(4,72) = 3.3014$, $p = .015$); CAHAI ($F(4,69.179) = 3.83$, $p = .0072$); and MoCa ($F(4,72) = 2.94$, $p = .026$).

Significant improvements compared to baseline (V2), ensued for the FMUE score at V4 ($t = -4.32$, $p = .000049$), V5 ($t = -3.037$, $p = .0033$) and V6 ($t = -2.26$, $p = .00018$); for the FMUE-C at V4 ($t = -2.57$, $p = .012$) and V6 ($t = -2.79$, $p = .0068$); for the CAHAI, at V3 ($t = -2.34$, $p = .022$), V4 ($t = -2.34$, $p = .022$), V5 ($t = -3.89$, $p = .00023$) and V6 ($t = -2.01$, $p = .049$); for the MoCA at V4 ($t = -2.49$, $p = .015$), V5 ($t = -2.40$, $p = .019$) and V6 ($t = -3.11$, $p = .0027$).

The mean ± SD values and statistics for all clinical assessments at all visits are shown in Tab. 2.

Table 2. The table shows the mean ± SD for all clinical assessments at V2-V6. * Indicates one missing value. *** Indicates three missing values. In addition, the overall model output for the time effect is displayed. Significant results are marked in bold.

	V2	V3	V4	V5	V6	Statistics
FMUE	10.84 ± 4.26	11.33 ± 5.58*	13.32 ± 5.81	12.58 ± 5.65	13.11 ± 6.48	**F(4, 70.99) = 6.27, p = .00022**
FMUE (C-hand)	1.16 ± 1.35	1.28 ± 1.33	1.79 ± 1.58	1.37 ± 1.27	1.84 ± 1.76	**F(4, 71.051) = 3.054, p = .022**
ARAT	4.33 ± 2.96*	4.74 ± 3.01	4.79 ± 2.55	5.39 ± 3.61*	4.89 ± 3.24	F(4, 70.036) = 1.48, p = .22
CAHAI	20.94 ± 5.19***	23.89 ± 6.50	23.89 ± 5.67	25.84 ± 6.60	23.47 ± 6.54	**F(4, 69.938) = 3.75, p = .0081**
FMLE	13.58 ± 5.32	12.37 ± 5.19	13.74 ± 4.81	12.63 ± 4.66	14.58 ± 5.02	**F(4, 72) = 3.30, p = .015**
MoCA	24.63 ± 3.54	25.47 ± 3.39	26.11 ± 2.90	26.05 ± 3.30	26.47 ± 2.52	**F(4, 72) = 2.94, p = .026**

Moreover, the findings for the primary outcome (i.e., FMUE) are visualised in Fig. 6.

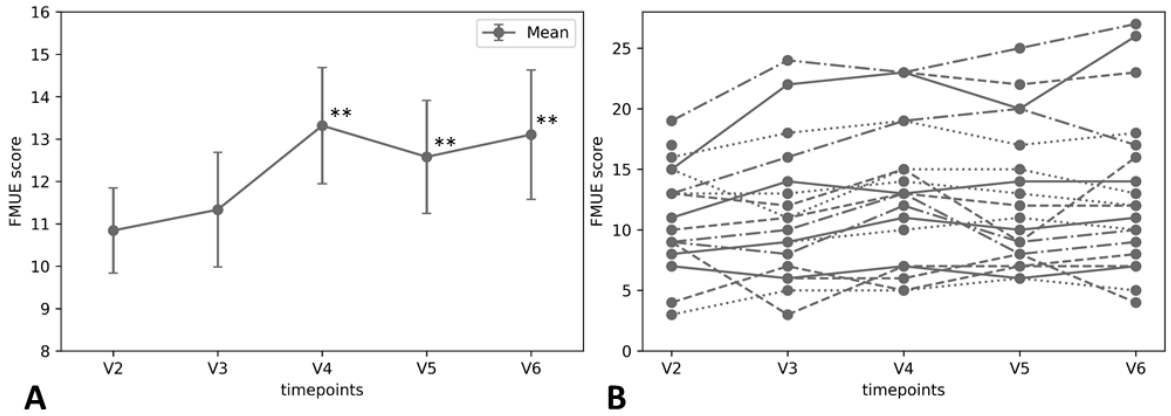

Figure 6. FMUE scores over time.

- **A.** Mean FMUE values ± SEM over time. There is a significant overall time effect for the FMUE. Post hoc tests revealed a significant increase in FMUE scores at V4, V5 and V6 compared to V2 (baseline). ** indicates $p < .01$.
- **B.** Individual FMUE trajectories over time.

On average, the increase in FMUE from V2 to V6 was 2.05 ± 3.21. In the following, we describe significant findings only, and report all other findings in the respective tables.

3.2.3 The tACS order determines the degree of FMUE improvement

The model revealed a significant linear time effect (F(1, 73.00) = 18.10, p = .000010) and interaction of order and time (F(1, 73.00) = 4.76, p = .029). Furthermore, we performed analyses without the factor order and evaluated linear time effects separately for the ipsi-/contralesioal and contra-/ipsilesional groups. For the ipsi-/contralesioal group, there was a significant effect of time (F(1, 33.99) = 18.22, p = .000020). Post hoc tests comparing all visits of the ipsi-/contralesioal group to V2 showed significant FMUE improvements from at V4 (t = -2.50, p = .017) and at V6 (t = -3.58, p = .0010).

Hence, the patients that received ipsi-/contralesioal tACS showed more motor improvements over time. Fig. 7 shows the mean ± SEM of FMUE scores separately for the ipsi-/contralesioal and contra-/ipsilesional groups.

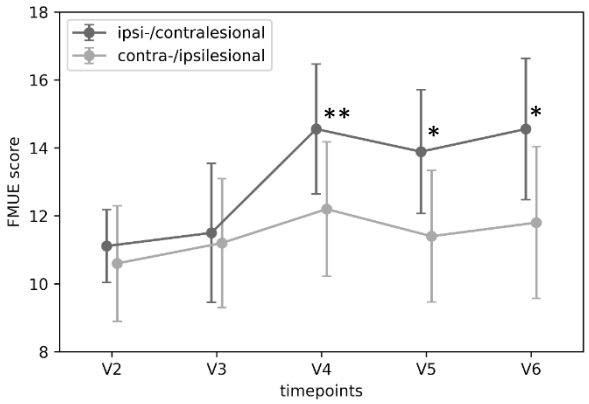

Figure 7. FMUE values (mean ± SEM) over time split according to the applied tACS stimulation order (ipsi-/contralesional- vs. contra-/ipsilesional stimulation). The dark line indicates the mean scores of patients undergoing the ipsi-/contralesional sequence (i.e., from V2-V4 ipsilesional stimulation, and from V4-V6 contralesional stimulation). The lighter line indicates the mean scores of patients undergoing the contra-/ ipsilesional sequence (i.e., from V2-V4 contralesional stimulation, and from V4-V6 ipsilesional stimulation). For the ipsi-/contralesional sequence, there was a significant overall time effect (F(1,38) = 6.39, p = .011). Post hoc results are displayed in the figure. * indicates p < .05 and ** indicates p < .01.

3.3 Ipsi- and contralateral CSE

3.3.1 Ipsi- and contralateral CSE peak at different visits

For each hemisphere, linear mixed models were applied to assess overall time effects of the MEPs. MEP data was log-transformed for statistical analyses.

The cMEP peak-to-peak amplitudes showed a significant time effect ($F(4,61.829) = 2.74$, $p = .036$, see Fig. 8A). Post hoc testing revealed a significant increase at V4 compared to V2 ($t = -2.77$, $p = .0072$). For the cMEP occurrence, we also found a significant time effect ($F(4, 62.661) = 2.71$, $p = .038$). A follow-up, post hoc test revealed a significant increase of cMEP occurrence from V2 to V4 ($t = -3.04$, $p = .0034$). At V4, the cMEP occurrence rate was 68% in comparison to 38-53% at all other visits.

