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COOPERATIVE HAND MOVEMENTS AND THEIR POTENTIAL FOR STROKE REHABILITATION

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Thesis summary

Eating, washing and dressing oneself are just a few examples of upper limb tasks we perform every day with little effort. For people suffering from a stroke, these tasks can become challenging due to sensorimotor impairments of the upper limb. Consequently, providing efficient and evidence based therapeutic strategies is crucial to improve their quality of life and independence. Cooperative, object-oriented hand movements underlie an enhanced neural coupling of the upper limbs reflected in a strong bilateral neural organization including enhanced bilateral muscle reflexes and sensory processing after unilateral nerve stimulation. This neural characteristic is partly preserved in stroke survivors indicating that tracts of the non-affected hemisphere are strongly involved in the control of the affected arm. A training of cooperative hand movements based on this neural behaviour might be promising for a better sensorimotor recovery of the upper limb. Still, not much is known about the neural control of these movements and no therapy approach focussing on these movements is currently available. Thus, the aim of this thesis was to get a more profound understanding of the sensorimotor control underlying cooperative hand movements and to evaluate their potential for stroke rehabilitation.

One central mechanism reflecting task-specific neural coupling during cooperative hand movements is the robust occurrence of upper limb reflexes contralateral to the site of stimulation. The limits and the functional role of this coupling was more closely investigated in the first two studies of this thesis.
In **study 1,** we tested the assumption that shared sensory input from both hands is an important component for the neural coupling and assessed bilateral reflex responses during unimanual sensory deprivation in healthy individuals. We observed that contralateral reflex responses were enhanced in the sensory deprived limb and reduced in the non-deprived limb. This indicates an interhemispheric disbalance due to the mismatch of shared sensory input from both hands that might have led to an imbalanced efferent output in favour of the sensory deprived limb. Despite the unilateral sensory deficit, clear contralateral reflexes occurred in both arms suggesting that sensory feedback mainly of the non-deprived hand is processed and integrated in both hemispheres which is sufficient to preserve the neural coupling.

The goal of **study 2** was to investigate the behaviour of bilateral reflex responses under varying movement velocity and resistance. We observed that the magnitude of the ipsilateral and contralateral responses linearly increased with muscular pre-activity associated with increasing velocities and resistances. Further, clear contralateral reflex responses were observed even at low movement velocities and low loads. These results demonstrate that neural coupling is a robust mechanism and serves to quickly match the forces between the

limbs to maintain task success. This finding might be important for the potential application of cooperative hand movements in stroke rehabilitation since even patients with limited movement capacity could benefit from the neural coupling supporting the control of the affected limb.

After a closer investigation of the bilateral reflex behaviour after unilateral stimulation, cooperative hand movements were investigated in a different framework. We hypothesized that the integrated sensory feedback between both hands that is received due to the interaction on a shared object increases the predictability of the task. A better predictability could influence how muscle activation is adjusted and how incoming sensory information is filtered. In **study 3,** we demonstrated lower co-activation of forearm muscles and stronger reduction of somatosensory evoked potentials (SEPs) during a cooperative as compared to non-cooperative tasks. This finding suggests a more efficient sensorimotor control during cooperative compared to other bimanual tasks due to the well predictable integrated sensory feedback of both hands. This enhanced predictability allows to perform the task with less co-activation as it is less necessary to be prepared for external disturbances. Additionally, the saliency for any external sensory input is reduced.

The first three studies provided novel insights into the sensorimotor control of cooperative hand movements and support their potential for application in stroke rehabilitation. Ultimately, the focus of the thesis was to evaluate the potential of cooperative hand movements for neuro-rehabilitation. In **study 4**, ARCO therapy was developed as a novel self-administrable and home-based therapy focusing on cooperative hand movements. This therapy was tested for its feasibility and efficacy to improve upper limb function in chronic stroke survivors. After 2 weeks of training in a clinical setting and 4 weeks of unsupervised home-training, stroke patients showed significant improvements in upper limb function and impairment. Questionnaires supported feasibility for application in a clinical setting and for self-administration at the patient’s homes. We suggest ARCO therapy to be a novel and promising approach for stroke rehabilitation complementing existing therapies.

Taken together, this thesis contributes to the understanding of the sensorimotor control underlying cooperative hand movements and provides a promising scientific basis for its application in stroke rehabilitation. With ARCO therapy, a novel therapeutic approach focussing on cooperative hand movements was developed which is easily accessible, feasible, and effective to improve upper limb function. Future investigations of cooperative hand movements regarding their underlying control and functional effects with larger sample sizes and in different clinical populations are necessary to optimize its application in neurorehabilitation. Yet, we suggest cooperative hand movement therapy to be a promising approach for the application in current stroke rehabilitation programs.

Thesis Summary (german)

Essen, sich waschen, oder sich anzuziehen sind nur einige Beispiele für Bewegungsaufgaben unserer Arme, welche wir täglich ohne große Mühe bewältigen. Für Personen, welche von einem Schlaganfall betroffen sind, können diese Aufgaben eine Herausforderung darstellen aufgrund von sensorimotorischen Defiziten der oberen Extremität. Die Anwendung von effizienten und wissenschaftlich fundierten Therapien ist deshalb wichtig um die Lebensqualität und Unabhängigkeit dieser Personen zu verbessern. Kooperative, objektorientierte Handbewegungen unterliegen einer aufgabenspezifischen neuronalen Kopplung im Sinne einer starken bilateralen neuronalen Organisation. Diese zeigt sich in beidseitigen Muskelreflexen und beidseitiger sensorischer Prozessierung nach einseitiger Nervenstimulation. Dieses neuronale Verhalten ist im Schlaganfallpatienten teilweise erhalten, was auf eine stärkere Beteiligung von Bahnen der nicht betroffenen Gehirnhälfte in der Kontrolle des betroffenen Armes schließt. Ein Training, basierend auf kooperativen Handbewegungen und ihrer neuronalen Charakteristik könnte vielversprechend für eine bessere Erholung von sensorischen und motorischen Defiziten der oberen Extremität sein. Es ist immer noch wenig über die neuronale Kontrolle dieser Bewegungen bekannt und es gibt derzeit keinen Therapieansatz welcher diese Bewegungen fokussiert. Deshalb war das Ziel dieser Doktorarbeit, ein besseres Verständnis über die sensorimotorische Kontrolle dieser Bewegungen zu erlangen und ihr Potential für die Rehabilitation von Schlaganfällen zu ermitteln.

Ein zentraler Mechanismus, welcher sich in der aufgabenspezifischen neuronalen Kopplung während kooperativen Handbewegungen zeigt, sind robuste Reflexantworten in der oberen Extremität kontralateral des stimulierten Armes. Die Grenzen und die funktionelle Rolle dieser Kopplung wurde in den ersten beiden Studien dieser Arbeit genauer untersucht.

In **Studie 1** wurde die Annahme getestet, dass die geteilte sensorische Information von beiden Händen eine wichtige Komponente für die neuronale Kopplung ist. In gesunden Probanden wurden deshalb bilaterale Reflexantworten während dem Entzug der sensorischen Wahrnehmung von einer Hand gemessen. Wir konnten beobachteten, dass die kontralateralen Reflexe im sensorisch gestörten Arm erhöht, und im nicht gestörten Arm reduziert waren. Dies schließt auf ein inter-hemisphärisches Ungleichgewicht, welches durch die unterschiedliche sensorische Information beider Hände bedingt ist und zu einer ungleichen efferenten Versorgung zugunsten des sensorisch gestörten Armes geführt haben könnte. Weiterhin konnten wir trotz des sensorischen Defizites, klare kontralaterale Reflexe beobachten. Dies könnte darauf hinweisen, dass sensorische Information von der nicht gestörten Hand in beiden

Gehirnhälften prozessiert und integriert wird, was ausreicht um die neuronale Kopplung der Arme aufrecht zu erhalten.

Das Ziel von **Studie 2** war es, das Verhalten der bilateralen Reflexantworten unter unterschiedlichen Bewegungsgeschwindigkeiten und Widerständen zu untersuchen. Wir konnten beobachten, dass die Grösse der ipsilateralen und kontralateralen Antworten linear zur muskulären Voraktivierung anstieg, was mit der steigenden Bewegungsgeschwindigkeit und dem steigenden Widerstand zusammenhing. Weiterhin sahen wir eindeutige Reflexantworten, selbst bei geringer Geschwindigkeit und geringem Widerstand. Diese Ergebnisse zeigen, dass die neuronale Kopplung ein robuster Mechanismus ist, welcher dazu dient, die Kräfte beider Arme anzupassen um eine erfolgreiche Durchführung der koopertiven Bewegungsaufgabe aufrechtzuerhalten. Diese Ergebnisse könnten wichtig für die potenzielle Anwendung von kooperativen Handbewegungen in der Rehabilitation von Schlaganfällen sein. Selbst Patienten mit eingeschränkter Bewegungskapazität könnten von der neuronalen Kopplung, welche die Kontrolle der betroffenen Extremität unterstützt, profitieren.

Nach einer näheren Untersuchung der beidseitigen Reflexe nach einseitiger Stimulation, wurden kooperative Handbewegungen in einem anderen Rahmen untersucht. Wir nahmen an, dass die integrierte sensorische Information, welche durch die Interaktion beider Hände über ein gemeinsames Objekt empfangen wird, die Vorhersehbarkeit der Bewegungsaufgabe steigert. Eine bessere Vorhersehbarkeit könnte die Muskelaktivierung beeinflussen und wie eingehende sensorischen Informationen gefiltert werden. In **Studie 3** konnten wir eine geringere Koaktivierung der Muskeln des Unterarms und eine stärkere Reduzierung von somatosensorisch evozierten Potenzialen (SEPs) während kooperativen im Vergleich zu nicht kooperativen Handbewegungen zeigen. Diese Ergebnisse suggerieren eine effiziente sensorimotorische Kontrolle aufgrund der gut vorhersehbaren integrierten sensorischen Information beider Hände. Diese erhöhte Vorhersehbarkeit erlaubt die Durchführung der Bewegung mit weniger Koaktivierung, da es weniger vonnöten ist, parat für externe Störungen zu sein. Zusätzlich ist die Empfänglichkeit für jegliche externe sensorische Information verringert. Eine stärkere Koaktivierung steht im Bezug zu einem höheren motorischen Aufwand und ist ein scheint ein Grund für Spastizität bei Schlaganfallpatienten zu sein. Deswegen könnte ein Training von kooperativen Handbewegungen Spastizität und die Anhäufung von Ermüdung verringern.

Die ersten drei Studien gaben neue Einblicke in die sensorimotorische Kontrolle von kooperativen Handbewegungen und unterstützen ihr Potential für ihre Anwendung in der Rehabilitation von Schlaganfall. Letztlich war der Fokus dieser Arbeit das Potential von kooperativen Handbewegungen für die Neurorehabilitation zu beurteilen. In **Studie 4** wurde ARCO Therapie als eine neue, selbst- und von zu Hause durchführbare Therapie entwickelt, welche kooperative Handbewegungen fokussiert. Diese Therapie wurde auf ihre Anwendbarkeit und Effizienz untersucht, die Funktion der oberen Extremität in chronischen Schlaganfallpatienten zu verbessern. Nach zwei Wochen Training in der Klinik und vier Wochen selbstständigen Heimtraining konnten signifikante Verbesserungen der Funktion der oberen Extremität gezeigt werden. Fragebögen unterstützten eine gute Anwendbarkeit für die Durchführung dieses Trainings sowohl in einem klinischen Umfeld als auch bei einem selbst-durchführbaren Training für zu Hause. Wir suggerieren, dass ARCO ein neuer und vielversprechender Ansatz für die Rehabilitation von Schlaganfallpatienten ist, um derzeitige Therapien zu ergänzen.

Zusammengefasst trägt diese Arbeit zum Verständnis der sensorimotorischen Kontrolle von kooperativen Handbewegungen bei und bietet eine vielversprechende wissenschaftliche Basis für Ihre Anwendung in der Schlaganfallrehabilitation. Mit ARCO wurde ein neuer therapeutischer Ansatz entwickelt welcher kooperative Handbewegungen fokussiert, einfach zugänglich und anwendbar ist, und effektiv in Bezug auf die Verbesserung der Funktion der oberen Extremität ist. Zukünftige Untersuchungen von kooperativen Handbewegungen bezüglich ihrer zugrundeliegenden Kontrolle und funktionalen Auswirkungen in größeren Stichproben und unterschiedlichen klinischen Populationen sind jedoch nötig, um ihre Anwendung zu optimieren. Dennoch zeigen unsere Ergebnisse, dass kooperative Handbewegungstherapie ein vielversprechender Ansatz für die Anwendung in derzeitigen Rehabilitationsprogrammen bei Schlaganfallpatienten ist.

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Chapter 1

General Introduction

1.1 Stroke

With approximately 15 million new incidents every year, stroke has become a global health problem (Johnson et al., 2019). It is the leading cause of adult disability resulting in huge financial burdens for the health care system (Lapchak and Zhang, 2017; Thrift et al., 2017). Stroke can be described as an acute disruption of oxygen supply to the brain either due to a blocking of blood supply or by rupture of blood vessels (Ojaghihaghighi et al., 2017) leading to irreversible damage of the respective brain areas. Impairments after stroke are highly individual and depend on the location and size of the damaged brain tissue (Laredo et al., 2018). Besides affected sensory (e.g., proprioception, touch) and cognitive (e.g., memory, attention, comprehension) capacity, motor impairments are known to be the most common and serious consequences affecting about 80% of stroke survivors (Langhorne et al., 2011). Paresis of the upper limb is reported to be the most frequent impairment affecting 60-70% of patients (Langhorne et al., 2009; Sommerfeld et al., 2004). It remains impaired in 30% to 66% of the patients even after 6 months whereas only 11% of these were shown to recover completely (Kwakkel et al., 2003). The upper limb is crucial for simple and complex tasks in numerous activities of everyday life (ADL). Thus, one central goal in stroke rehabilitation is the recovery of upper limb movements and associated functions to ultimately regain independence and quality of life.