The iMEP peak-to-peak amplitudes showed a significant time effect ($F(4, 63.0641) = 3.06$, $p = .023$; see Fig. 8B). The post hoc tests revealed significant increases from V2 to V4 ($t = -2.38$, $p = .020$) and from V2 to V6 ($t = -2.59$, $p = .023$). In contrast, the absence of a significant time effect for the iMEP occurrence rates ($F(4, 61.201) = 0.54$, $p = .71$) indicates a stable amount of iMEPs of around 30-50% at all visits.

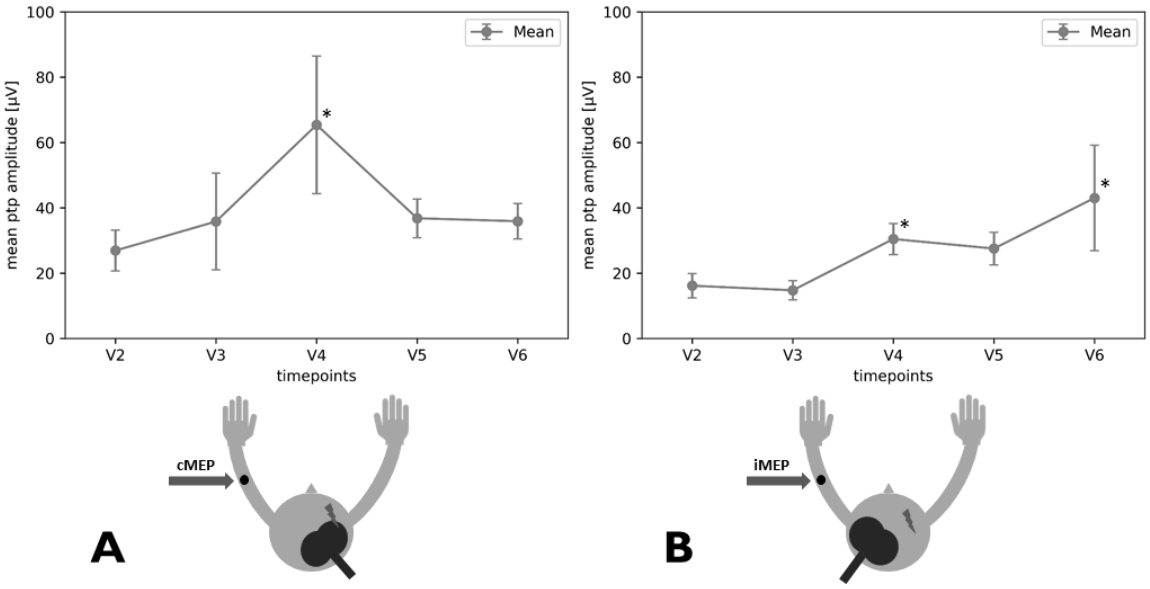

Figure 8. Contra- and ipsilateral MEPs over time (mean ± SEM of peak-to-peak amplitudes). For both measures, EMG was measured and analysed from the paretic EDC. The arrow indicates the lesioned hemisphere. Visits V3-V6 were individually compared to V2 in case of a significant overall time effect. * Indicates $p < .05$. Please note that statistical analyses were performed on log-transformed data while the raw data is displayed here.

A. Contralateral MEPs over time (V2-V6). As indicated in the pictogram, the ipsilesional hemisphere with TMS.

B. Ipsilateral MEPs over time (V2-V6). For this measurement, the contralesional hemisphere is probed with TMS.

3.3.2 The tACS order has a significant impact on ipsilateral CSE

The effects of tACS order on CSE were analysed separately for each hemisphere (Fig. 9).

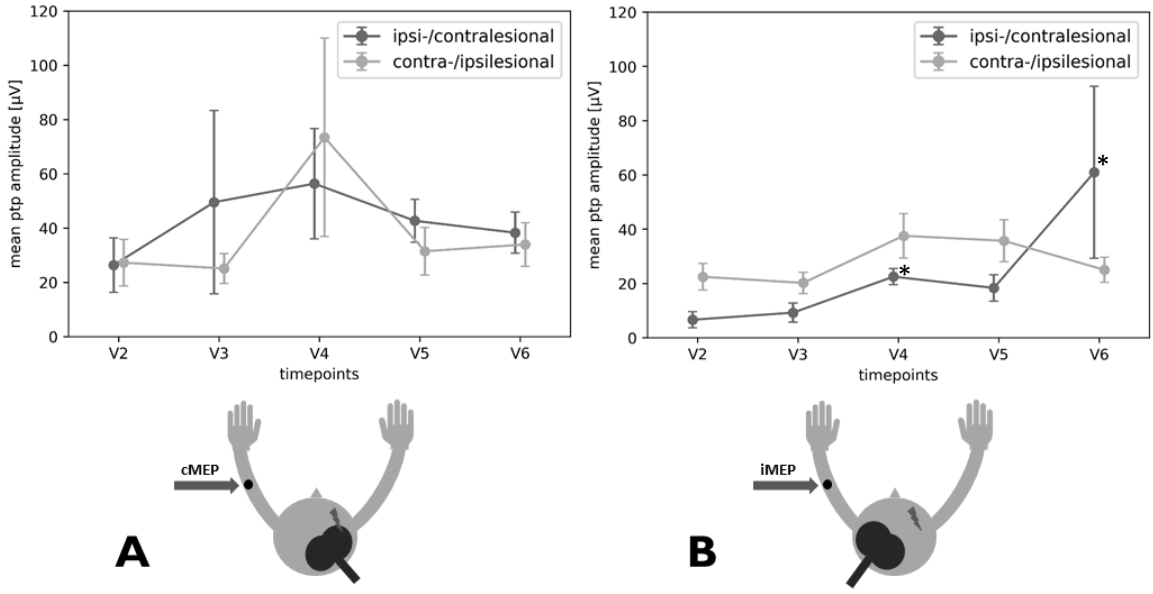

Figure 9. Both the ipsi- and contralateral MEPs (mean ± SEM of peak-to-peak amplitudes) are shown over time (V2-V6) according to the applied tACS stimulation order. The dark line indicates the mean amplitudes of patients undergoing the ipsi-/contralesional sequence (i.e., from V2-V4 ipsilesional stimulation, and from V4-V6 contralesional stimulation). The lighter line indicates the mean amplitudes of patients undergoing the contra-/ ipsilesional sequence (i.e., from V2-V4 contralesional stimulation, and from V4-V6 ipsilesional stimulation). Please note that statistical analyses were performed on log-transformed data while the raw data is displayed here.

For both measures, EMG was measured and analysed from the paretic EDC. The arrow indicates the lesioned hemisphere.

A. Contralateral MEPs over time split according to the applied tACS stimulation order. As indicated in the pictogram, the ipsilesional hemisphere is probed with TMS.

B. Ipsilateral MEPs over time split according to the applied tACS stimulation order. For this measurement, the contralesional hemisphere is probed with TMS. For the ipsi-/contralesional sequence, there was a significant main effect for time ($F(1,38) = 6.39$, $p = .011$). Results from post hoc tests comparing individual visits of the ipsi-/contralesional sequence are shown in the figure. * Indicates $p < .05$.

For the iMEPs, there was a significant main effect of time (F(1, 66.697) = 12.68, p = .00069), a significant main effect for order (F(1, 53.368) = 9.79, p = .0028) and a significant interaction of order and time (F(1, 66.697) = 6.034, p = .017; see Fig. 9B). Next, we performed further analyses of the linear time effects for the ipsi-/contralesioal and contra-/ipsilesional group, separately. For the ipsi-/contralesioal group, there was a significant time effect (F(1,38) = 6.39, p = .011). Post hoc tests showed significant increases from V2-V4 (t = -3.23, p = .023) and from V2-V6 (t = -3.70, p = .014).

3.4 Changes in cortical TMS-Map Parameters

3.4.1 Overall MEP response

When considering the cumulative MEP occurrence in all patients for all sessions, MEPs could be elicited at all grid-points in both hemispheres (see Fig. 10).

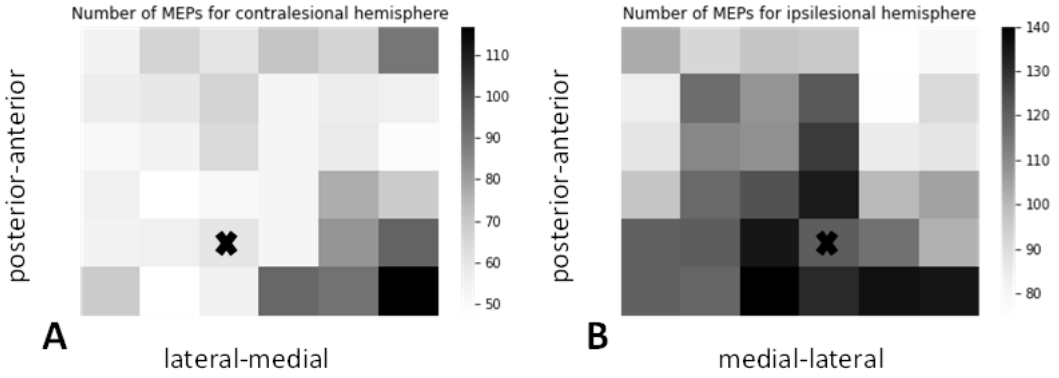

Figure 10. This figure shows, for each hemisphere separately, the cumulative MEP occurrence in all patients for all sessions. The motor hotspot is marked with a black cross. For each grid-point, the overall number of MEPs that could be elicited is displayed. In sum, MEPs could be elicited in both hemispheres at all grid-points. However, each hemisphere revealed a specific cortical area, where most MEPs occurred.

A: In the contralesional hemisphere, most responses occurred when probing the medial sensorimotor cortex.

B: In the ipsilesional hemisphere, most responses occurred when probing around the motor hotspot and in the premotor cortex.

However, each hemisphere revealed a specific cortical area, where most MEPs occurred. In the contralesional hemisphere, most responses ensued when probing the medial sensorimotor cortex. In the ipsilesional hemisphere, most responses ensued when probing around the motor hotspot and in the premotor cortex.

3.4.2 Increased map area for contralesional hemispheres

In the contralesional hemisphere, there was an overall increase of the motor map area over time ($F(1, 52.91) = 5.07$, $p = .029$). Post hoc tests revealed significant increases in map area comparing V2-V4 ($t = -2.60$, $p = .012$) and V2-V6 ($t = -2.85$, $p = .0063$).

3.4.3 Increased map volume for both hemispheres

For the ipsilesional hemisphere, the map volume showed an overall significant increase over time ($F(1, 53.07) = 10.88$, $p = .0017$). The post hoc tests revealed an increase from V2-V6 ($t = -2.70$, $p = .0093$).

For the contralesional hemisphere, the map volume also showed a significant increase over time ($F(1, 53.45) = 6.32$, $p = .015$). Post hoc testing identified an increase from V2-V6 ($t = -2.38$, $p = .021$); this change, however, did not survive correction for multiple comparisons (adapted $\alpha = .0125$)

3.4.4 Posterior shift of contralesional center of gravity (CoG)

In the contralesional hemisphere (Fig. 11), the CoG shifted incrementally in the posterior direction over time ($F(1, 54.49) = 5.37$, $p = .024$). This change, however, did not survive correction for multiple comparisons (adapted $\alpha = .0125$; V2-V6 ($t = 2.29$, $p = .026$)).

All findings regarding the map parameters, the average values and statistics over time can be found in table 3.

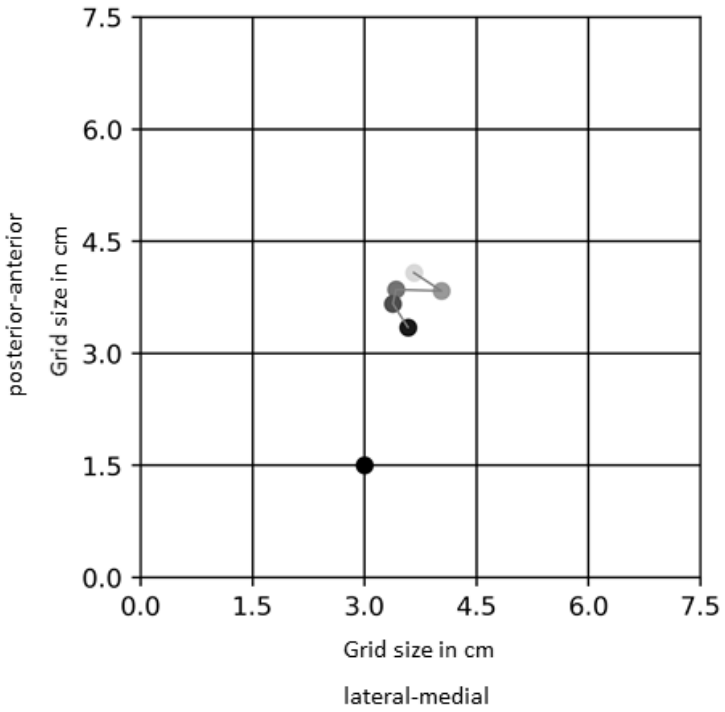

Figure 11. Center of gravity **(**CoG) shift in the contralesional (left) hemisphere over time. Each line represents a row of the 6x6 grid with 1.5cm between grid-point, resulting in a 7.5x7.5 cm grid. The stimulated grid points are represented by the line intersections. The CoG in the contralesional hemisphere was estimated by analysing iMEPs elicited in the impaired EDC, i.e., revealing ipsilateral connections. The five connected dots represent the locations of the CoG in the contralesional hemisphere at different visits (V2-V6; from light to dark). The lightest dot represents V2 and the darkest V6. For topographical orientation, the motor hotspot of the healthy EDC in the contralesional hemisphere is marked as a black dot. The CoG is shifting posteriorly in the course of the intervention period towards the motor hotspot location.

Table 3. Mean (± SD) of TMS-map parameters for both hemispheres from V2 to V6. The area represents the number of active grid-sites. CoG values are displayed in cm. The reference point of the map was the motor hotpot of the contralesional side that was mirrored to the ipsilesional hemisphere. The motor hotspot is located at 3cm/1.5cm and at 4cm/1.5cm (x/y) within the contralesional and ipsilesional hemisphere, respectively. Hence, values for the x-CoG greater than 3cm or smaller than 4cm (for the contra- and ipsilesional hemisphere, respectively) reflect a CoG more medial to the motor hotspot. For the y-Cog, a value larger than 1.5 cm indicates a CoG that is more anterior to the motor hotspot.

TMS-Map parameter	V2	V3	V4	V5	V6	Statistics
Area – ipsilesional	15.59 ± 8.03	16.33 ± 8.87	19.07 ± 9.52	16.43 ± 9.25	18.86 ± 10.51	F(1, 53.36) = 0.880, p = .35
Area – contralesional	11.91 ± 5.25	14.93 ± 6.31	17.64 ± 6.87	12.31 ± 5.38	18.50 ± 9.92	**F(1, 52.91) = 5.07, p = .029**
Volume – ipsilesional [μV]	159.51 ± 109.15	281.75 ± 535.26	543.74 ± 896.53	456.87 ± 823.36	654.36 ± 830.84	**F(1, 53.07) = 10.88, p = .0017**
Volume – contralesional [μV]	67.35 ± 46.00	87.80 ± 67.93	175 ± 218.54	95.65 ± 58.18	209 ± 230.42	**F(1, 53.45) = 6.32, p = .015**
x-CoG – ipsilesional [cm]	3.30 ± 1.27	3.49 ± 1.17	3.34 ± 1.16	3.16 ± 1.47	3.76 ± 0.88	F(1, 51.47) = 0.36, p = .55
x-CoG – contralesional [cm]	3.88 ± 1.28	4.00 ± 0.82	3.34 ± 0.86	3.57 ± 1.41	3.68 ± 0.71	F(1, 53.07) = 1.20, p = .28
y-CoG – ipsilesional [cm]	3.66 ± 0.99	4.03 ± 0.99	3.42 ± 0.78	3.38 ± 1.32	3.58 ± 1.03	F(1, 51.06) = 1.22, p = .27
y-CoG – contralesional [cm]	4.07 ± 0.79	3.83 ± 0.68	3.85 ± 0.78	3.66 ± 1.06	3.34 ± 0.54	**F(1, 54.49) = 5.37, p = .024**

3.5 Significant patient-reported improvements in stroke-specific domains

For stroke-specific questionnaires, i.e., the ArmA-A, ArmA-B and 9 subscales of SIS, similar linear mixed models as for the time effects of the clinical assessments were applied. Overall, there was a significant effect of time for the ArmA-A ($F(2, 27.35) = 4.48$, $p = .021$), ArmA-B ($F(2,30,91) = 4.71$, $p = .016$), SIS-1 ($F(2,34.53) = 8.13$, $p = .0013$), SIS-6 ($F(2,30.99) = 8.28$, $p = .0013$), SIS-8 ($F(2,26.64) = 4.29$, $p = .024$) and SIS-9 ($F(2,33.15) = 6.54$, $p = .0040$).