1.2 Importance of scientific based motor rehabilitation

Numerous rehabilitation strategies have been shown to improve upper limb function including electrical stimulation, non-invasive brain stimulation, mental training and movement-based approaches. Especially the latter has been reported to be very effective in promoting recovery (Cauraugh and Summers, 2005). However, recovery after stroke is a complex process and its progress is highly variable. It depends on the size and location of the lesion and the degree of the initial impairment (Langhorne et al., 2011). Motor recovery post-stroke relies on neuroplasticity, i.e. the ability of the brain for structural and functional reorganization due to spontaneous neurobiological recovery or in response to therapy. More specifically, neuroplasticity after stroke includes compensatory functional changes of the non-damaged tissue around the injury (Calautti and Baron, 2003) or the activation of undamaged ipsilateral (i.e., contralesional) cortical areas and pathways (Baker, 2011; Strens et al., 2003). Thus, understanding the neural control of movements underlying specific upper limb therapies and how they promote neuroplasticity is important for their application in rehabilitation (Summers et al., 2007; Winstein et al., 2003). Various unimanual and bimanual therapy approaches were developed based on the underlying neural control of the motor tasks they involve. For example, it is known that observing movements induce similar cortical activations as when the same movement is actively performed (Grezes and Decety, 2001). This concept is used in mirror therapy during which a mirror is placed in front of the patient to reflect movements of their non-affected limb. This creates the illusion of moving the affected limb which is thought to stimulate the ipsilesional hemisphere to support movements of this limb and to promote its recovery (Thieme et al., 2018). As another example, deafferentation of a single limb can induce a learned “non-use” of this limb (Taub, 1980). Such a non-use can lead to reductions in the respective motor areas of that limb (Liepert et al., 1995). Based on these findings, Constrained Induced Movement Therapy (CIMT) was developed to prevent a learned non-use of the affected limb in stroke patients. This is achieved by immobilization of the non-affected limb forcing an engagement of the affected limb in activities (Wittenberg and Schaechter, 2009). In fact, CIMT has been shown to promote cortical reorganization reflected in increased cortical activation and enlargement of the motor map in the ipsilesional hemisphere (Liepert et al., 1998; Schaechter et al., 2002).

Besides strategies using one limb, simultaneous use of both limbs in motor therapy is considered an effective way to promote recovery of upper limb function (Cauraugh and Summers, 2005). Bilateral movement training in stroke is thought to utilize the contralesional hemisphere via transcallosal connections to support a stronger activity of the ipsilesional hemisphere and crossed facilitation of the limbs (Summers et al., 2007). For example, active-passive bilateral priming (Stinear et al., 2008; Stinear et al., 2014) or bilateral training with rhythmic auditory cueing (Whitall et al., 2000) are thought to promote upper limb function due to rebalancing of interhemispheric excitation and inhibition. Together, these findings suggest that understanding the sensorimotor control and neural mechanisms of upper limb movements is important for the development of novel therapeutic strategies.

In the past years, cooperative hand movements were shown to underlie a promising neural basis which may has the potential for a novel and efficient scientific-based therapy approach to improve upper limb function.

1.3 Neural control of cooperative hand movements

In many daily tasks, the use of more than one arm is necessary to perform functional actions and to solve complex tasks. These tasks can differ in their goal and in the way the limbs are utilized. Vast research has targeted bimanual separate, cyclic, and symmetrical movements

(Donchin et al., 1998; Kelso, 1984; Scholz and Kelso, 1990; Swinnen, 2002) and a broad neural network has been shown to be involved in their control including bilateral primary motor cortex (M1), supplementary motor areas (SMA), premotor cortex (PMC), primary (S1) and secondary (S2) somatosensory cortex, and the cerebellum (Donchin et al., 1998; Goble et al., 2010; Grefkes et al., 2008; Michels et al., 2018).

However, the successful accomplishment of many daily activities often requires a fine cooperation of both hands. This subgroup of bimanual movements, cooperative hand movements, involves mutual interaction of both hands on a shared object including tasks such as opening a bottle, inflating a bike tire, winding up a blind, and carrying a tray. Despite their significance for everyday life, these movements and their underlying neural control are so far not well investigated (Kantak et al., 2017; Obhi, 2004). However, a few studies examined cooperative hand movements using imaging and neurophysiological methods and indicated a task-specific neural control in these movements.

Similar to earlier studies showing a functional coupling between lower and upper limbs when their synergy is required (e.g., as during walking) (Dietz, 2002; Michel et al., 2008), such a coupling mechanism was also observed between the upper limbs. More specifically, unilateral ulnar nerve stimulation or mechanical disturbance resulted in reflex responses not only ipsilateral but also contralateral to the side of stimulation (Dietz et al., 2015; Mutha and Sainburg, 2009). Interestingly these studies showed that the contralateral reflexes were enhanced during cooperative compared to non-cooperative tasks indicating a stronger neural coupling between the upper limbs during cooperative tasks. It is generally possible to elicit such bilateral reflexes also during non-cooperative but temporally coupled movements (Caldelari et al., 2020). But a robust and enhanced release of the contralateral response is usually only seen during cooperative tasks (Dietz et al., 2015; Schrafl-Altermatt and Dietz, 2016a; Mutha and Sainburg, 2009). Since similar latencies of ipsi- and contralateral reflexes were reported (Dietz et al., 2015), ipsilateral non-crossed pathways were thought to be involved in the processing of the contralateral reflex as a transcallosal route would cause a delay of at least 8ms (Cracco et al., 1989). An involvement of ipsilateral efferent pathways in the neural coupling is supported by a recent observation by our group (unpublished results) showing enhanced ipsilateral motor evoked potentials (iMEPs) during cooperative compared to non-cooperative tasks.

Further, functional magnetic resonance imaging (fMRI) revealed a stronger bilateral activation and functional connectivity of the secondary somatosensory cortex (S2) during cooperative compared to non-cooperative tasks (Dietz et al., 2015). This suggests that shared sensory input of both hands is processed and integrated in bilateral S2 areas possibly leading to the enhanced contralateral reflex during cooperative tasks. This is supported by other studies demonstrating S2 to be involved in the integration of sensory input from both sides of the body (Disbrow et al., 2001; Hari et al., 1998; Lin and Forss, 2002).

Not only ipsilateral efferent but also ipsilateral afferent pathways seem to be more strongly involved in the control of cooperative hand movements. For instance, a study by Schrafl-Altermatt and colleagues investigated somatosensory evoked potentials (SEPs) over the contralateral and ipsilateral primary sensory cortex (S1) (2014). In their study, the ipsilateral to contralateral SEP amplitude ratio increased in favour of the ipsilateral hemisphere indicating that ipsilateral afferent pathways are strongly involved in cooperative hand movements and contribute to task-specific neural coupling. Together, cooperative tasks seem to underlie a stronger bilateral neural organization compared to non-cooperative tasks. For a simplified schematic depiction of the neural control of cooperative hand movements based on previous investigations, see Figure 1.1.

While the existence of this neural coupling is described, it is not known how sensitive it is to changes in movement demands or availability of sensory perception. Early studies showed that reflexes to mechanical perturbations or electrical stimuli change depending on the magnitude of background muscle activity, that is, the higher the background activity, the higher the reflex (Marsden et al., 1972; Marsden et al., 1976; Matthews, 1986; Pruszynski et al., 2009b). Similarly, motor evoked potentials (MEP) in response to transcranial magnetic stimulation increased with higher muscular pre-activation (Taylor et al., 1997). Interestingly, ipsilateral MEPs can be reliably evoked in axial and proximal muscles, while its occurrence in more distal forearm or hand muscles require a strong pre-activation and stimulus intensity (Bawa et al., 2004; Ziemann et al., 1999). It is therefore conceivable that a certain movement demand might determine the occurrence and magnitude of contralateral reflexes during cooperative hand movements. Further, processing and integration of afferent input from both hands has been suggested to be a crucial parameter for the neural coupling during cooperative tasks (Dietz et al., 2015, Schrafl-Altermatt and Dietz, 2014). Accordingly, disturbance of the sensory perception might contribute to a change in the neural coupling. Therefore, the first two studies of the thesis aimed to investigate possible limits of the task-specific neural coupling mechanism regarding changes in the movement demand and sensory perception.

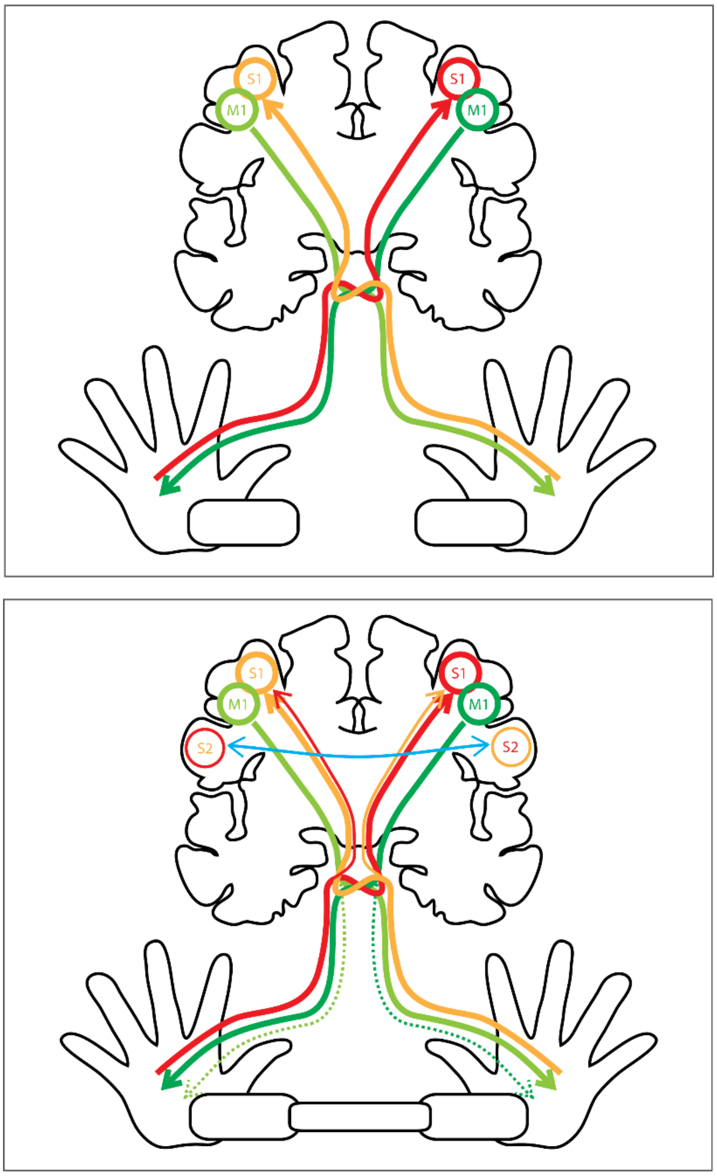


Figure 1.1: Simplified afferent and efferent neural control during cooperative- and non-cooperative hand movements. Non-cooperative tasks underlie more “crossed-control” (top panel). Right primary sensory cortex (S1) receives sensory afferent input from the left hand and left S1 receives input from the right hand. Motor output to each hand is mostly generated by the contralateral hemisphere. During cooperative hand movements (bottom panel), S1 areas receive additional sensory input from the ipsilateral hands which is integrated between S2 areas. Efferent output is more bilateral compared to non-cooperative tasks. Adapted from Dietz and Schrafl-Altermatt 2016.

One obvious difference between cooperative hand movements and other movements is that the hands are physically coupled over a shared object. Receiving integrated sensory feedback from the cooperating partner has been shown to have implications for a more optimal motor control (Blakemore et al., 1998b; Johansson and Westling, 1984). When movements are supported by the cooperating hand, integrated feedback allows for a precise prediction of grip forces and a minimal safety margin (Johansson and Westling, 1984). This more efficient control is proposed to underlie internal forward models which constantly predict future sensorimotor states and consequences of our actions. These predictive models are also relevant in filtering incoming sensory information (Blakemore et al., 1999; Wolpert et al., 1995). It is therefore conceivable that the available integrated feedback from both hands during cooperative hand movements allows for a more accurate prediction of future sensorimotor states which could lead to different adaptions of muscular activation and processing of sensory input compared to non-cooperative tasks. This assumption was tested in study 3 of the present thesis.

1.4 Cooperative hand movements in stroke

Impairments in the contralesional limb following stroke limits the coordinated use of both hands which is necessary to perform various tasks of daily living. Many of these tasks require a cooperative interaction of both hands but research on the impact of stroke on the control of cooperative hand movements is so far sparse (Kantak et al., 2017). Results from a recent study suggest that especially cooperative movements are difficult to perform after stroke. While patients were able to maintain a symmetric coordination of both hands during bimanual reaching, coordination was impaired when cooperation of both hands was required to lift a box, reflected in several asymmetric peaks in grip and load forces (Kantak et al., 2016). Other studies showed that the task-specific neural coupling during cooperative hand movements that was observed in healthy participants, is partly preserved in stroke survivors. More specifically, unilateral nerve stimulation on the affected limb during cooperative hand movements led to impaired ipsilateral reflexes while no contralateral reflex responses were observed (Schrafl-Altermatt & Dietz, 2016a). In contrast, stimulation of the non-affected limb led to normal reflexes in the ipsilateral limb but also to reflexes in the contralateral, affected limb. This preserved efferent output to the affected limb might involve a transmission of the reflex from ipsilateral efferent pathways from the non-affected hemisphere possibly via uncrossed cortico-spinal (Welniarz et al., 2017) or reticulo-spinal tract (Soteropoulos et al., 2011). This contralateral reflex behaviour seems to be dependent on the severity of the impairment since they can be observable in both limbs in mildly affected patients while they can be also non-observable in severely affected patients (Schrafl-Altermatt and Dietz, 2016a). Nevertheless, these findings suggest that in stroke patients the non-affected hemisphere is strongly involved in the control of the affected limb during cooperative tasks preserving the neural coupling between limbs. Similarly, the task specific processing of afferent input during cooperative hand movements in healthy individuals has also been shown in stroke survivors. More specifically, the application of an electric stimulus to the affected limb during cooperative hand movements resulted in stronger ipsilateral SEPs in the non-affected hemisphere compared to non-cooperative hand movements (Schrafl-Altermatt and Dietz, 2016b). This finding demonstrates a stronger afferent input to the non-affected hemisphere. Together, the previous studies indicate an important role of the non-affected hemisphere in the control of the affected limb during cooperative hand movement control.