Compared to V2, significant effects could be found at V6 for the ArmA-A ($t = 2.91$, $p = .0071$), SIS-6 ($t = -4.064$, $p = .00031$), SIS-8 ($t = -2.90$, $t = .0074$) and SIS-9 ($t = -3.59$, $p = .0010$). For the SIS-1, significant improvements compared to V2 could be detected for both V4 ($t = -3.017$, $p = .0032$) and V6 ($t = -3.71$, $p = .00073$).

Taken together, patients reported significant improvements in their ability to take care of their affected arm (ArmA-A), the strength of the paretic hand (SIS-1), their mobility at home (SIS-6), social activities (SIS-8) and their perceived recovery from stroke (SIS-9).

3.6 Predictors of the primary outcome measure (FMUE)

The correlation of baseline parameters (V2) with the final primary outcome measure at the last follow-up (V6) is shown in Tab. 4 (FMUE) and 5 (FMUE-C).

For the FMUE at follow-up (V6), significant correlations could be found with regard to the baseline FMUE ($r = .89$, $p < .001$), cMEP peak-to-peak amplitude ($r = .64$, $p = .005$), NIHSS ($r = -.68$, $p = .002$) and CAHAI ($r = .61$, $p = .006$) at V2.

Table 4. Correlation of baseline parameters (V2) with final FMUE scores (at V6). Significant correlations ($p < .05$) are in bold. The corrected significance level is $\alpha = .014$. Accordingly, significant findings are marked with *, when they survived the multiple comparisons correction, and with ° if not.

Baseline (V2) scores	Correlation with follow-up (V6) FMUE scores	p-value	N
Time Since Stroke	.027	.46	19
Age	-.28	.13	19
FMUE	**.89**	**< .001***	19
cMEP	**.64**	**.005***	15
iMEP	-.32	.12	15
ARAT	**.50**	**.018°**	18
CAHAI	**.61**	**.006***	16
MOCA	-.31	.098	19
FMLE	**.42**	**.037°**	19
NIHSS	**-.68**	**.002***	16
Area contralesional	.009	.49	12
Area ipsilesional	-.12	.36	12
Volume contralesional	.041	.45	12
Volume ipsilesional	.48	.056	12
CoG-x contralesional	-.086	.40	12
CoG-y ipsilesional	.11	.37	12
CoG-y contralesional	.11	.37	12
CoG-y ipsilesional	**-.67**	**.008°**	12

Table 5. Correlation of baseline parameters with final FMUE-C hand scores (at V6). Significant correlations ($p < .05$) are in bold. The corrected significance level is $\alpha = .011$. Accordingly, significant findings are marked with *, when they survived the multiple comparisons correction, and with ° if not.

Baseline (V2) scores	Correlation with follow-up (V6) FMUE-C scores	p-value	N
Time Since Stroke	-.18	.23	19
Age	-.28	.12	19
FMUE	**.55**	**.007***	19
cMEP	**.61**	**.007***	15
iMEP	-.10	.36	15
ARAT	.14	.29	18
CAHAI	**.68**	**.002***	16
MOCA	-.33	.083	19
FMLE	.33	.087	19
NIHSS	-.30	.13	16
Area contralesional	.22	.24	12
Area ipsilesional	-.43	.080	12
Volume contralesional	**.70**	**.006***	12
Volume ipsilesional	.31	.17	12
CoG-x contralesional	-.002	.50	12
CoG-y ipsilesional	.20	.27	12
CoG-y contralesional	.013	.48	12
CoG-y ipsilesional	**-.57**	**.026°**	12

In Fig. 12, the relationship between baseline and follow-up FMUE is visualised for all patients. Notably, also patients with a poor FMUE score at baseline experienced clinically meaningful improvements after the intervention (Fig. 12).

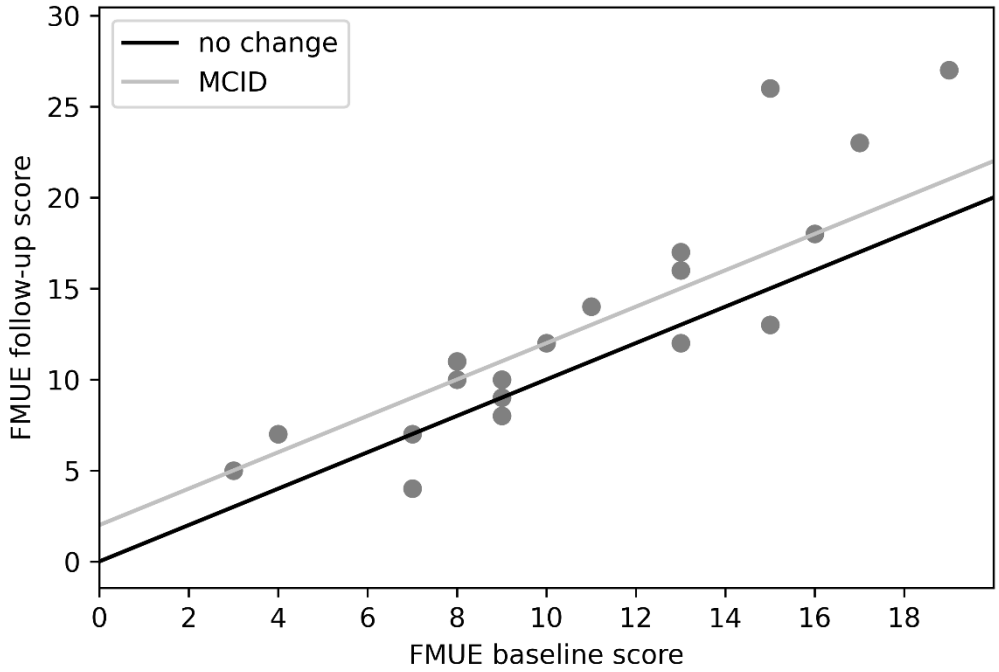

Figure 12. Relationship of baseline (V2) and follow-up (V6) FMUE scores. Black line indicates no change. All points above the black line indicate an improvement from V2 to V6, the ones below a decrease. The grey line indicates the minimal clinical important change. Hence, all dots on or above the grey line reflect a clinically meaningful improvement.

For the FMUE-C at follow-up (V6), significant correlations could be found with regard to baseline FMUE ($r = .55$, $p = .007$), cMEP peak-to-peak amplitude ($r = .61$, $p = .007$), CAHAI ($r = .68$, $p = .002$) and contralesional MEP volume ($r = .70$, $p = .006$) at V2.

In addition, Tab. 6 and 7 show the correlations of baseline scores with the magnitude of change from V2 to V6 of the FMUE and FMUE-C scores, respectively. The contralesional TMS map volume at baseline (V2) was the only parameter to predict the magnitude of clinical improvement, specifically, hand motor recovery from V2 to V6 (FMUE-C; $r = .80$, $p = .001$).

Table 6. Correlation of baseline parameters with the magnitude of change in FMUE scores from baseline (V2) to follow-up (V6). Significant correlations ($p < .05$) are in bold. The corrected significance level is $\alpha = .0028$. ° Indicates indicates when the findings did not survive correction for multiple comparisons.

Baseline (V2) scores	Correlation with delta FMUE scores (V6-V2)	p-value	N
Time Since Stroke	.05	.42	19
Age	-.07	.37	19
FMUE	**.46**	**.024°**	19
cMEP	.44	.052	15
iMEP	-.19	.24	15
ARAT	.23	.18	18
CAHAI	**.53**	**.018°**	16
MOCA	-.32	.091	19
FMLE	.31	.10	19
NIHSS	-.38	.076	16
Area contralesional	.002	.50	12
Area ipsilesional	-.004	.50	12
Volume contralesional	.44	.075	12
Volume ipsilesional	.43	.080	12
CoG-x contralesional	-.33	.14	12
CoG-y ipsilesional	.27	.20	12
CoG-y contralesional	.26	.21	12
CoG-y ipsilesional	-.17	.30	12

Table 7. Correlation of baseline parameters with magnitude of change in FMUE-C hand scores from baseline (V2) to follow-up (V6). Significant correlations ($p < .05$) are in bold. The corrected significance level is $\alpha = .0028$. Accordingly, significant findings are marked with *, when they survived the multiple comparisons correction, and with ° if not.

Baseline (V2) scores	Correlation with delta FMUE-C scores (V6-V2)	p-value	N
Time Since Stroke	.028	.46	19
Age	.042	.43	19
FMUE	.18	.23	19
cMEP	.24	.20	15
iMEP	-.24	.19	15
ARAT	.098	.35	18
CAHAI	**.50**	**.025°**	16
MOCA	-.13	.30	19
FMLE	.095	.35	19
NIHSS	-.20	.23	16
Area contralesional	.15	.32	12
Area ipsilesional	.072	.41	12
Volume contralesional	**.80**	**.001***	12
Volume ipsilesional	.32	.16	12
CoG-x contralesional	-.029	.47	12
CoG-y ipsilesional	.084	.40	12
CoG-y contralesional	-.41	.096	12
CoG-y ipsilesional	.014	.48	12

4 Discussion

4.1 Contribution to the field

This thesis aimed to identify the potential of a novel high-dose training combined with neurostimulation in a cohort of severely affected chronic stroke patients. Furthermore, the goal was to study underlying physiological mechanisms. To this end, methodological questions were addressed first.

Parameters to measure clinical effectiveness in severely affected chronic stroke patients

First, the optimal parameters were identified for this specific patient population, i.e., regarding both the clinical cut-off value for clinical relevance of the findings as well as concerning the acquisition of cortical TMS-maps. Being more specific, in addition to previous recommendations for cortical maps in a similar patient cohort [114], the potential of large bilateral TMS-Maps was demonstrated.

Besides that, to decide on the effectiveness of an intervention, the question is if a change is clinically meaningful, i.e., if possible improvements make a change for the patients' management, as expressed by the MCID [140]. While there are cut-off values for stroke patients described in the literature [107,141], none of them is applicable for the group of severely affected chronic stroke patients. Thus, within this thesis, an appropriate MCID was determined for the presented patient cohort.

Taken together, these parameters can inform future studies in the context of severely affected stroke patients to both obtain appropriate measures of clinical effectiveness.

Effective intervention for motor recovery in severely affected chronic stroke patients

While there is only little research regarding interventions to support motor recovery in severely affected chronic stroke patients [33,34], within this thesis, a high-dose program combined with neurostimulation was suggested. The effectiveness of the intervention was shown by improved motor impairment, subjective changes in stroke-related domains as well as physiological changes. Hence, this could form a basis for future interventions in this context.

Insights in mechanisms of motor recovery in severely affected chronic stroke patients

Furthermore, the underlying recovery mechanisms were studied and discussed. In line with previous research, our findings support theories that propose motor recovery via ipsilateral

pathways in case of high corticospinal tract damage [52,86,90,92]. Additionally, we showed that also contralateral pathways originating in the ipsilesional hemisphere were facilitated and therefore additionally support concepts regarding recovery via the ipsilesional hemisphere [52,86]. Based on the different timing and amount of change, we assume that the remaining potential of the ipsilesional hemisphere was used first, while then recruiting the contralesional hemisphere in later stages of the recovery process.

For future studies in this patient cohort, this suggests to first facilitate the ipsi- and then the contralesional hemisphere by targeted neurostimulation.

4.2 Refined methods to study the presented patient cohort

Definition of clinically meaningful findings in severely affected chronic stroke patients

Besides statistical significance, in clinical trials it is inevitable to also consider the clinical meaningfulness of the results, referred to as MCID. This reflects a minimal change score that would make a relevant change in the patients' outcome [140]. While there are values in the literature for subacute [141] and chronic stroke patients [107], to our knowledge, there are no applicable numbers for a cohort of chronic stroke patients with severe motor impairment. To fill this gap in literature, within this thesis, an applicable value was determined for the presented patient cohort. This was done by applying both anchor- and distribution based methods, as done in previous literature [107,135–138]. The observations suggest that an increase of 2 FMUE points can be interpreted as a clinically meaningful change. This relevant finding can serve as an objective basis for the interpretation of future studies evaluating the effectiveness of interventions in this patient cohort.

Bilateral TMS-maps are a promising tool in studying physiological mechanisms

The evaluation of bilateral TMS-Maps to the paretic hand showed that the detection of corticospinal connectivity in severely affected stroke patients could be improved by investigating larger cortical areas in both hemispheres. This approach also revealed more extended brain areas in both hemispheres to be connected to paralysed muscles. Previous work indicated that poststroke motor recovery is associated with plastic changes in brain areas distant from the primary motor cortex, such as the premotor cortex or supplementary motor

areas [14,34,86,92,114,142]. However, the cortical map sizes that were investigated in previous studies have been highly variable [108]. Future work will need to elaborate the best grid sizes, distances between grid points and number of pulses at each grid point to further optimise the detection of corticospinal connectivity in this patient cohort.

Furthermore, the results indicate that corticospinal connectivity from the non-lesioned hemisphere to the paralysed muscle corresponded to the motor impairment level. While motor recovery is often associated with reorganisation within the lesioned hemisphere [86,90,143], corticospinal pathways originating in the non-lesioned hemisphere and connecting to the affected ipsilateral extremity have been suggested to play a key role in promoting recovery in severely impaired patients [86,90,92]. Notably, cortical maps have previously been described for both hemispheres, but they have – to the best of our knowledge - only been investigated concerning connections to the contralateral extremity [108]. Therefore, information on ipsilateral pathways to the affected extremity is scarce and the presented findings may provide new insights.

Moreover, these findings may also be of interest for algorithms predicting the recovery potential after stroke. Current approaches apply about eight stimuli over the motor hotspot of the lesioned hemisphere only [94,112,113,131], and may therefore miss functionally relevant corticospinal connectivity. This may explain seemingly contradictory findings in previous studies that observed substantial motor recovery in the “absence” of MEP [144].

In summary, assessing large motor maps of both hemispheres may better predict the recovery potential of severely impaired stroke patients. Furthermore, the findings are consistent with the concept of compensatory plasticity in the contralesional hemisphere and may be relevant for designing novel interventions, e.g., by targeting alternate corticospinal pathways.