The exact pathways involved in the functional coupling of the upper limbs, both in healthy and stroke individuals, are still not known. However, cooperative hand movements seem to be promising for their application in stroke rehabilitation as these movements are frequently required in daily life and strongly involve ipsilateral efferent and afferent pathways from and to the non-affected hemisphere in the control of the affected limb. A focussed training of these movements could therefore strengthen these pathways to optimize the recovery of the affected limb. Although cooperative hand movements seem to have a potential for their integration in stroke rehabilitation, there is currently no therapy approach focussing on this movement type. This gap is addressed in the second part of the thesis where the aim was to develop and evaluate a novel therapy approach focussing on cooperative hand movements.

1.5 Investigating cooperative hand movements and developing a therapy using a custom-built device

Everyday examples of cooperative hand movement tasks are cutting bread, peeling a carrot, winding up a blind and opening a bottle. To simulate such tasks, an existing custom-built device already applied in previous studies (Schrafl-Altermatt and Dietz, 2014; Schrafl-Altermatt and Easthope, 2018) was also used in the present thesis (Fig. 1.2). It consists of two handles that are connected over a shoe-type break. Rotational force applied from one hand to one handle is transferred to the other handle and has to be reciprocally counteracted by the other hand creating a cooperative movement setting (i.e., opening a bottle). Tightening or loosening of the break adjusts the current resistance and thus the force needed for the counteractive rotation of the handles. This allows for the execution of a repetitive and controlled cooperative hand movement task. Simultaneously, it is possible to apply neurophysiological methods to investigate the neural characteristics of this movement task as it was done in the first part of the present thesis.

The second focus of the present thesis was to develop and evaluate a novel therapeutic approach focussing on cooperative hand movements. Here, the aforementioned device was used as the therapy's core component on which cooperative hand movements are task-specifically trained. However, the device was modified to address several important factors contributing to a successful and efficient therapy.

One of these key factors is motivation. Especially when therapies include many repetitions of the same task or movement, patients lose interest due to monotony (O'Brien et al., 2019; Saywell et al., 2017). To overcome this issue, a playful and enjoyable training environment should be provided to maintain intrinsic motivation and to ensure a high training dose. This can be achieved by the use of virtual reality which becomes more and more popular in therapies (Holden, 2005; O'Brien et al., 2019; Villiger et al., 2017). Therefore, we developed a virtual reality system including several entertaining exergames for our device. The device was equipped with a potentiometer and a force sensor to record the relative position of the handles and the current resistance of the movement, respectively. These signals were transferred to a laptop via an integrated Bluetooth sensor and were used to control the available exergames by the manipulation of the handles.

To further prevent monotony and to increase the variety of cooperative tasks, two additional handles are available (Fig. 1.2, top right). They include a small nut simulating screwing in a nut onto a bolt and a crank simulating winding up a blind. These different handles can be easily attached and detached on one side of the device.

Other important aspects we aimed to address were accessibility and self-administration. Many robot-assisted therapies are now widely used and have been shown to be effective in restoring upper limb function (Franceschini et al., 2020; Klamroth-Marganska et al., 2014; Lum et al., 2004). However, some devices used for robotic therapy are stationary and need therapeutic supervision which limits permanent accessibility. In contrast, our device is portable and allows for self-administrable and unsupervised training at the patient's homes. Not only the device but also the corresponding virtual reality software are simple and intuitive to control. To support the usability of the device and the corresponding software, a handbook can be provided for each patient (see appendix). Further, the software automatically records information such as training duration, choice of games, and number of handle rotations to provide a detailed report about training content. This is especially important when training is performed without therapeutic surveillance. The development and evaluation of cooperative hand movement therapy using the described device is addressed in chapter 5.

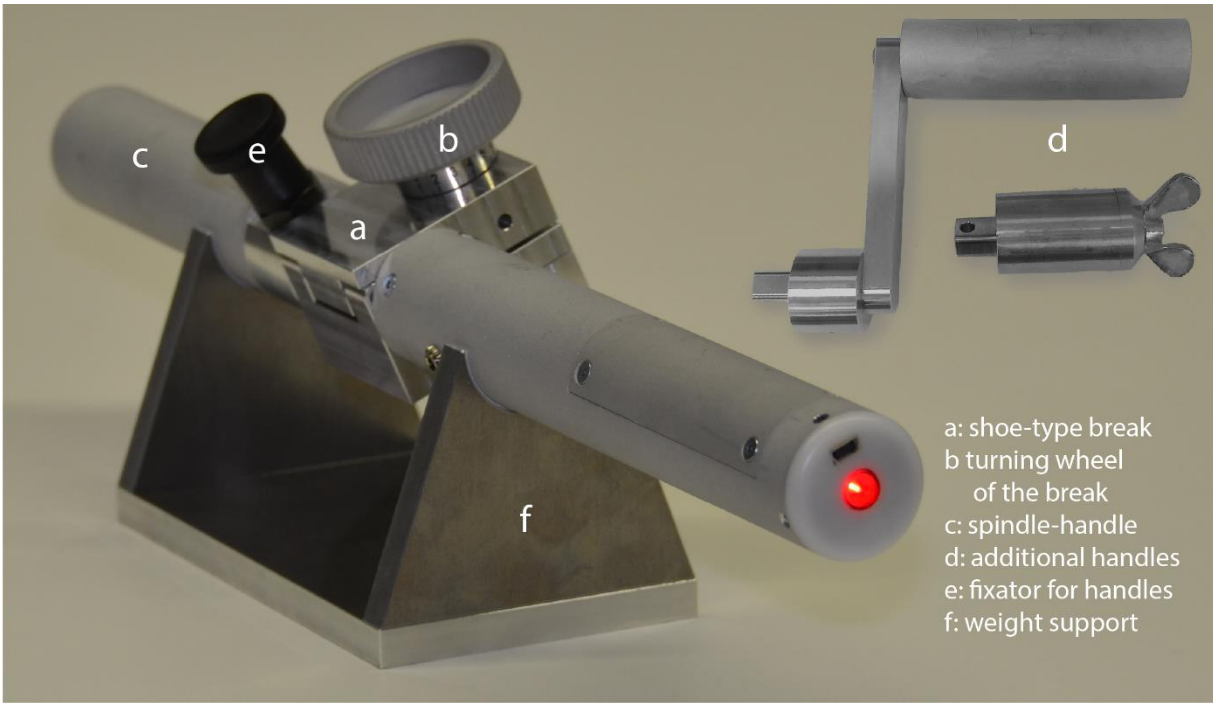


Figure 1.2: Device used in the experiments of the present thesis to simulate cooperative hand movements. It consists of two handles that are connected over a shoe-type break (a). Reciprocal wrist flexion and extension movements on the handles create a cooperative hand movement setting as force applied from one hand to one handle has to be counteracted by the other hand. Rotation of the turning wheel between the handles modifies the resistance, and thus the force needed for counteractive rotations (b). For the neurophysiological experiments (Chapter 2-4) the cylindrical “spindle” handle was used to simulate a bottle opening task (c). Additionally, a “crank” and a “nut” handle was used during the therapy (d) to increase the variety of cooperative tasks (d). These handles can be easily attached and detached using a fixator on the left side of the device (e). The device can be mounted on a separate weight support to compensate for the weight of the device (f).

1.6 Chapter overview

The overall objective of this thesis was to gain further insight into the sensorimotor control of cooperative tasks and to develop and evaluate a therapy approach based on these movements.

In **chapter 2** we aimed to assess how unimanual disturbances of sensory input effects the neural coupling since the processing and integration of sensory input from both hands has been suggested to be a crucial factor. Therefore, we assessed bilateral reflex responses during unilateral transient sensory deprivation of the hand. Contralateral reflex responses were enhanced on the sensory deprived limb and reduced on the non-deprived limb. The reduced sensory input from one hand might have disturbed the functional coupling between cortical sensory areas leading to the imbalance in efferent output. Clear contralateral reflexes occurred in both limbs despite sensory feedback of mainly one hand. This might suggest that sensory feedback of the non-deprived limb is processed and integrated in both hemispheres which preserves the neural coupling between the upper limbs.

In **chapter 3**, we investigated whether the neural coupling is sensitive to alterations in movement demands. Bilateral reflex responses were assessed after unilateral nerve stimulation during cooperative hand movements performed with different velocities and resistances. We observed that both the ipsi- as well as the contralateral reflexes linearly increased with the level of background activity associated with the increasing movement velocities and resistances. Clear contralateral reflex responses occurred even with low muscular pre-activation. Thus, the neural coupling seems to be a robust mechanism which serves to quickly and precisely match the forces between the limbs to ensure a successful solving of cooperative tasks.

In **chapter 4** we assessed whether the well predictable integrated sensory feedback from both hands during cooperative hand movements influences the adjustment of muscle activation and filtering of incoming sensory inputs. We demonstrated lower co-activation of forearm muscles and stronger reduction of SEPs during cooperative object manipulation as compared to non-cooperative object manipulations. These findings suggest that cooperative tasks underlie an efficient predictive forward control during which co-activation and the salience for external sensory input is reduced. This is associated with the availability of integrated feedback of both hands which increases predictability of the task.

In **chapter 5**, we developed ARCO (Cooperative Arm Rehabilitation) as a novel therapy approach focussing on cooperative hand movements and evaluated its feasibility and efficacy to improve upper limb function in chronic stroke survivors. We designed ARCO as self-administrable therapy with the possibility to apply it not only in a clinical setting but also at home without therapeutic supervision to improve accessibility. Patients trained for 2 weeks in a clinical setting followed by 4 weeks at home. Questionnaires revealed a positive feedback and a good feasibility for ARCO therapy. Upper limb function recovered significantly during the therapy. Therefore, ARCO therapy is proposed to have the potential for further application in stroke rehabilitation complementing existing therapies.

Chapter 6 summarizes and discusses the findings of this thesis followed by possible limitations. Additionally, future considerations for the investigation of cooperative hand movements and their application in neuro-rehabilitation are provided.

Chapter 2

Cooperative hand movements: Effect of a reduced afference on the neural coupling mechanism

Felix A. Thomas, Volker Dietz, Thiemo Scharfenberger & Miriam Schrafl-Altermatt: *Cooperative hand movements: effect of a reduced afference on the neural coupling mechanism. NeuroReport* **29**, 650-654 (2018).

2.1 Abstract

The aim of this study was to evaluate the influence of unilateral reduction of afferent input on the 'neural coupling' mechanism during cooperative hand movements. This 'neural coupling' is reflected in the task-specific appearance of contralateral reflex responses in forearm muscles to unilateral arm nerve stimulation. Sensory input from the right hand was reduced by ischemic nerve block at the right wrist. Ipsilateral and contralateral reflex responses elicited by stimulation of the ulnar nerve either at the left or the right wrist proximal to the nerve block were recorded in forearm extensors during the performance of cooperative hand movements. During ischemia of the right hand, a significant difference was found in the magnitude of the contralateral responses, that is, contralateral reflex responses in the right arm were significantly higher compared with the left arm ($p = 0.04$). Ipsilateral reflex responses were not affected by ischemic nerve block. The reduced afference from the ischemic hand during cooperative hand movements is assumed to weaken the activity in ipsilateral pathways involved in the neural coupling mechanism. Consequently, a shift in the interhemispheric balance might lead to the relative increase and decrease in the contralateral responses to left and right nerve stimulation, respectively. The study provides novel information on the involvement of ipsilateral hemispheres in the performance of cooperative hand movements.

2.2 Introduction

Most studies on upper limb motor control have focused on unimanual or bimanual non-cooperative (e.g. pro-supination) hand movements (Swinnen, 2002; Zehr and Kido, 2001). However, a number of activities of daily living, such as opening a bottle, require cooperative hand movements. It has been discovered that cooperative hand movements underlie a task-specific neural coupling mechanism that is not involved in the control of other bimanual movement tasks (Dietz et al., 2015). This task-specific coupling is reflected in the occurrence of bilateral electromyographic (EMG) reflex responses following unilateral arm nerve stimulation (Dietz et al., 2015; Schrafl-Altermatt and Dietz, 2016a). Furthermore, a functional MRI study reported extra-activation and functional coupling of bilateral secondary somatosensory (S2) cortical areas (Dietz et al., 2015). It appears that the shared sensory input from each hand to both hemispheres (Disbrow et al., 2001) is integrated and processed in S2 areas, which plays a key role in the task-specific neural coupling. In addition, increased amplitudes of ipsilateral somatosensory evoked potentials (Schrafl-Altermatt and Dietz, 2014; Schrafl-Altermatt and Dietz 2016b) indicate an involvement of ipsilateral and contralateral hemispheres in the neural coupling of cooperative hand movements. The objective of this study was to explore the effect of an artificially reduced afference because of ischemic nerve block (INB) from the right hand during cooperative hand movements on contralateral reflex responses and thus on the neural coupling mechanism. INB is a technique to induce a transient reduction in sensory perception and, consequently, in ascending drive to the brain (Brasil-Neto et al., 1993; Levy et al., 2002; McNulty et al., 2002; Sadato et al., 1995; Ziemann et al., 1998; Ziemann et al., 2001). It is hypothesized that the amplitudes of contralateral reflex responses following unilateral nerve stimulation are reduced in both right and left forearm muscles. This hypothesis is based on the assumption that ipsilateral and contralateral afferent pathways are involved in the neural coupling mechanism (Dietz et al., 2015; Schrafl-Altermatt and Dietz, 2014) and that disruption of the balance between the two hemispheres can lead to changes in the neural coupling (Schrafl-Altermatt and Dietz, 2016a). Accordingly, partial blocking of group I afferents of one hand was expected to lead to a bilateral reduction of reflex responses to unilateral nerve stimulation.

2.3. Methods

This study was approved by the local Ethics Committee of the Canton of Zürich and conformed to the standards set by the declaration of Helsinki. Before the experiment, all participants provided written informed consent. Twenty-four healthy individuals (15 women) with a mean age of 26 ± 3.1 years were included.

2.3.1 Experimental protocol

The protocol comprised the recording of EMG reflex responses in the ipsilateral and contralateral forearm extensor muscles to unilateral ulnar nerve stimulation during cooperative hand movements before (PRE), during (INB), and after (POST) ischemia of the right hand (Fig. 2.1a and b). In all conditions, volunteers were lying in a supine position. Cooperative hand movements (mimicking bottle opening and closing movements) were achieved by alternating rhythmic counteractive wrist flexion and extension movements (one movement cycle 1.33 s) on a device similar to that described previously (Dietz et al., 2015; Schrafl-Altermatt & Dietz, 2016a). The order of the side of nerve stimulation was pseudorandomized, that is, stimulations were applied first either at the right or left ulnar nerve during PRE, INB, and POST conditions, but the order was consistent throughout the conditions. Thus, the experiment consisted of six recording blocks (i.e. one block for each condition and side of stimulation). Throughout the experiment, the changes in the individual sensory perception were monitored.