4.3 Clinically relevant improvements of the impairment level

Previous literature in the context of severely affected chronic stroke patients is limited. However, a few studies have evaluated the effectiveness of interventions in this patient cohort. While some studies reported only limited effectiveness [83,145], others detected increases between 2-3 FMUE points with different interventions [33,34,94]. Within the presented study, patients improved on average around 2 FMUE points after 180 hours of

intervention. This increase is clinically meaningful. Specifically, 12 of 19 patients who completed the study experienced clinically meaningful improvements in motor impairment. Furthermore, the patients improved specifically in the FMUE-C hand subscale, indicating decreased impairment in the paretic finger/hand. Prior to the study, their clinical status was stable despite conventional therapy. While the effectiveness of high-dose training has been shown in mild-moderately affected patients [30,47,48], to our knowledge, this study is the first to show the effectiveness of such a high-dose training combined with neurostimulation in severely affected chronic stroke patients. Subjectively, the patients also experienced significant improvements in their ability to take care of their affected arm, the strength of the paretic hand, their mobility at home, social activities (SIS-8) and their perceived recovery from stroke. We furthermore found significant increases in the patient's cognitive abilities, as indexed by the MoCA. The latter have been found to be associated with motor functions [146]. Within this study, the most prominent improvements were measurable not directly after the training but three months after the first training block. This suggests that we observed no compensational mechanisms, but recovery that involves slow biological processes and leads to long-term improvements [35,147,148]. We found a decrease in motor impairment that remained stable until last follow-up suggesting long-term improvements and plastic changes. Taken together, we propose that our training induced true motor recovery mechanisms.

4.4 Physiological changes in the course of the clinical trial

In addition to clinical and subjective changes, we furthermore studied physiological changes with TMS in the course of the study. We studied both hemispheres with TMS at the motor hotspot as well as over a large area, i.e., by TMS-maps. In the following, the findings for each hemisphere are discussed separately.

4.4.1 Physiological changes within the ipsilesional hemisphere

Within the ipsilesional hemisphere, we found significant changes of the contralateral CSE when stimulating the motor hotspot three months after the first intensive training block. However, after that, the contralateral CSE decreased again. Additionally, we found an increase in the volume of the ipsilesional cortical representation which peaked at the last visit. This was in line with previous literature as numerous studies indicate that a favorable hand motor

recovery after a stroke is associated with an increase of the size and volume of cortical hand motor representation within the ipsilesional hemisphere [108,149–152]. However, when considering the ipsilesional motor map area, our study did not show an increase. However, in contrast to other studies, our patients were severely affected. As these patients experienced a higher degree of corticospinal tract damage, the possible extent of cortical remapping might be limited [153].

While the contralateral CSE derived from the motor hotspot in the lesioned hemisphere peaked after the first training block, the volume increased over the whole period. This suggests that areas beyond the motor hotspot were strengthened over time. This would be in line with literature suggesting preserved neural pathways from distant brain regions taking over functions, such as the premotor cortex or supplementary motor areas [14,34,52,142]. As we did not find a common shift of the centre of gravity (CoG), we assume a more distributed pattern to be involved in the recovery of hand motor impairments. In previous literature, the direction of CoG shifts was highly variable between studies [108]. Furthermore, no clear association could be found, e.g., with motor impairment, neither in previous [108], nor in the present study. Hence, this might be highly individual between patients and depending on preserved pathways [52].

4.4.2 Physiological changes within the contralesional hemisphere

For the contralesional hemisphere, we found significant improvements of ipsilateral CSE at the motor hotspot over the whole intervention period. The peak of ipsilateral CSE was at the final visit. Furthermore, we found an increased map area and volume in the course of the study as well as a posterior change of the cortical representation (CoG), which all peaked at the final visit. While changes within the ipsilesional cortical representation in the context of stroke patients were investigated previously [108,152], to our knowledge, this study is the first to report changes of the cortical representation of the paretic arm within the contralesional hemisphere. Hence, putting the derived parameters in context is somewhat difficult. However, map parameters within the same hemisphere regarding the cortical hand motor representation of the healthy (not the paretic) hand have been described earlier, i.e., crossing pathways from the non-lesioned hemisphere to the non-affected hand [96,108,116,152,154]. While it is not directly comparable, one might assume that plastic changes within one

hemisphere affect both ipsi- and contralateral pathways. Hence, we will refer to these findings here:

While the area and volume were typically found to increase within the ipsilesional hemisphere during recovery, within the contralesional hemisphere, the findings were mixed [108]. Most studies reported a decrease of the map area [96,152,154]. However, it was suggested that this is depending on the motor impairment level: while patients with mild impairment showed a decrease of cortical representation within the contralesional hemisphere [108], patients with severe motor impairment showed increases [108,116]. Thus, we support these findings by an increased motor area and map volume in severely affected patients during recovery. Furthermore, we detected a posterior shift of the location of the cortical hand motor representation, i.e., the CoG, within the contralesional hemisphere. This implies that the cortical representation shifted towards the motor hotspot of the connections to the healthy hand, i.e., towards the primary motor cortex. Previously, it was consistently reported to change in posterior direction [108,155] and could be associated with improved motor function [108].

To sum up, we show increased corticospinal excitability of the contralesional hemisphere over the whole period, i.e., from V2-V6. This implies the recruitment of ipsilateral motor pathways in the course of motor rehabilitation in severely affected chronic stroke patients, as suggested earlier [52,86,92].

4.5 Implications for neurostimulation in severely affected chronic stroke patients

Taken together, in the course of the study, we found bilateral increases in CSE that peaked at different visits.

In this context, the contralesional volume at baseline predicted the amount of change of the FMUE-C (hand) score. This implies the potential of the contralesional hemisphere in the context of severely affected chronic stroke patients in the restoration of motor functions, as postulated previously [52,90,92]. Additionally, a higher residual contralateral CSE at baseline correlated with the final FMUE and FMUE-C. This indicates that higher residual contralateral connections are associated with a better clinical status at the end the intervention. This again is in line with the common assumption that motor recovery is associated with reorganisation

within the ipsilesional hemisphere [108,152]. In this context, the common theory is that of a competitive role of the two hemispheres after stroke [84,85]. However, there are theories suggesting the interhemispheric inhibition model to be oversimplified [52,86,90]. Furthermore, the potential of the non-lesioned hemisphere and respective ipsilateral pathways to promote functional recovery has been repeatedly suggested [52,86,90,92]. In this context, it has been proposed that neither of the perspectives is sufficient on its own [52,86]. In contrast, the individual residual structural reserve seems to be an essential role for recovery [52].

In the present study, we observed a complementary role of the two hemispheres, supporting parts of all above mentioned theories. Both hemispheres were strengthened throughout the study. However, the timepoints of facilitation differed between hemispheres. Importantly, the order of conditions had an influence on the effects. When applying the ipsilesional stimulation first, the clinical improvements were higher. Additionally, the ipsilateral CSE showed higher increases. We conjecture that the brain first tries to reorganise within the ipsilesional hemisphere [108,152] and gradually recruits the contralesional hemisphere [52,90,92] to restore motor functions. In line with Coscia et al. 2019, our findings suggest future interventions to be applied in a staged-approach in which one intervention is applied until a certain improvement is reached and then another intervention will be applied [32]. Specifically, in the context of severely affected chronic stroke patients, that could mean to apply one block of a high-dose training combined with neurostimulation targeting contralateral pathways from the ipsilesional hemisphere. The following blocks could then target the contralesional hemisphere. In this context, a threshold of impairment level, i.e., indexed by FMUE values, could serve as a decision criterion of when to target the contralesional hemisphere [90]. However, the exact application needs further consideration. While one block of ipsilesional stimulation led to relevant FMUE effects, the second training block with contralesional stimulation did result in physiological but not further clinical effects. Hence, additional blocks strengthening the contralesional hemisphere might be necessary. Besides that, different technologies and stimulation protocols could also be taken into account [32].

In summary, the present findings suggest a staged approach [32], and to stimulate the hemispheres in a sequential order. While the optimal procedure remains to be clarified, the observations indicate targeting first the ipsi- and then the contralesional hemisphere.

4.6 Limitations

One limitation of this study is the small sample size related to the specific patient cohort and the long study period. While we report these observations, they need to be verified in larger cohorts [32]. As this is a major challenge for single-centres, the effort could be undertaken by multi-centre approaches [32].

For ethical reasons, we decided to perform a within-subject design with a waitlist control period, in which all patient received intensive training with concurrent stimulation. Thus, the presented study did not include a control group undergoing the training program without stimulation. Consequently, it is not possible to fully disentangle the effect of the training itself from the added benefit of the stimulation. Additionally, while there is evidence for the effectiveness of both beta-tACS [73,77] and near-threshold NMES [82] in the context of chronic stroke patients, the exact contributions of both stimulation techniques need to be determined in order to better understand the exact mechanisms.