2.3.2 Electrical nerve stimulation

Participants were stimulated 15 times every 3–8 s in each of the experimental conditions. The stimuli were used to evoke EMG reflex responses in the right and left extensor carpi radialis muscle. Stimulations were triggered randomly within the movement cycles. They were applied by a KeyPoint Focus (Natus, Pleasanton, California, USA) through self-adhesive surface electrodes (Ambu A/S Neuroline 700; Ambu A/S, Ballerup, Denmark) that were placed over the ulnar nerve at the wrist on the left side and proximal to ischemia on the right side with an interelectrode distance of 2 cm (cathode proximal to anode). Stimulation intensity was set to 150% of the motor threshold (MT), that is, the lowest intensity resulting in a visible twitch of the abductor digiti minimi muscle. Stimulations consisted of a burst of four biphasic pulses of 1ms duration per pulse, each separated by 2 ms, resulting in a total stimulus duration of 10 ms.

2.3.3 Electromyographic recordings

EMG activity of the extensor carpi radialis of both forearms was recorded (proximal to ischemia) using disposable self-adhesive AG/AgCl dual surface electrodes with an interelectrode distance of 1.75 cm (Noraxon, Scottsdale, Arizona, USA). Data were sampled (1500 Hz), band-pass filtered (10–10 000 Hz), and post-processed as described previously (Schrafl-Altermatt and Dietz, 2016a). The root mean square (RMS) of the rectified EMG signal was calculated for the time window between 75 and 135 ms after stimulus onset as this period is known to include the main components of the late (i.e. N2, P2) ipsilateral and contralateral reflex response (Dietz et al., 2015). The RMS values were normalized by dividing them by the RMS of the rectified background activity calculated over the prestimulus time window from −30 to −10 ms.

2.3.4 Ischemic nerve block

INB was achieved by a pneumatic tourniquet applied at the right wrist. The tourniquet was inflated after the PRE condition above systolic pressure (250mmHg) and was maintained constant until completion of the reflex recordings of the INB condition, which was started after 25 min of ischemia and lasted over about 10 min. Subsequently, the tourniquet was released and participants recovered for 15 min before the POST condition was performed.

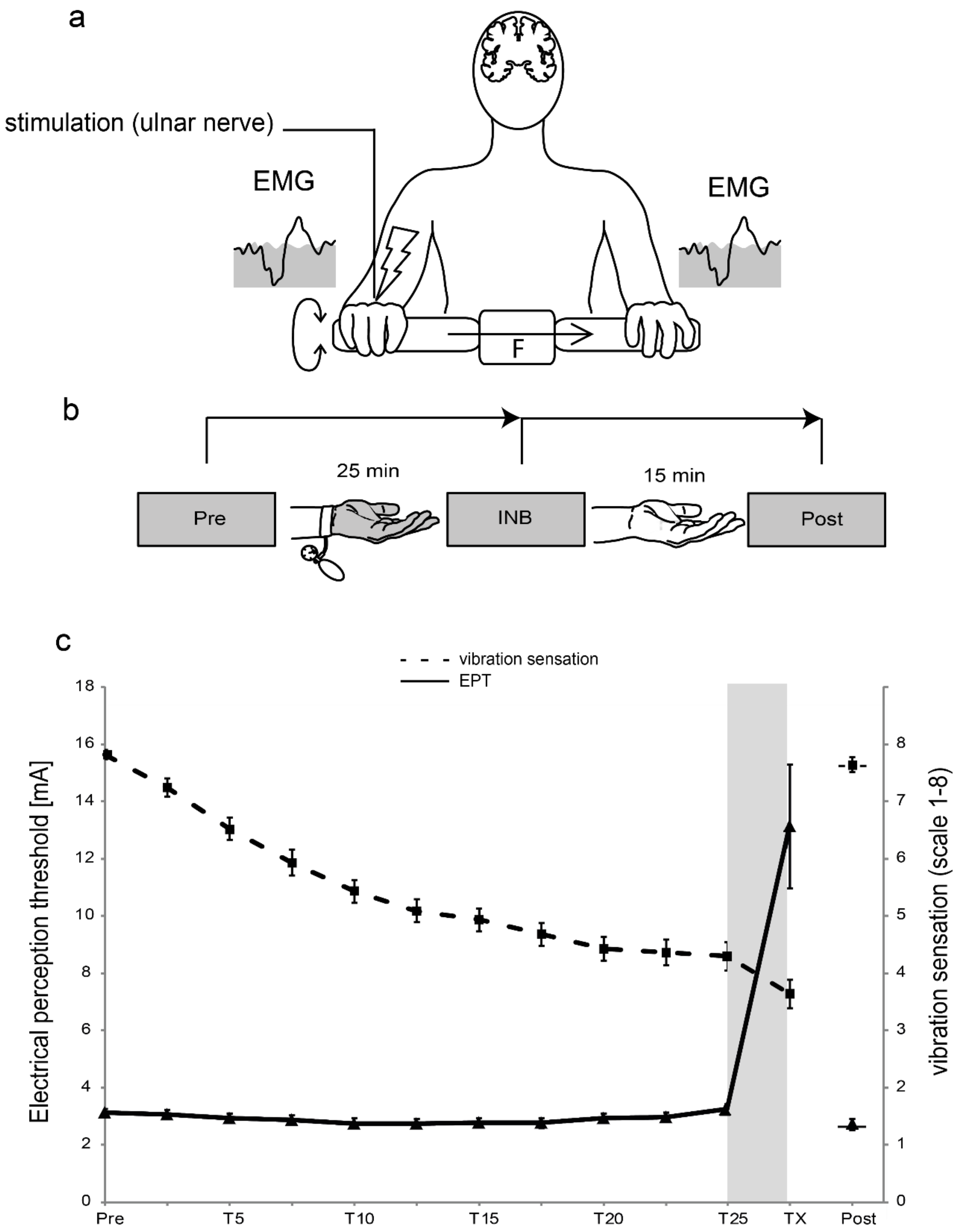


Figure 2.1: Study design. a) Experimental Setup. b) Measurement protocol. The experimental setup was performed in the conditions Pre, INB and Post. c) Course of sensory perception during ischemic nerve block (INB) starting at T0. Left axis: Electrical perception threshold (EPT). Right axis: Vibration sensation (right axis). The grey bar displays the time period of the ‘INB’ condition where reflex responses were recorded. This period lasted until TX (i.e. release of INB). Error bars represent the standard error (SE). Note that for EPT Pre-T25 triangles overlap the error bars.

2.3.5 Sensory perception monitoring

During the 25 min of INB, sensory perception of the right hand declined. During this phase and during the 15-min recovery phase after INB, sensory perception was assessed every 2.5 min (Fig. 2.1c). Two different methods were used to assess perception: electrical perception threshold (EPT) and vibration sensation (VS). For EPT, electrical stimulations were applied at the palmar side of the right middle finger with a frequency of 3.1 Hz with stepwise increasing intensity until the participant reported a sensation (average of three trials). For VS, a tuning fork was applied at the metacarpophalangeal joint of the right middle finger until the participant reported the cessation of VS (scale ranging from 8 to 1, where 8 is normal perception).

2.3.6 Statistical analysis

Data processing and analysis were carried out using MatLab v. 2013b (Mathworks, Natick, Massachusetts, USA) and Soleasy (Alea Solutions GmbH, Zurich, Switzerland). SPSS, version 23 (IBM Statistics, Chicago, Illinois, USA) was used for all statistical procedures. After log10 transformation, differences in the normalized RMS of the EMG reflex responses for the entire sample were calculated using a 2 × 3 repeated-measures analysis of variance (ANOVA) [stimulation side (right, left) × conditions (PRE, INB, POST)] with interaction. Side differences in MT and post-hoc tests were performed using paired t-tests corrected for multiple comparisons with Bonferroni's correction. Corrected p values below 0.05 were considered significant. In addition, effect sizes were calculated for the ANOVA as partial eta-squared (η_P^2) and for paired t-tests as Cohen's d. If not stated otherwise, all values are given as mean ± SD.

2.4 Results

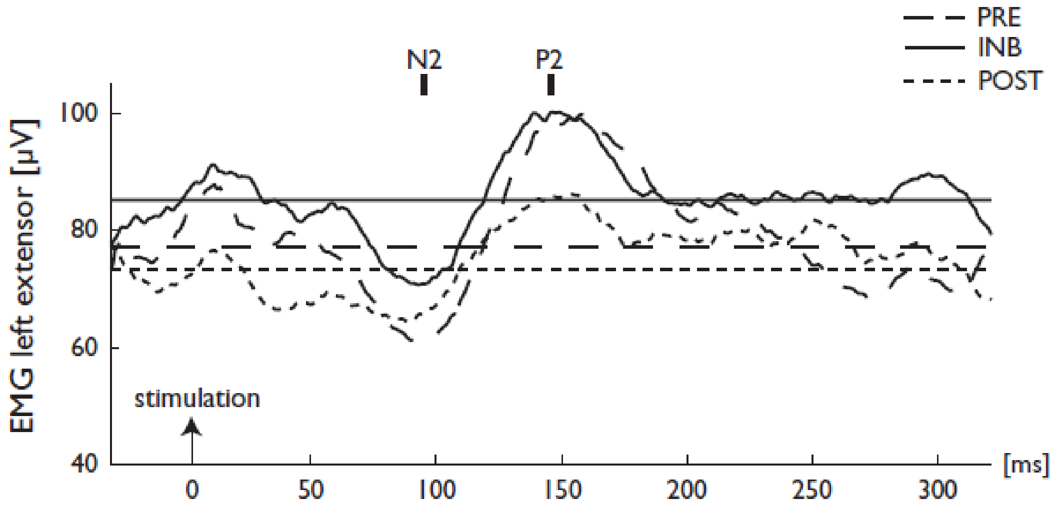
2.4.1 Reduced sensory perception

EPTs started at 3.0 ± 0.7 mA before the PRE condition and amounted to 3.24 ± 0.7 mA before INB. A steep increase in EPT occurred from T25 to TX, that is, during the INB condition, resulting in an EPT of 13.3 ± 10.1 mA after the INB condition. VS was 7.8 ± 0.36 at the beginning of the experimental procedure and decreased almost linearly during ischemia, resulting in a VS of 4.2 ± 1.1 before and 3.6 ± 1.1 after the INB condition, respectively. After TX, when INB was released, both EPT and VS returned to baseline values.

2.4.2 Ipsilateral and contralateral muscle reflex responses

Figure 2.2a shows the grand averages (n= 21) of the contralateral EMG reflex responses in the left forearm extensor muscle during the three experimental conditions (PRE, INB, and POST) of cooperative hand movements. All responses were clearly above the respective level of background EMG. During INB, contralateral reflex responses in the left arm were smaller compared with PRE. In contrast, the contralateral reflex response in the right extensor was increased during INB compared with PRE (Fig. 2.2b). These differences were not statistically significant. In Fig. 2.3, the quantitative data of the extensor reflex responses (expressed as reflex RMS normalized to the background activity RMS) are shown. No significant effect of INB could be observed in ipsilateral reflex responses, either in the right (PRE: 2.45 ± 0.74; INB: 2.74 ± 0.99; POST: 2.76 ± 1.41) or in the left (PRE: 2.62 ± 1.03; INB: 3.45 ± 3.35; POST: 2.38 ± 0.83) extensor [side: $F_{(1,20)} = 0.26$, $p = 0.80$, $\eta_P^2 = 0.003$; conditions: $F_{(2,40)} = 1.59$, $p = 0.23$, $\eta_P^2 = 0.14$; side × condition: $F_{(2,40)} = 1.15$, $p = 0.33$, $\eta_P^2 = 0.11$]. For contralateral reflex responses, repeated-measures ANOVA showed a significant interaction effect of side and condition [$F_{(2,40)} = 3.99$, $p = 0.02$, $\eta_P^2 = 0.17$]. Post-hoc tests indicate that this interaction effect is because of the significant difference in the right (PRE: 1.95 ± 0.66; INB: 2.22 ± 1.1; POST: 1.54 ± 0.42) and left (PRE: 2.02 ± 1.46; INB: 1.57 ± 0.40; POST: 1.86 ± 1.04) extensor muscles during INB ($p = 0.04$, $d = 0.265$). Here, we observe increased reflex responses in the right extensors compared with reduced responses in the left extensors (Fig. 3b). However, ANOVA showed no significant main effects for either the side of stimulation [$F_{(1,20)} = 0.99$, $P = 0.33$, $\eta_P^2 = 0.05$] or the condition [$F_{(2,40)} = 2.36$, $p = 0.108$, $\eta_P^2 = 0.11$].

(a) Contralateral reflex responses in the left extensor muscle



(b) Contralateral reflex responses in the right extensor muscle

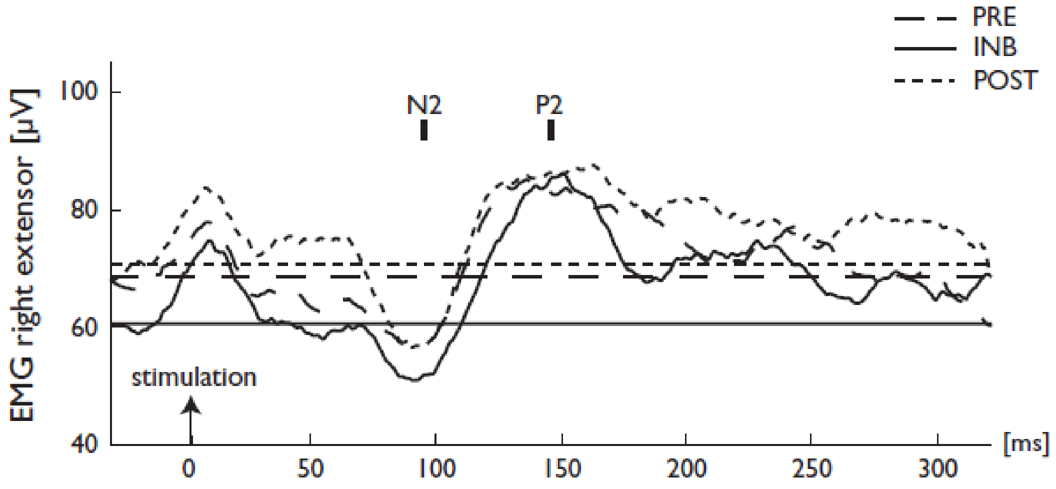
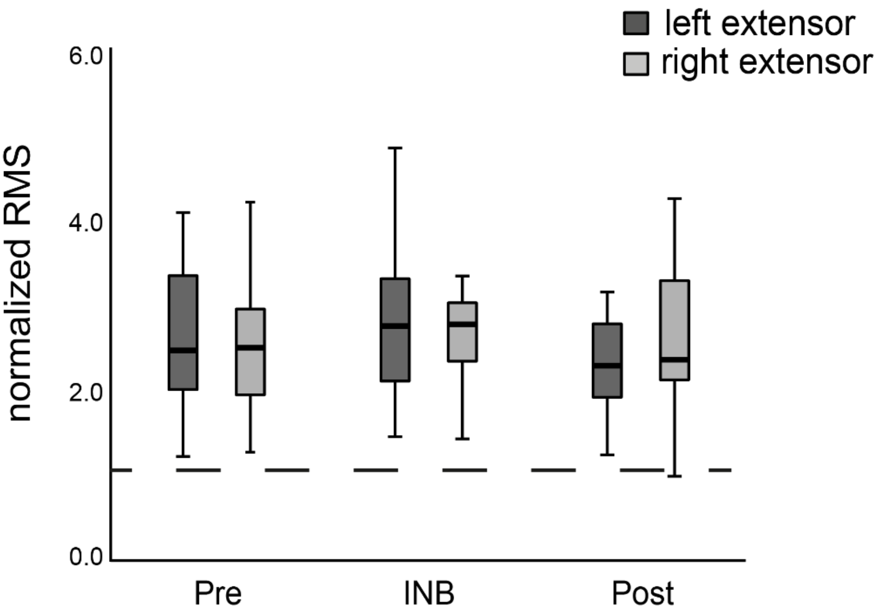


Figure 2.2: Grand averages (n = 21) of contralateral reflex responses recorded before (Pre), during (INB) and after (Post) ischemic nerve block. a) Contralateral reflex responses in the left forearm extensor muscle (i.e. stimulation of the right ulnar nerve). b) Contralateral reflex responses in the right forearm extensor muscle (i.e. stimulation of the left ulnar nerve). Horizontal lines display the respective RMS value of the background activity. N2 & P2 mark the peaks of the reflex responses. EMG: Electromyography


a ipsilateral reflex response

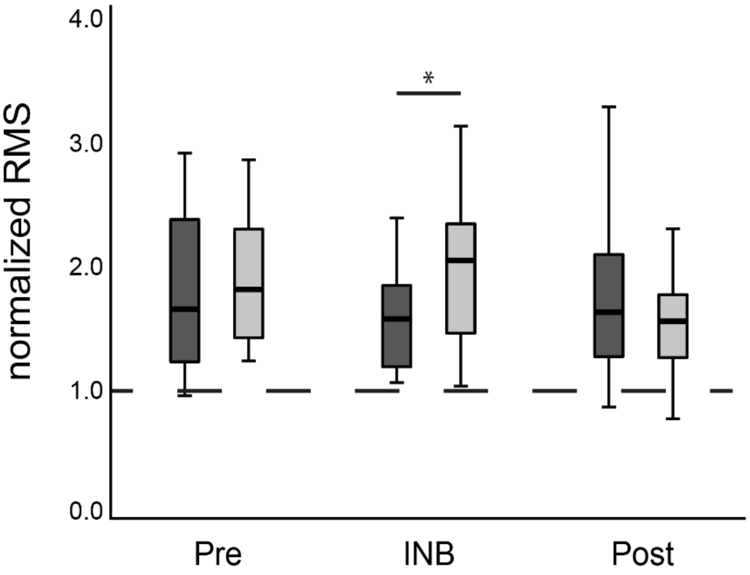

b contralateral reflex response

Figure 2.3: Quantitative RMS values of ipsi- and contralateral reflex responses normalized to the background activity before (Pre), during (INB) and after (Post) ischemic nerve block. The quantified averages of the reflex EMG responses in the forearm extensor muscle from the whole subject sample (n = 21) are displayed (a) ipsilateral and (b) contralateral to the site of stimulation. The dashed horizontal line displays the background activity. Boxes represent the interquartile range (25th-75th percentile) separated by the median. Asterisks indicate a significant difference ($p<0.05$).

2.5 Discussion

The aim of this study was to explore the influence of reduced afferent input from the right hand, achieved by INB, on the neural coupling mechanism underlying cooperative hand movements. The main result consisted of significantly increased contralateral reflex responses in the right compared with the left arm during INB. Ipsilateral reflex responses were neither different between the sides nor the PRE, INB, and POST conditions. INB on an upper limb is known to induce short-term changes in the sensorimotor cortex including an increased output to muscles proximal to ischemia following transcranial magnetic stimulation during rest (Brasil-Neto et al., 1992; Ridding and Rothwell, 1995; Ziemann et al., 1998). Translated to our study, enhanced reflex responses in right forearm extensors would be expected to occur. This was, however, only true for contralateral responses and not for ipsilateral ones. The lack of general increase in muscle responses proximal to INB in our study was most probably because of the dynamic movement conditions used here. It has been shown that increased muscle responses can only be observed in resting muscles, an effect that becomes lost with muscle activation (Ridding and Rothwell, 1995, 1997). Therefore, the increase in contralateral reflex responses cannot be explained by known INB effects, that is, the modulation of reflex amplitude found here seems to be specific for the neural coupling. In view of our hypothesis, the side difference in reflex amplitude modulation was unexpected. We only partially succeeded with our goal to further elucidate the pathways involved in neural coupling. The main finding might best be interpreted on the basis of the observations made so far, that is, the essential role of ipsilateral hemispheres in the neural coupling mechanism. The enlarged ipsilateral somatosensory evoked potential during cooperative hand movements (Schrafl-Altermatt and Dietz, 2014) indicates an enhanced afferent inflow to the ipsilateral hemisphere that becomes task-specifically processed in the S2 cortical areas (Dietz et al., 2015). This area is known to exchange and integrate the afferent input from both hands (Dietz et al., 2015; Lin and Forss, 2002), leading to interhemispheric unification (Hari et al., 1998). In this study, the afferent input from the right hand is reduced compared with that from the left hand. It is assumed that this asymmetrical afferent input from the hands causes a bias in the unification. Thus, during INB, an imbalance in the functional coupling of S2 areas is expected to occur (Dietz et al., 2015), leading also to an imbalance in the generation of the contralateral reflex responses. The reduced contralateral response in the left forearm extensors might be caused by an attenuation of neural coupling from the right to the left side because of the reduced afference originating from the right cooperating hand. As a consequence, the increase in the contralateral reflex amplitude in the right forearm extensors might be because of a shift in the interhemispheric balance (Kičić et al., 2008; Ziemann et al., 1998). An interesting aspect of this study is that the effects of INB were only related to the behaviour of contralateral reflex responses. This confirms previous findings of task-specific activation of ipsilateral pathways during cooperative hand movements by an interaction of the two hemispheres. A shift in balance between the hemispheres might impact the bilateral efferent reflex output. Despite the sensory deficit of one hand, distinct contralateral reflex responses occurred irrespective of the site of stimulation, that is, the neural coupling remained preserved. In contrast, neural coupling was strongly impaired, with absent contralateral reflex responses in stroke patients when the affected arm with slight sensory deficit was stimulated (Schrafl-Altermatt & Dietz, 2016a). This difference might be because of an impaired processing of sensory information in the affected hemisphere (Lemon, 2008).

2.6 Conclusion

This study underlines the significance of the interaction between ipsilateral and contralateral hemispheres in the control of cooperative hand movements by a neural coupling mechanism. The study shows that a reduced sensation of one hand during cooperative movements leads to an imbalance in the processing and interhemispheric unification of the shared bimanual afferent input. Consequently, the distribution of bilateral reflex output to unilateral nerve stimulation is asymmetrical.

Chapter 3

Automatic gain control of neural coupling during cooperative hand movements

Felix A. Thomas, Volker Dietz & Schrafl-Altermatt, M. *Automatic gain control of neural coupling during cooperative hand movements*. *Scientific reports* **8**, 5959 (2018)

3.1 Abstract

Cooperative hand movements (e.g. opening a bottle) are controlled by a task-specific neural coupling, reflected in EMG reflex responses contralateral to the stimulation site. In this study the contralateral reflex responses in forearm extensor muscles to ipsilateral ulnar nerve stimulation was analyzed at various resistance and velocities of cooperative hand movements. The size of contralateral reflex responses was closely related to the level of forearm muscle activation required to accomplish the various cooperative hand movement tasks. This indicates an automatic gain control of neural coupling that allows a rapid matching of corrective forces exerted at both sides of an object with the goal ‘two hands one action’.

3.2 Introduction

The neural control of bimanual hand movements is known to be task-and condition-specific (Donchin et al., 1998; Goble et al., 2010; Grefkes et al., 2008; Johansson et al., 2006; Puttemans et al., 2005; Swinnen, 2002; Theorin and Johansson, 2007). Cooperative hand movements, such as opening a bottle, were shown to be task-specifically controlled by a ‘neural coupling’ mechanism (Dietz et al., 2015). This neural coupling is thought to coordinate the movements between the two hands, i.e. one hand supports the action of the other one. It is task-specifically reflected in the appearance of EMG reflex responses in the activated forearm muscles of both sides to unilateral arm nerve stimulation, while during bimanual non-cooperative hand movements only ipsilateral reflex responses appear (Dietz et al., 2015). This observation indicates an involvement of both ipsi-and contralateral hemispheres in the control of cooperative hand movements. Hitherto, the neural coupling mechanism was investigated using a standard protocol, i.e. movement speed 0.75 Hz and 20% maximal voluntary contraction (MVC). The aim of this study was to evaluate the effect of varying movement resistance and velocity on the neural coupling. From earlier studies it is known that the amplitude of reflex activity ipsilateral to the site of stimulation depends on the level of background muscle activity of the muscle that becomes perturbed by stretching (Marsden et al., 1972; Marsden et al., 1976; Matthews, 1986; Pruszynski et al., 2009a) or by electrical arm nerve stimulation (Uysal et al., 2012). This behaviour was interpreted as an automatic servo action to rapidly compensate for movement perturbations. In this study the perturbation induced during cooperative hand movements does not consist in a muscle stretch but in a non-noxious arm nerve stimulation with the focus directed to the reflex behaviour contralateral to the site of stimulation. It is hypothesized that the behaviour of contralateral reflex responses is coupled to that of the ipsilateral ones in order to match the forces exerted at the object between the two sides, i.e. a more demanding movement condition might lead to a stronger neural coupling.

3.3. Methods

This study was approved by the local Ethics Committee of the Canton of Zürich and conformed to the standards set by the declaration of Helsinki. All subjects were informed about the experiment and had to give written consent before any measurements were conducted.

3.3.1 Experimental protocol

EMG reflex responses to unilateral right ulnar nerve stimulation were recorded in forearm extensor and flexor muscles of both sides (Fig. 3.1) during cooperative hand movements in fifteen healthy subjects (age: 27.0 ± 6.2 years; 10 female/5 male). For the cooperative movement tasks a device was used that allowed counteractive rotations of handles, similar to that described previously (Dietz et al., 2015). With this device, movements were performed with rhythmic alternating antiphase wrist extension and flexion mimicking a “bottle opening” task (Fig. 3.1). For different movement conditions, three velocities (0.5Hz, 0.75Hz and 1Hz,i.e, one flexion/extension cycle lasted for about 2s, 1,33s or 1s, respectively) and three resistances (10%, 20% and 30% of maximal voluntary contraction (MVC)) were chosen. Every resistance condition was performed at each of the three movement frequencies resulting in a total of nine conditions. MVC was determined as the highest value of three maximal isometric wrist extension movements of the non-dominant arm. A mechanical break between the handles of our device allowed to change the resistance exerted by the break. Thus, the resistance could be exactly set to the individual & MVC for each subject and for every condition. Frequencies were indicated by a metronome.

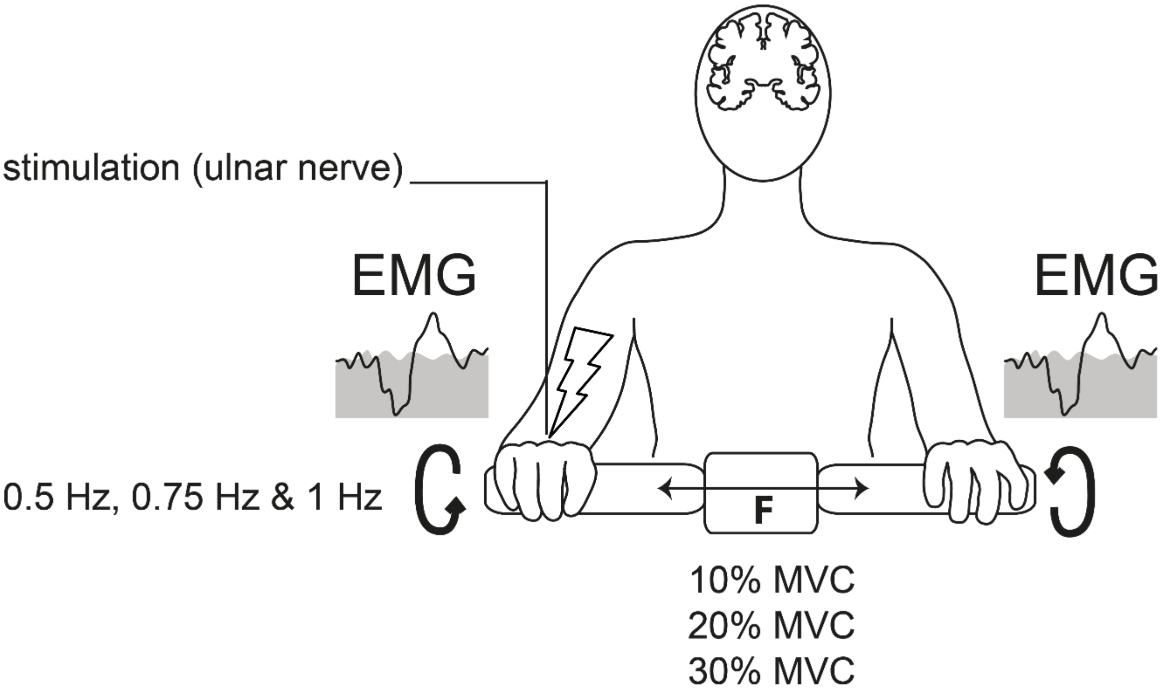


Figure 3.1: Experimental setup and device used. Electrical stimulations were applied during cooperative hand movements with different movement demands (i.e. three wrist extension/flexion frequencies against three resistances). The handles of the device used are mechanically coupled i.e. during cooperative hand movements the torque produced from one limb has to be counteracted by the other limb.