Additionally, we could show the facilitation of ipsilateral motor pathways while demonstrating clinical improvements in severely affected chronic stroke patients. However, we lack a deep understanding of the exact mechanisms even though there are numerous theories and suggestions available in the literature [98,100]. While the potential of ipsilateral motor pathways in the context of motor rehabilitation has been discussed previously [86,92,95], it is not yet understood if ipsilateral motor pathways are capable of fully recovering motor functions [156,157]. It has been postulated that the restoration of fine hand movements is not possible via ipsilateral pathways due to high spinal branching [156]. While we report improvement in hand motor impairments, our findings are not contradictory to this, as with the FMUE-C no fine hand movements are assessed. Therefore, the potential of ipsilateral pathways in restoring hand motor functions needs to be further evaluated.

While we followed the guidelines by Kwakkel et al. 2017 in the performed assessments within the presented trial [106], it is possible that the traditional clinical scales (e.g., FMUE) were not

sensitive enough to detect small changes in the presented patient cohort. For example, in the FMUE, the possible responses are no, partial or full function as compared to the less affected limb [105]. Hence, if the patients are able to perform slight movements, further improvements that do not represent full function do not change the score. This might also explain why there was no further improvement in FMUE scores after the second training block. Thus, for patients with very limited residual motor functions, appropriate scales should be developed which capture also slight improvements. In this context, objective measures, such as robotic assessed movement trajectories, e.g., range of motion or movement velocity, could play a key role [82,158–161].

Finally, while we have shown the highest effects three months after the second training block, longer observations periods need to be assessed in future studies. Furthermore, we do not know if the high-dose intervention was acting as a booster leading to permanent recovery of motor functions or if a continuous training is necessary in order to keep the effects. In the high-dose study by Ward et al., 2019, the last evaluation took place six months after the training. Interestingly, the amount of improvement in both motor impairment and function was highest six months after the intervention [30] This at least suggests that further improvements are conceivable after our intervention period as well. However, this must be proven both for our patient cohort and for effects that are beyond six months.

4.7 Future research

While this thesis provides evidence for the effectiveness of a high-dose training program in the context of chronic stroke patients with severe motor impairment, multiple factors require further consideration. In general, future research should test the intervention in larger cohorts. In the following, key aspects and future research questions are discussed in more detail.

Understand physiological mechanisms in more detail

First, in addition to behavioural changes following the intervention, we reported physiological measures obtained with TMS. While this allowed some insights in the underlying physiological mechanisms, further techniques could give rise to the latter [94]. A recent review highlighted the importance of a deep understanding of the underlying mechanisms in order to improve

neurotechnology-aided interventions, especially after severe stroke [6]. In the course of the study, further EEG and EMG data was acquired during the physiological assessments and training. Secondary analyses of these data might allow further insights, for example, with regard to the oscillatory activity [162–164] or cortico-muscular interactions [34,164,165]. Thus, contributions of functionally relevant cortical regions to motor recovery can be studied [34,165].

Additionally, in future studies, neuroimaging techniques, such as functional magnetic resonance imaging or diffusion tensor imaging or combined approaches could allow a better understanding of the underlying processes [18,166–168]. This might also give more insights in functions, neural network interactions and mechanisms of involved ipsilateral pathways [18,98,168].

Determine optimal target site for neurostimulation

In general, we aimed to apply both cortical and peripheral stimulation to associatively target the motor tract [60,169]. The primary motor cortex has been the primary target for neurostimulation interventions so far [6,59,170]. However, in the context of recovery, other brain regions have been suggested to play a key role, such as the premotor cortex or secondary motor areas [6,34,51]. In the context of stimulating the contralesional hemisphere, recent research especially highlighted the importance of the ventral premotor cortex [171]. Thus, the optimal stimulation spot in the context of severely affected patients remains further consideration [90]. Additionally, targeting individualised areas could further enhance the effects [6].

Optimal dose needs to be determined

As the current dose of standard rehabilitation approaches was shown to not be sufficient, applying higher doses has been suggested [35]. Most studies applying high-doses report doses of < 50 hours [42,44–46]. In the context of chronic stroke patients, three studies reported the application of much higher doses (90 and 300 hours) with clinically relevant improvements [30,47,48], as shown by the presented study as well. Importantly, in one of the studies applying 300 hours of training, there was no mid-training plateau [48]. This suggests the need and efficiency of such high doses for chronic stroke patients. In the present study, clinical improvements occurred after the first training block, and remained constant until the last visit.

However, we detected physiological changes after the second block as well. This suggests ongoing physiological processes. However, this exact dose-response relationship requires further consideration and should be evaluated in future research [37,40].

Additionally, besides the promising potential of applying high-dose interventions, practical considerations must be taken into account [30]. While the integration of such time-consuming therapies in clinical practice is challenging [30], the needs and abilities of the patients must be taken into consideration as well [172]. A follow-up study to the 90-hour training program in Ward et al. 2019 [30] reported perceptions from patients that have participated in their 90-hour program [172]. While the patients reported that the program was exhausting, they also reported that the benefits from the program were superior [172]. For future high-dose studies, evaluating user perceptions in a similar way could help understanding what is possible and best for the patients.

Personalised rehabilitation approaches

While in most studies the same intervention is applied to all patients, there is the common understanding that there is no “one-size-fits-all” approach [86,90,173]. In this context, it has been repeatedly suggested to personalise the rehabilitation interventions [32]. In line with previous suggestions [32] and based on the findings of this study, the feasibility and effectiveness of applying this intervention in a staged-approach should be determined. This could be realised as a highly individual rehabilitation approach in which for each patient individually the next steps and parameters can be decided. In this context, also other parameters, like the optimal dose of intervention might be individualised [41].

Evaluate feasibility of home-based training

Finally, a limitation of such high-dose training programs is the integration in current clinical practice [30,174]. A solution to this could be to apply the intervention as a home-based training [175]. Overall, the application of home-based rehabilitation in the context of motor recovery after stroke was previously shown to lead to improvements in motor function [175,176]. While it offers a lot of advantages, such as a high flexibility, patients can also face challenges when being involved in a home-based rehabilitation program [175]. One of these could be the loss of the encouraging surrounding in which patients can participate together and motivate each other [172] as well as the absence of therapists that can support the

patients [175]. Furthermore, the setup at home differs greatly from the setup within laboratories [175].

Summed up, applying high-dose trainings as home-based rehabilitation interventions offer a promising potential to integrate time-consuming rehabilitation programs such as the presented high-dose training in everyday life [175]. However, the feasibility for our particular intervention and the possible setup requires further consideration.

4.8 Conclusion

Taken together, this thesis provides evidence that further recovery is possible in severely affected chronic stroke patients. We first provided and evaluated refined methods to measure effects within this specific patient cohort. This could help future studies evaluating the potential of targeted therapies. Furthermore, we demonstrated the effectiveness of a high-dose training program combined with neurostimulation. These changes were accompanied by neurophysiological changes. Future research is necessary concerning aspects like the optimal dose of stimulation [37,40], pure training effects [30], ipsilateral pathways [90,92,157], long-term effects [30], the possible application as home-based training [175] as well as tests in larger cohorts.

5 Appendix

A. Detailed description of the six training tasks

For tasks 1-5, the patients received visual cues on a computer screen as guidance and were given visual feedback on their performance. For this purpose, movement sensors were integrated in the equipment that was used for the training tasks (see details below). Peripheral stimulation during these tasks was always applied during the extension phase of the task.

Task 1 – Finger extension. Each finger extension repetition (or trial) consisted of 4s of extension, 4s of flexion, and finally 2s of rest. The patients were instructed to support the opening of the affected hand with the unaffected hand by placing the unaffected hand as a fist inside the affected hand. During each trial the patients attempted to simultaneously open both hands and extend the fingers. By placing the affected hand inside the unaffected hand, a passive opening of the affected hand was present for each trial, even in the absence of active finger movements. As this hand positioning did not work for all patients (e.g., due to high spasticity), sometimes this approach was adapted to the movement capabilities of the patients. One adaption was for example to fold their hands and then stretch the fingers of both hands in this position mainly by moving the healthy palm away from the other one.