3.3.2 Electrical nerve stimulation

The ulnar nerve of the right arm was stimulated with a Keypoint Focus (Natus®, Pleasanton, USA) through self-adhesive surface electrodes (Ambu® A/S Neuroline 700, Denmark) 10 times every 3-8s during each of the conditions. The movement condition in previous studies (i.e. 20% MVC with 0.75Hz frequency (Dietz et al., 2015; Schrafl-Altermatt and Dietz, 2016a; Schrafl-Altermatt and Dietz, 2014) allowed for 30 stimulations (i.e. 15 per side) while the condition 1Hz frequency against 30%MVC in the present protocol is difficult to maintain for a similar duration. Thus, we reduced the number of stimulations to 10 in order to prevent fatigue and to maintain a standardized movement execution throughout every condition. The stimulation electrodes (inter-electrode distance 2cm, cathode proximal) were placed just proximal to the wrist crease. Stimulations were triggered randomly within the movement cycles. Stimulations were timed to the onset of the movement cycle in previous studies. We used a slightly different device in the present study where automatic triggering of a stimulation related to a specific position was not possible. Stimulation intensity (SI) was set at 150% above motor threshold (MT - first visible twitch of the abductor digiti minimi). Stimulations consisted of a

333Hz train of four biphasic pulses of 1ms duration resulting in a total stimulus duration of 10ms. There are two factors which have determined the number of executed movement cycles namely the movement frequency of the condition (0.5Hz, 0.75Hz, and 1Hz) and the stimulus frequency (variation between 3 and 8 seconds). Ten stimulations were applied in each condition. Given an example frequency of 1Hz (i.e. 1 movement cycle/s), participants performed between 30-80 movement cycles (depending on the stimulations) for this condition.

3.3.3 EMG recordings

EMG activity of wrist extensor (extensor carpi radialis) and flexor (flexor carpi ulnaris) muscles of both forearms was recorded (Noraxon, Scottsdale, AZ, USA) using two single hydrogel knob surface electrodes (Kendall^{TM} H124SG, 2.4 cm diameter), sampled (1500 Hz), band-pass filtered (10–10.000 Hz) and post-processed as previously described. The root mean square (RMS) of the rectified signal in the time window between 75 ms and 135 ms after stimulation onset was calculated including the main components (i.e. N2, P2) of the reflex response. The RMS of the rectified reflex response was normalized to the background activity −30 ms to −10 ms pre-stimulation. Different levels of MVC between the subjects resulted in heterogeneous levels of the corresponding background EMG in the different conditions. Therefore a normalization procedure of background EMG was performed for every subject before the descriptive analysis (e.g. grand average) of the data. The absolute and the normalized RMS values of the reflex responses were grouped for the different movement conditions (i.e. for each velocity condition the mean values of the reflex responses obtained during the movements against three resistances were averaged, and vice versa, for each resistance condition the mean values of the reflex responses obtained during the three velocities were averaged).

3.3.4 Statistical analysis

All statistical procedures were performed using the SPSS version 23 (IBM® Statistics). To test whether a contralateral reflex response was evoked, absolute EMG RMS values of every condition and the grouped RMS values were tested with a two-sided Wilcoxon signed rank test in relation to the corresponding background RMS. One-way repeated measures ANOVAs were used to compare the grouped absolute RMS reflex responses between the movement conditions. Paired two-sided T-Tests were chosen as post-hoc tests. Grouped normalized RMS values were not normally distributed, thus, Friedman tests were used to detect possible between the different movement conditions. The correlation between background muscle activity and reflex magnitude was calculated with Pearson correlation for grouped ipsilateral and contralateral responses. In all tests, p-values lower than 0.05 were considered as significant. All tests were corrected for multiple comparisons with a Bonferroni correction. If not stated otherwise, absolute and normalized RMS values are given as median and interquartile range (IQR, 25th-75th percentile).

3.4 Results

Data was analyzed from all fifteen subjects. All subjects were able to perform the nine movement conditions (i.e. each movement velocity was performed against each movement resistance, Fig 3.1). The analysis of reflex responses was focused on the forearm extensor muscles contralateral to the stimulation site as a marker for the neural coupling mechanism. Distinct reflex responses were present in the forearm muscles contralateral to the site of nerve stimulation during all conditions. Wilcoxon signed ranked tests revealed that RMS values of the reflex response differed significantly from those of the background EMG in all conditions (all $p < 0.01$). Fig. 3.2b shows the relationship between reflex amplitudes and level of background EMG. The grand averages of the contralateral reflex responses are shown during a movement frequency of 0.75 Hz at three resistances. The plots show that the stronger the level of background activity was, the larger were the reflex response amplitudes. Fig. 3.2c shows the box plot of the absolute RMS values of the reflex responses grouped for the three movement velocities/frequencies and resistances. The reflex amplitude increased significantly from 0.5Hz (51.2, 36.2 – 61.8 µV) to 0.75Hz (56.4, 47.3 – 79.8 µV) ($t(14) = -3.69$, $p = 0.014$) and from 0.5Hz to 1Hz (64.7, 55.7 – 83.6 µV) ($t(14) = 3.71$, $p = 0.014$). The RMS of the reflex responses grouped for the three resistances increased significantly from 10% (42.4, 31.7 – 59.5 µV) to 20% MVC (65.6, 52.2 – 70.3 µV) ($t(14) = -3.69$, $p = 0.014$), from 10% to 30% ($t(14) = -5.43$, $p = 0.0005$) and from 20% to 30% MVC (72.4, 55.5 – 98.3 µV) ($t(14) = -4.04$, $p = 0.007$). When the reflex amplitudes were normalized to the background activity, Friedman tests revealed no significant difference between the resistances ($Chi^2(2) = 1.733$, $p = 0.42$) or velocities ($Chi^2(2) = 0.133$, $p = 0.93$) conditions (Fig. 3.2c). Pearson correlation coefficient revealed a strong correlation between the level of background muscle activity and the magnitude of the reflex response for both contralateral ($r = 0.860$, $p < 0.001$, Fig 3.3a) and ipsilateral ($r = 0.810$, $p < 0.001$, Fig. 3.3b). The mean latency of the contralateral EMG reflex responses across all movement conditions amounted to 88.7 (80.7 – 93.3 ms). There was no significant difference in latency between the different conditions.

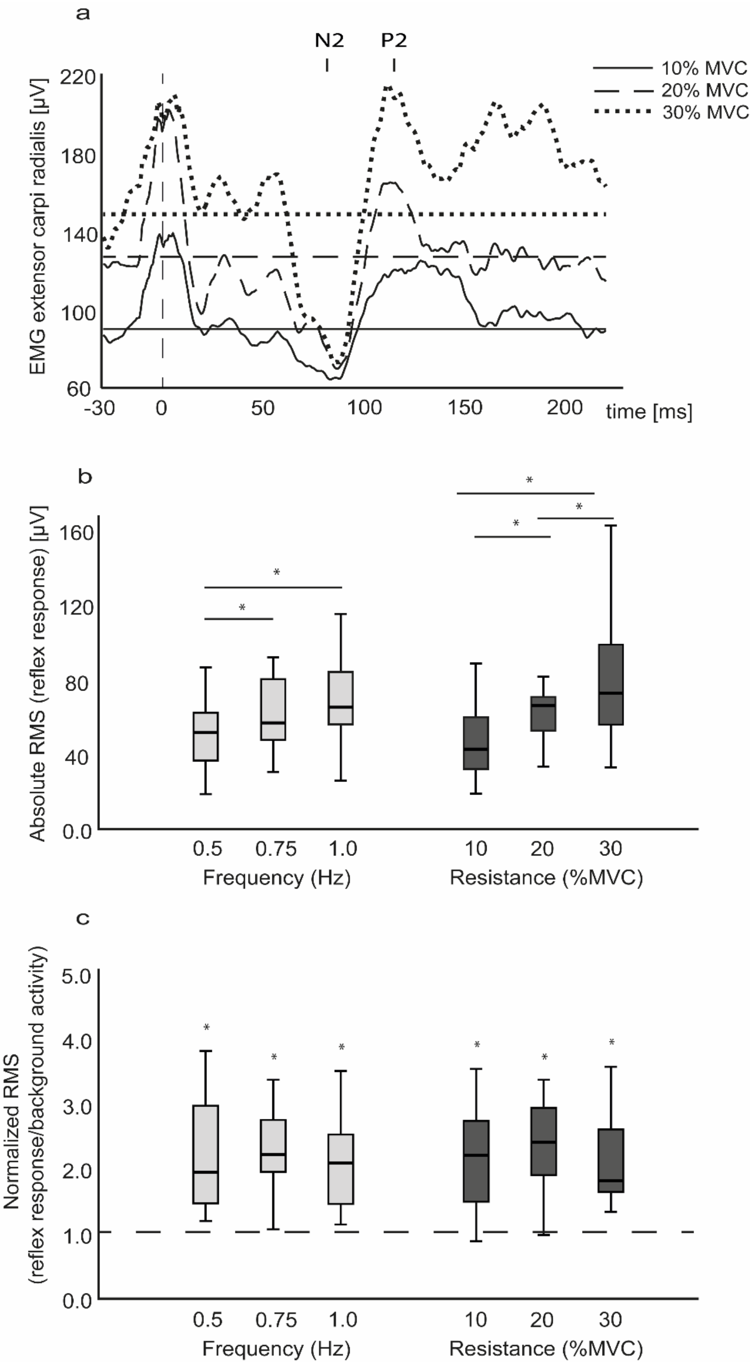


Figure 3.2: Influence on the contralateral EMG reflex response to different movement conditions. a) Grand averages of the contralateral EMG reflex responses at 0.75Hz movement velocity against three resistances from all subjects (n=15). The horizontal lines indicate the levels of pre-stimulus muscle activity of the forearm extensor. The vertical dashed line indicates the time point of stimulation. N2 and P2 represent the negative and positive components of the contralateral reflex response (see methods); b) Absolute contralateral EMG reflex response amplitudes from all subjects (given as RMS). Asterisks indicate significant differences between conditions; c) Contralateral EMG reflex responses normalized to prestimulus muscle activity (horizontal dashed line) from all subjects. Asterisks indicate significant differences between reflex response and prestimulus muscle activity. In b and c, boxes represent the interquartile range (25th-75th percentile) separated by the median. Outliers were removed from the box-plots for illustration purpose.

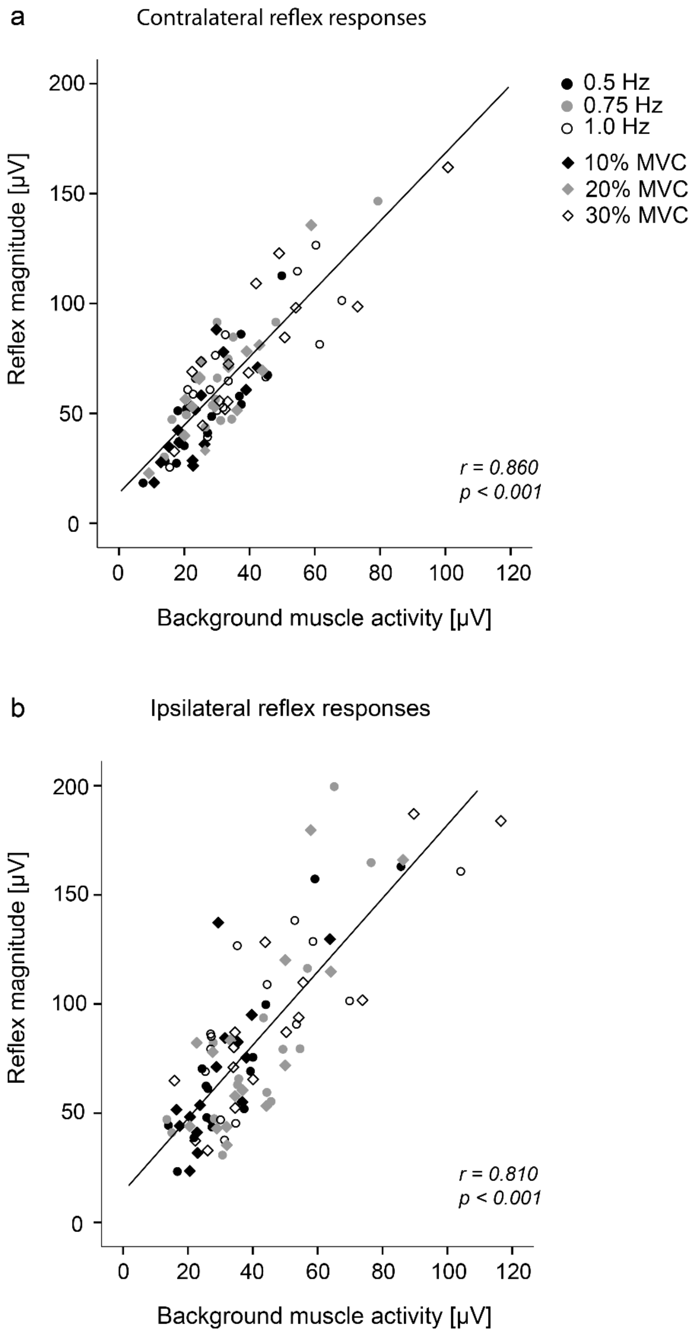


Figure 3.3: Relationship between the level of background muscle activity [µV] and the reflex magnitude [µV] in the extensor muscle for all subjects a) contralateral and b) ipsilateral to the side of stimulation (n=15). Samples were grouped according to the movement conditions ‘velocity’ and ‘resistance’ (see Methods section). Both plots show a strong linear correlation i.e. the higher the level of background muscle activity, the higher the corresponding reflex response.

3.5 Discussion

The aim of this study was to explore the influence of movement velocity (i.e. change in frequency) and resistance during cooperative hand movements on the neural coupling mechanism. This neural coupling is reflected in the task-specific appearance of reflex EMG responses (i.e. not present during separate non-cooperative movements) in forearm muscles contralateral to the site of stimulation (Dietz et al., 2015). The main result obtained were, 1. Contralateral reflex responses appeared in all movement conditions even at slow velocity and low resistance; 2. The increase in size of contralateral reflex responses paralleled the level of forearm muscle activity associated with higher movement velocities and resistances, i.e. the ratio of reflex response amplitude to background EMG amplitude remained constant. It has been shown for cyclic movements of the upper limb that cutaneous reflexes are modulated depending on the movement phase (Zehr and Kido, 2001). Randomly released stimuli might therefore lead to non-standardized reflex magnitudes within a movement condition. However, averaging all EMG responses within one condition will minimize a possible bias in reflex magnitude related to different movement phases. This issue is further compensated by normalizing the reflex magnitude to pre-stimulus muscle activity (instead of normalization to unstimulated (dummy) EMG within the same time window; see section “EMG recordings”). In earlier studies on the behavior of reflex responses a dependency of the ipsilateral reflex response on the intensity of mechanical stimulation was thought to compensate for limb disturbance (Marsden et al., 1972; Marsden et al., 1976; Matthews, 1986) (for review Deuschl and Lücking, 1990). Later on, the appearance of reflex responses not only in the perturbed limb but also in non-stimulated, synergistically acting limb muscles was described to occur during functional movements such as locomotion (Kloter et al., 2011), arm cycling (Zehr and Kido, 2001) or cooperative hand movements (Dietz et al., 2015). In these studies not mechanical stimuli but nerve stimulation was used to induce limb perturbations. The present study shows that the contralateral reflex response amplitude to unilateral nerve stimulation automatically increases with the level of background EMG, i.e. with the effort exerted by the hands, produced by muscles of both forearms involved in the performance of the cooperative task. Such an increase of reflex gain with the level of muscle activation was hitherto reported only for perturbing the ipsilateral thumb muscle (Marsden et al., 1976). An automatic gain scaling of short latency spinal reflexes was described (Pruszynski et al., 2009). Such a behaviour can hardly be expected to occur in forearm muscles contralateral to the site of stimulation. Here we can show for the first time that such an automatic gain scaling of long-latency reflex activity occurs contralateral to the site of stimulation. It is suggested that this reflex behaviour reflects the functional significance of the neural coupling. By this mechanism, the level of forearm muscle activation, required for an effective performance of the various cooperative hand movement tasks becomes matched between the two sides, i.e. the reciprocal forces acting on an object have to be adjusted to a level that is needed to overcome the resistance and to rapidly compensate any perturbation (e.g. unilateral nerve stimulation) simultaneously on both sides. Any difference in effort produced between the hands would not allow the successful performance of the task, e.g. to open a bottle. This observation fits with the idea of an ‘automatic gain scaling’ or ‘automatic servo action’ of reflex behaviour (Marsden et al, 1972; Marsden et al, 1976; Matthews et al, 1986; Pruszynski et al, 2009). Based on the present study this reflex behavior on the ipsilateral stimulated side can now be extended to the contralateral cooperative but not perturbed hand/arm. It has to remain open what exact pathways are mediating the automatic adjustments. Nevertheless it is obvious that ipsi- as well as contralateral hemispheres have to be involved in the neural coupling mechanism. The observations made here support the idea of a ‘two hands—one action’ mechanism. However, it has to remain open in how far this idea can be generalized to more complex movements requiring unequal contributions of both hands for a unified action. In conclusion it could be shown that during cooperative hand movements an automatic scaling of reflex activity does not only take place ipsilateral (Marsden et al, 1976; Matthews et al, 1986) but also contralateral to the site of stimulation.

Chapter 4

Movement predictability modulates sensorimotor processing

Thomas FA., Wenderoth N., Schrafl-Altermatt M., *Movement predictability modulates sensorimotor processing. (In preparation)*

4.1 Abstract

An important factor for optimal sensorimotor control is how well we are able to predict sensory feedback from internal and external sources during movement. If predictability decreases due to external disturbances, the brain is able to adjust muscle activation and the filtering of incoming sensory inputs. However, little is known about sensorimotor adjustments when predictability is increased by availability of additional internal feedback. In the present study we investigated how modifications of internal and external sensory feedback influence the control of muscle activation and gating of sensory input. Co-activation of forearm muscles, somatosensory evoked potentials (SEP) and short afferent inhibition (SAI) were assessed during three object manipulation tasks designed to differ in the predictability of sensory feedback. These included manipulation of a shared object with both hands (predictable coupling), manipulation of two independent objects without (uncoupled) and with external interference on one of the objects (unpredictable coupling). We found a task-specific reduction in co-activation during the predictable coupling task compared to the other tasks. Less sensory gating, reflected in larger amplitudes of subcortical SEP components, was observed in the unpredictable coupling task. SAI behaviour was closely linked to SEPs indicating an important function of subcortical sites in predictability related SEP gating and their direct influence on M1 inhibition. Together, these findings suggest that the unpredictable coupling task cannot only rely on predictive forward control which is compensated by enhancing co-activation and increasing the saliency for external stimuli by reducing sensory gating at subcortical level. This behaviour serves as a preparatory step to compensate for external disturbances and to enhance processing and integration of all incoming external stimuli to update the current sensorimotor state. In contrast, predictive forward control is accurate in the predictable coupling task due to the integrated sensory feedback from both hands where sensorimotor resources are economized by reducing muscular co-activation and increasing sensory gating.

4.2. Introduction

One important factor for optimal sensorimotor control is how well one is able to predict sensory feedback from internal and external sources during movement. If predictability is low, for example, due to random perturbations from the environment, the brain typically adapts motor output by increasing joint stiffness via elevated muscular co-activation (for review see Franklin and Wolpert, 2011). Additionally, sensory processing is modulated depending on the sensorimotor context in which the movement is performed. One account proposes that sensory perception is attenuated when sensory events are highly predictable, particularly, when they result from one's own movement. In this situation, the brain is believed to use internal forward models which constantly predict future sensory and motor states of the body. More specifically, when a motor command is executed, an "efference copy" is generated and used to predict the associated sensory consequences which are subsequently subtracted from the actually perceived sensation. This results in a top-down modulation in form of attenuating sensory input depending on the accuracy of the prediction (Bays et al., 2008; Blakemore, 2017; Blakemore et al., 2001; Blakemore et al., 1998a; Wolpert et al., 1995). For example, a force matching task has revealed that forces are perceived as being weaker when they are self-generated than when they are generated externally (Shergill et al., 2003).

In addition to the mechanism of sensory attenuation described above, a separate line of research has demonstrated that responses to external sensory input are principally reduced during movement execution or preparation, a mechanism known as "sensory gating". Sensory gating can be probed via sensory evoked potentials (SEP), which are typically reduced when measured during voluntary movement of the stimulated body part as compared to rest (Chéron and Borenstein, 1987; Papakostopoulos et al., 1975; Rushton et al., 1981). Even though attenuated perception of self-generated sensory events shows similarities to reduced responses to external stimuli during movement, the first mechanism depends on the predictability of sensory consequence while the latter is a more generalised gating of all external inputs depending on the current motor behaviour (Brown et al., 2013; Lei et al., 2018). Recently, it has been argued that both mechanism are functionally different and that predictability of sensory events does not seem to interact with the general gating phenomenon (Palmer et al., 2016). In their study, a force matching task was used in which the force of a reference press on the resting finger had to be matched by either using the other limb to press on a force lever that was on top of the resting finger, or by pressing a lever on a separate robot which induced the press. Despite the difference of predictability of the force received by the resting hand, SEP amplitude was not different between the tasks. However, the sensory feedback during movement of electrically stimulated arm was similar in both conditions. Thus, whether changing the predictability of sensory feedback of ongoing movements modulates general gating remains unknown.

To answer this question, we designed three object manipulation tasks in which we modified the predictability of the sensory feedback by adding either integrated bimanual feedback or an external perturbation. The bimanual coordination task required participants to perform rhythmic reciprocal wrist extension/flexion movements on one or more devices which transmits rotational forces applied on one handle to the other (Fig. 4.1). Predictability of the interlimb coordination pattern was enhanced by providing tactile feedback via a mechanical coupling which allows participants to sense interaction forces between the hands (Fig. 4.1a). In this condition, participants could use the tactile information to continuously update their internal model, thereby increasing the predictability of how one limb has to move relative to the other. Conversely, predictability of the interlimb coordination pattern was reduced by applying external forces to one arm (Fig. 4.1c). Accordingly, the adaptation to the external perturbation required the participant to constantly process and integrate somatosensory feedback between the two limbs. Note that this paradigm ensured that participants performed the exactly same movements in all three conditions while only the sensory context was experimentally manipulated. Using this setup we addressed three major research questions. First, we investigated whether co-contraction differed between the experimental conditions. It is well known that the central nervous system modifies mechanical properties of a limb depending on the predictability of the task (Franklin and Wolpert, 2011; Hogan, 1984). For instance, studies have shown an increase in hand grip force when the predictability of an object’s weight decreased (Bracewell et al., 2003) or when the object was externally perturbed (Blakemore et al., 1998b). Other studies applied unpredictable force fields during unimanual upper limb reaching tasks resulting in an increase in joint stiffness (Burdet et al., 2001; Mitrovic et al., 2010), which is suggested to be controlled by an increase in muscular co-activation around that joint (Franklin and Wolpert, 2011; Hogan, 1984). The relationship between predictability and mechanical properties has mostly been studied by changing external factors of the task. It remains unclear whether internal differences of movement predictability result in similar adaptations. Here, we hypothesize that co-contraction is lowest when shared sensory feedback during bimanual cooperative movements increases task predictability. Second, we investigated whether sensory processing differs between the conditions. This was probed either by evoking SEPs or by probing sensorimotor integration via short afferent inhibition (SAI). It has been shown that a sensory volley generated by electrical nerve stimulation inhibits the subsequent motor response induced by transcranial magnetic stimulation (TMS) (Chen et al., 1999; Sailer et al., 2002; Tokimura et al., 2000). SAI quantifies this sensory-to-motor transformation which is thought to represent inhibitory influences from the sensory system to the primary motor cortex (M1). It has been shown that the intensity of the stimulation correlates with the inhibition of M1 (Bailey et al., 2016; Fischer and Orth, 2011). Weaker stimuli usually result in less inhibition. It is, however, still unknown if this is also the case if only the neural response to the electrical stimulation is reduced due to sensory gating while stimulation intensity itself is kept constant.

Together, we hypothesized higher co-activation during less predictable movements accompanied by less gating resulting in higher SEP amplitudes as well as a direct influence of this amplitude on SAI.

4.3. Methods

4.3.1 Participants

31 participants (mean age: 27 ± 5 years; 15 women; two left-handed) were recruited for the present study. Experiment 1 and 3 was conducted with all participants. A subsample of 17 participants were included in experiment 2 (mean age: 29 ± 7 years; 7 female, 1 left handed). The study was approved by the local ethic committee (Kantonale Ethikkommission Zürich; KEK-ZH 2016-02064) and participants gave written informed consent prior to study onset.

4.3.2 Movement Tasks

Three movement tasks, i.e. a predictable coupling (COOP), an uncoupled (NON) and a unpredictable coupling (EXT) task were compared in all experiments (Figure 4.1). Participants were seated comfortably at a desk and performed rhythmic reciprocal (i.e. anti-phasic) wrist extension and flexion movements using one or two copies of a custom-built device described previously (Schrafl-Altermatt and Dietz, 2014; Thomas et al., 2018). In short, it consists of two handles connected over a shoe-type brake and is mounted on a support. The rotational force applied to one handle is transferred to the other handle. Only one device was used for COOP (Fig.4.1a). Participants rotated both handles against the given resistance of the break. In this forward controlled movement, each hand receives well predictable integrated sensory feedback from its cooperating partner. For NON, two identical devices were used (i.e. one for each hand). The outer handles of both devices were mechanically fixed and participants performed rotations of the inner handles of the two physically uncoupled devices (Fig. 4.1b).

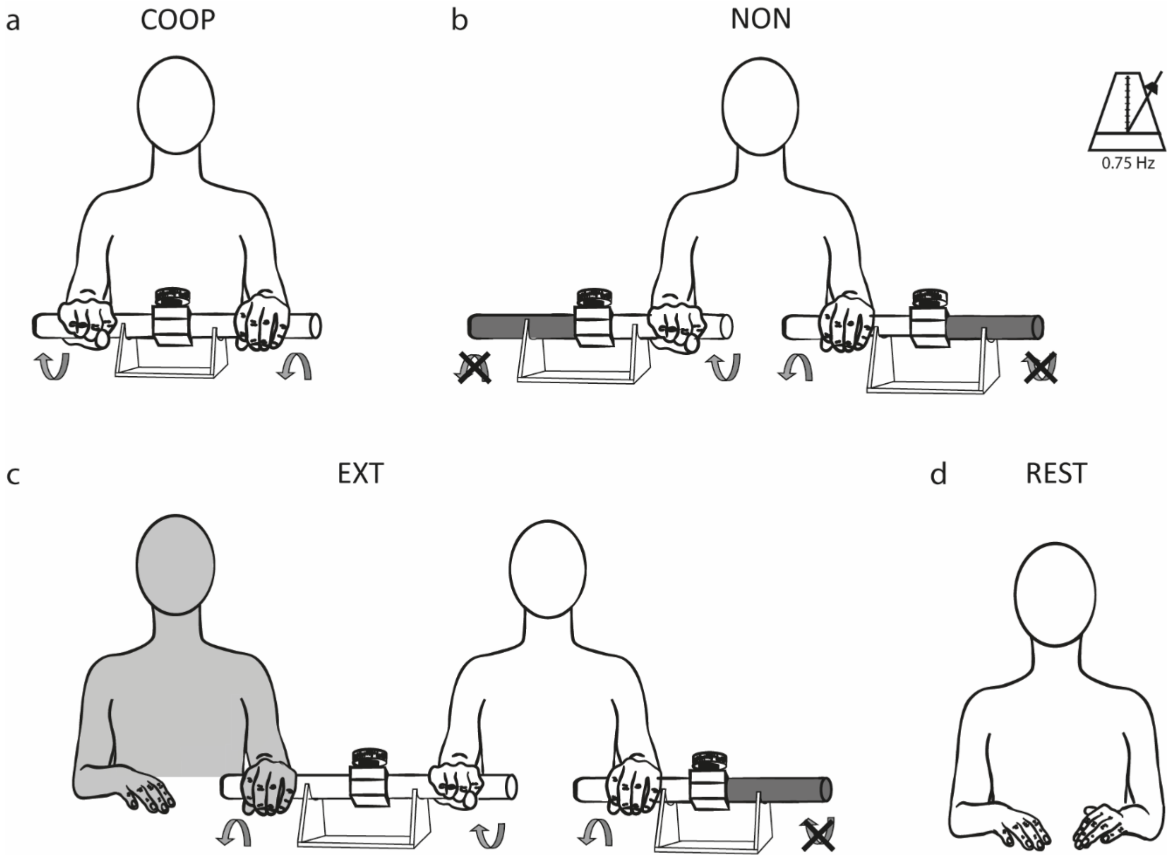


Figure 4.1: Experimental conditions. Participants were tested during three different movement tasks (a-c) and at rest (d). Rhythmic reciprocal wrist extensions and flexions were performed to rotate the handles of the device(s) with a frequency of 0.75Hz. In COOP (a), the rotational force produced by one hand was perceived and counteracted by the other hand and vice versa (predictable coupling). In NON (b), the outer handles of the device were fixed, and participants had to rotate the inner handles of the two independent devices (uncoupled). c) EXT was similar to NON with the addition of an external experimenter which manipulated the outer handle of the device used by the participant's dominant hand. The rotational force of the experimenter was perceived and had to be counteracted by the participant (unpredictable coupling). No movements were performed during REST (d).