Task 2 – Wrist extension. The second task focused on wrist movements by alternating extension and flexion of the wrist. For each trial, 6s of wrist extension was followed by 6s of wrist flexion and finally 2s of rest. For this task, patients held a wooden stick with a length of 50cm and a diameter of 3cm horizontally in front of their body with both hands. In the middle of the sticks, a sensor (Go Direct Acceleration Sensor, Vernier) was attached for information about the current location. In case the patients were not able to actively hold the stick with their paretic side, the hand was fixated to the stick.

Task 3 – Grip + Release. Each trial contained 4s of flexion, followed by 4s of extension, and finally 2s rest. The patients held a dynamometer (Go Direct Hand Dynamometer, Vernier) in each hand. For the flexion phase they were instructed to press as strongly as possible and for the extension they should release again. The patients were also instructed to focus on the release phase in particular (i.e., extension of the fingers).

Task 4 – Finger extension + breathing. The purpose of this task was to synchronise the opening and closing of the hands with a specific breathing cycle. During each trial, patients inhaled for 4s, exhaled for 4s, followed by 2s without breathing. The patients tried to extend the fingers during the inhalation phase and tried to close it again during the exhalation phase. All patients were strongly encouraged to try to open their paretic hand as much as they could even if not resulting in an actual movement. A respiration belt (Go Direct Respiration Belt, Vernier) was used to display each patient's current breathing phase on the computer screen.

Task 5 – Elbow extension. Within each trial, the task was to extend the elbow for 4s and then flex the elbow for 4s followed by 2s rest. To realise that the patients were asked to place both hands on top of a horizontally laying foam roller of 32cm with a diameter of 14cm in a comfortable position close to the body in front of the patients. Inside the foam roller, a sensor (Bittium Faros 360) was placed and used for information about the current positions. In case patients were not able to actively maintain the required position, the paretic hands were attached to the black roll with tape.

Task 6 – Activities of daily living. At the end of the training days, patients were asked to train activities of daily life according to some of the activities described by Broetz and colleagues [177]. The available training tasks were: 1) putting toothpaste on a toothbrush, 2) opening a bottle and put water in a glass, 3) taking a piece of food with fork from a plate and eat it, 4) grab and hold different sized bolts. Patients were asked to train 2-4 tasks per day. They were allowed to pick their preferred tasks each day but were encouraged to practice all the available tasks on at least two days across the training period. This task was without any stimulation or individual feedback.

B. Description of the clinical scales and questionnaires

The **ARAT** is a reliable tool for measuring functional ability of the paretic upper extremity [125,126]. The ARAT contains four subscales that assess grasping, gripping, pinching and gross movements of the paretic arm/hand. Each item is rated on a scale from 0-3 (0 = unable to perform any part of the task within 60s, 3 = normal performance), with a maximum total score of 57 (indicates full function). The MCID has been studied for patients that had a mean baseline ARAT score of 29.2 and has been suggested to be 5.7 points [178].

The **CAHAI** is a reliable performance test using items based on activities of daily life. Patients are asked to complete the tasks using both hands. The scale comprises 13 tasks with possible ratings from 1 (total assist by unaffected hand) to 9 (complete independence). The maximum score is 91. For CAHAI, no MCID was suggested but a minimal detectable change of 6.3 points was described instead [128].

The **MoCA** is a test for detection of mild cognitive impairments by testing different domains of cognition (visuospatial and executive function, language, episodic memory, attention/working memory). The maximum score is 30 and a score of 26 or higher reflect normal cognitive functions [179]. In the context of stroke rehabilitation, a MCID of 1.22 and 2.15 for anchor- and distribution-based calculations respectively was suggested [135].

FMLE. The FMLE is used to assess motor function of the lower extremity. Following the same approach as described for the FM-UE, the coordination/speed and reflex sections were excluded, which resulted in a maximum score of 22. The MCID for FM-LE has been suggested to be 10% of the total score [180] which would in our case resemble 2.2 points.

To account for changes in hand function as targeted by the intervention, part C (Hand) of the FMUE (**FMUE-C**) was separately analysed and reported.

To assess stroke severity, the **NIHSS** was performed at baseline. It includes measures of the following domains: level of consciousness, eye movements, visual fields, facial movements, arm and leg muscle, sensation, ataxia, aphasia, dysarthria, and neglect. The total score ranges from 0 to 42 (with a higher score indicating a higher stroke severity) [181].

The patients were also asked to complete the following questionnaires at the start of the first training block (pre1), the start of the second training block (pre2), and the final follow-up session: the Stroke Impact Scale (SIS) [182], ArmA-A and ArmA-B [183].

The **ArmA** is a valid and reliable patient-reported outcome measure that is divided in two sections: the ArmA-A and the ArmA-B [183,184]. The ArmA-A asks patients about their ability to take care of their affected arm (either by themselves with the unaffected side, by other people or a combination of both) and ranges from 0-28 points. The ArmA-B asks patients about the ability to use the affected arm for tasks or activities and ranges from 0-52. For both ArmA-A and ArmA-B, lower scores indicate a better performance. To our knowledge, no MCID has been reported yet for the ArmA-A and ArmA-B.

The **SIS** is a disease-specific questionnaire that consists of nine subscales measuring the impact of stroke on physical disability as well as further domains of health and daily life [182]. The first eight subscales contain a total of 64 items (SIS version 2) covering the following domains: strength, hand function, activities of daily living, mobility, communication, emotion, memory, and social participation. The first 63 items consist of a numeric rating scale ranging from 1-5. Higher scores indicate higher function/recovery [182]. The ninth subscale contains a single item that asks patients to rate their level of perceived recovery from their stroke from 0-100%. For the SIS, MCIDs for physical domains have been reported. On a group level, these are 9.2 for strength, 5.9 for activities of daily living (ADL), 4.5 for mobility, and 17.8 for hand function. However, these values were evaluated for the SIS version 3 [137]. In the context of the present clinical trial targeting improvements in upper extremity motor functions, we only analysed changes in physical domains (SIS-1, SIS-5, SIS-6, SIS-7) and the subjective health status (SIS-9).

6 Statement of Contributions

Statement of contributions according to § 9 (2):

This thesis was written at the Institute for Neuromodulation and Neurotechnology under the supervision of Prof. Alireza Gharabaghi. The data and analysis within this thesis were part of a clinical study that took place between 2018 and 2020 at the Institute for Neuromodulation and Neurotechnology led by Prof. Alireza Gharabaghi (ClinicalTrials.gov Identifier: NCT03947645).

Prof. Gharabaghi, Lukas Ziegler and I, Bettina Hanna Trunk, conceptualised the protocols for the visits V0 and V1. Lukas Ziegler and I collected the data of these timepoints. I analysed the data of these timepoints that is presented in this thesis.

Furthermore, I, Laura Arendsen, Nadezhda Pavlova, Felix Quirmbach, Robert Guggenberger and Prof. Gharabaghi conceptualised and set up the study from V2-V6. I, Laura Arendsen, Nadezhda Pavlova and Felix Quirmbach were involved in the data collection. Additionally, I, Laura Arendsen, Nadezhda Pavlova, Siegmar Raidt, Ethan Rich and Nelli Keksel supervised the daily training of the patients (V2-V3 and V4-V5). Furthermore, I, Laura Arendsen, Nadezhda Pavlova, Felix Quirmbach, Robert Guggenberger, Ge Tang, Marius Keute, Ethan Rich, Matthew Flood, Fjola Hyseni, Michael Valiadis, Sine Canbolat and Vaida Verhoef were involved in pre-processing the clinical data and I, Robert Guggenberger and Antonia Bernecker were involved in pre-processing the TMS-Map data (V2-V6).

Lastly, I analysed the presented data (V2-V6) and wrote this thesis myself.

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