Forward control in this task is similar as in COOP, however, predictability is less accurate due to the missing integrated sensory feedback. EXT was similar to NON but included an external experimenter manipulating the outer handle of the device used by the participant's dominant hand (Fig. 4.1c). The experimenter performed rhythmic movements according to the metronome and participants were instructed to counteract the experimenter's movements. Object manipulation during this condition cannot be controlled by forward mechanisms alone but rely on feedback control depending on the external influence. Consequently, prediction of sensory feedback in this task is less accurate. In REST (Fig. 4.1d) no movements were performed. In all conditions, participants fixated a cross on the screen placed in front of them. The order of conditions was randomized. Movement velocity was paced with a metronome with a frequency of 0.75Hz (i.e. one full movement cycle in 1.33s). The resistance induced by the break, that is, the force necessary to rotate the handles was ~1Nm.

4.3.3 Study Design

In experiment 1, co-activation of the dominant extensor carpi radialis (ECR) and flexor carpi radialis (FCR) was assessed during the movement tasks using electromyogpraphy (EMG). Each condition was performed once for 20s. In experiment 2, electroencephalography (EEG) was used to record somatosensory evoked potentials (SEP) in response to median nerve stimulation (MNS). Each condition was performed once for ~90s containing 200 stimulations of the median nerve. In experiment 3, SAI was investigated. Single pulse TMS was used to elicit motor evoked potentials (MEPs) in the dominant ECR. TMS was either preceded by MNS (to induce SAI) or followed by MNS (as a control). Three trials of ~60s duration containing 12 MNS/TMS pulse pairs were performed for each condition.

4.3.4 Electromyographic (EMG) recordings

Surface EMG activity (BagnoliTM Desktop System, Delsys, USA) was assessed on extensor carpi Radialis (ECR) and flexor carpi radialis (FCR) of both forearms using single differential electrodes. Data was sampled at 2000Hz (CED Power 1401, Cambridge Electronic Design), amplified (x1000), band-pass filtered (20-450Hz), rectified, offset-corrected and stored on a PC for offline analysis.

4.3.5 Somatosensory Evoked Potentials (SEP)

In experiment 2, SEPs were recorded with a 32-channel EEG-system (Brainvision actiCHamp, Brainproducts GmbH, Germany). The electrode positioned over S1, i.e. 5cm lateral and 2cm posterior to the vertex, on the dominant hemisphere was the region of interest. The ground electrode was placed on the forehead and signals were referenced to Fz with an impedance <10Ω accepted as background noise. EEG activity was sampled at 1000Hz, high-pass (0.5Hz) and low-pass filtered (250Hz) and re-referenced to the average. Independent component analysis (ICA) was further applied to remove artifacts (e.g. eye-blinks, heartbeat, and muscle-artifacts). For each condition, the continuous EEG-waveform was cut into epochs of -50ms before and 150ms after each stimulation and averaged.

4.3.6. Median nerve stimulation (MNS)

In experiments 2 and 3, the median nerve of the dominant side was stimulated (Digitimer DS7H, United Kingdom) proximal of the wrist crease through two circular surface electrodes (KendallTM Covidien MediTrace®, 35mm diameter, 2cm inter-electrode distance, cathode proximal). The stimulation consisted of a single square wave pulse of 400V with 1ms duration. Stimulation intensity was the sum of the individual perceptual threshold (PT, i.e. lowest intensity to perceive the stimulation) and motor threshold (MT, i.e. lowest intensity to evoke a visible twitch in the thenar muscles). In experiment 2, 200 stimulations were applied with a frequency of 3.1 Hz in each condition. In experiment 3, PNS was randomly applied to occur either 23ms before (conditioned MEP - MEP$_{\mathrm{C}}$) or 70ms after (non-conditioned MEP - MEP$_{\mathrm{NC}}$) the TMS pulse.

4.3.7 Transcranial Magnetic Stimuation (TMS)

In experiment 3, TMS was delivered to the motor cortex of the dominant hemisphere using a 80mm figure-of-eight coil connected to a Magstim 200 (Magstim, Whitland, United Kingdom). The coil was placed in a 45° angle away from the midline to induce a posterior-anterior oriented current flow over the hotspot for the ECR i.e. where the largest and most reliable MEPs could be evoked. Monophasic pulses were delivered every four to six seconds with an intensity evoking 50% of maximal MEP amplitude. During movement conditions, TMS pulses were triggered in the extension phase of the dominant hand by the participant's EMG activity. The trigger-threshold was set to ~50% of the maximal EMG activity produced during wrist extension (Fig.2). The TMS pulse occurred 80ms after the trigger. 12 TMS pulses were delivered in each of the three trials per condition resulting in a total of 144 stimulations.

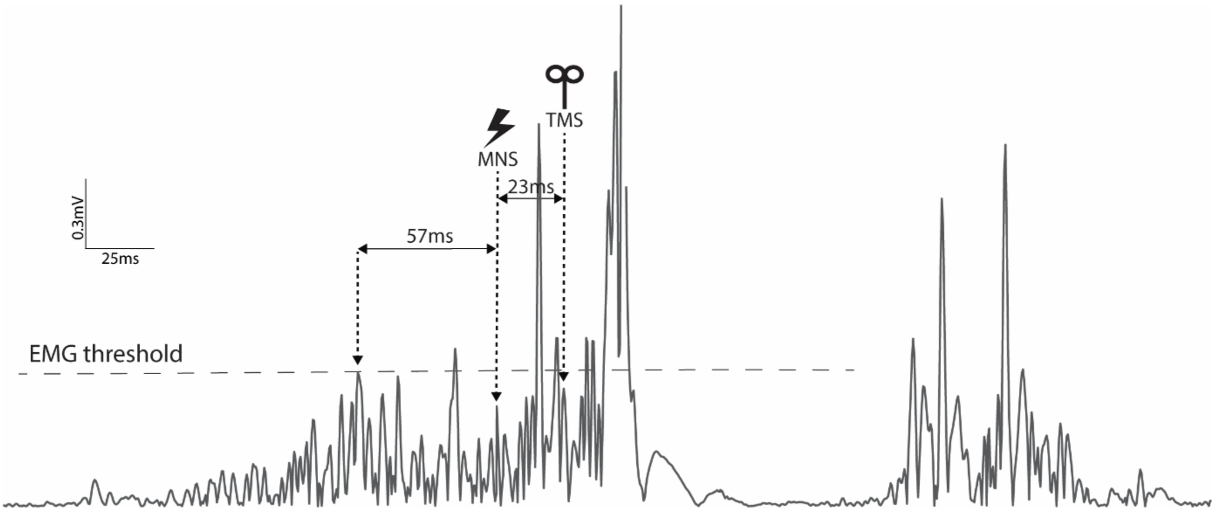


Figure 4.2: Stimulation protocol of experiment 3. Transcranial magnetic stimulation & peripheral nerve stimulation were triggered by the participant's individual EMG activity of the ECR. The threshold was set to ~50% of the maximal

EMG activity during extension of the dominant wrist. TMS was released 80ms after crossing the threshold. PNS occurred randomly either 23ms before or 70ms after TMS to induce SAI (MEP_C) or as a control (MEP_{NC}), respectively. The figure depicts an example EMG trace of the dominant ECR in a single participant during COOP. MNS occurred in this example 23ms before TMS.

4.3.8 Data Analysis

For calculation of the co-activation in experiment 1 between the ECR and FCR, the EMG signal was high-pass filtered at 1Hz and low-pass filtered at 6Hz to get the envelope of the EMG signal. The co-activation index was calculated with the formula:

$$co - acitvation\ index = \left(\frac{\text{overlap ECR/FCR}}{\text{AUC ECR}}\right)$$

where the area under the curve (AUC) of the overlapping EMG envelopes of the ECR and FCR is normalized to the AUC of the ECR (Bachinger et al., 2019; Frost et al., 1997). SEPs in experiment 2 were calculated as peak-to-peak amplitude of the P15/N20 and N20/P25 complexes in the averaged EEG-waveform. P15 was calculated as the local maximum between 12-18ms and N20 as the local minimum between 17-23ms. P25 was calculated as the local maximum between 22-28ms. Size of the MEPs in experiment 3 were calculated as root mean square (RMS) of the averaged MEPs over a 30ms window starting from MEP onset, which was visually determined. MEP RMS was normalized to the average background EMG RMS in a 30ms window before the TMS trigger. SAI was calculated as the percentual difference of the MEPC RMS in relation to the MEPNC RMS with the following formula:

$$\%inhibition = 1 - \left(\frac{\text{MEPc}}{\text{MEPnc}}\right) * (100)$$

Here, positive values indicate inhibition and negative values indicate facilitation.

One-way repeated measures ANOVAs were used to evaluate differences between conditions. Post-hoc pair-wise comparisons were calculated with Benjamini-Hochberg corrected one-sided paired t-tests. One-sided tests were chosen based on our a-priori hypothesis that co-activation, SEP amplitude and SAI decrease as a function of task predictability. Pearson correlation was used to assess the relation of the afferent volley (SEP) and M1 inhibition (SAI). For all statistical tests, a p-value < 0.05 was considered significant. If not stated otherwise, values are given as mean (±SD).

4.4 Results

4.4.1 Experiment 1 – Co-activation

The co-activation index between ECR and FCR was significantly lower for COOP (0.31 ± 0.1) compared to NON (0.36 ± 0.13) and EXT (0.37 ± 0.15) (condition main effect $F_{(2,60)} = 8.253$, $p = 0.001$; both post-hoc tests $t <= -3.262$, $p <= 0.002$). No difference was found between NON and EXT ($t = -0.77$, $p = 0.22$) (Fig. 4.3). This shows that the integrated feedback in the predictable coupling task seems to be a strong modulator in reducing co-activation.

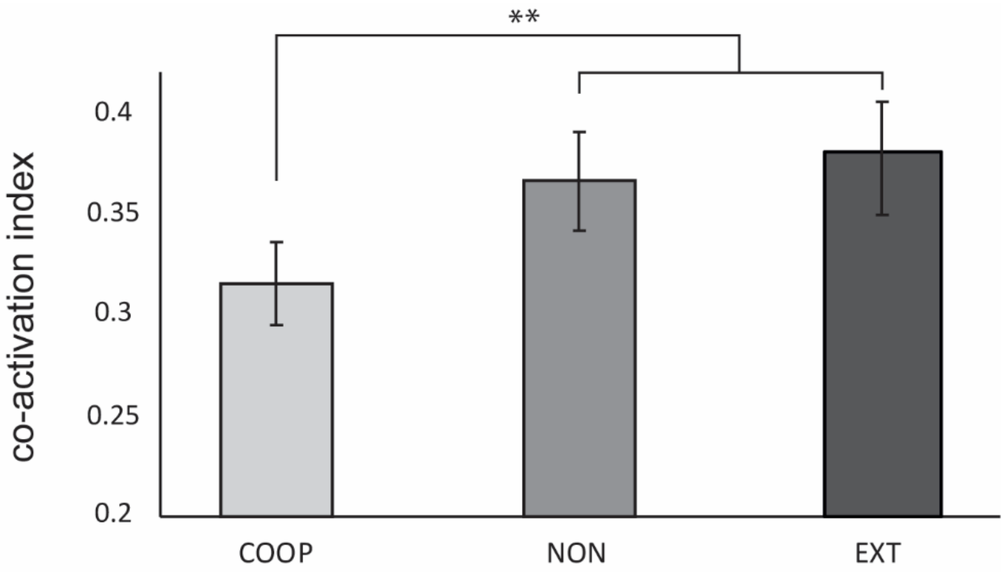


Figure 4.3: Experiment 1. Co-activation index was significantly decreased during COOP compared to NON and EXT. No difference was observed between NON and EXT. Error bars indicate standard error of the mean. **p < 0.002.

4.4.2 Experiment 2 – Somatosensory evoked potentials

Three participants had to be excluded due to major noise in the EEG signal. Data of 14 participants (age: 29 ± 6y; 7 women, all right handed) was considered. Repeated measures ANOVA revealed a significant difference in P15/N20 amplitude between tasks ($F_{(3,39)} = 8.61$, $p < 0.01$) (Fig. 4.4). Post-hoc tests revealed a significantly larger P15/N20 SEP during REST (1.40 ± 0.46 µV) compared to the movement tasks (all $p < 0.05$). Additionally, we observed a significantly smaller SEP amplitude during COOP (0.91 ± 0.41 µV) and NON (0.97 ± 0.35) compared to EXT (1.18 ± 0.35 µV, $t <= - 2.87$, $p <= 0.02$). COOP was not significantly different from NON ($t = 0.45$, $p = 0.33$). Similar as for the P15/N20 component, N20/P25 amplitude was significantly larger during REST (3.08 ± 2.71 [µV]) than in the movement tasks (COOP: 1.08 ±

1.17 µV; NON: 1.13 ± 1.13 µV; EXT: 1.16 ± 1.04 µV; $F_{(1.17,15.19)} = 15.67$, $p < 0.001$, all post-hoc tests, $p < 0.01$) however, no difference between the movement tasks was observed.

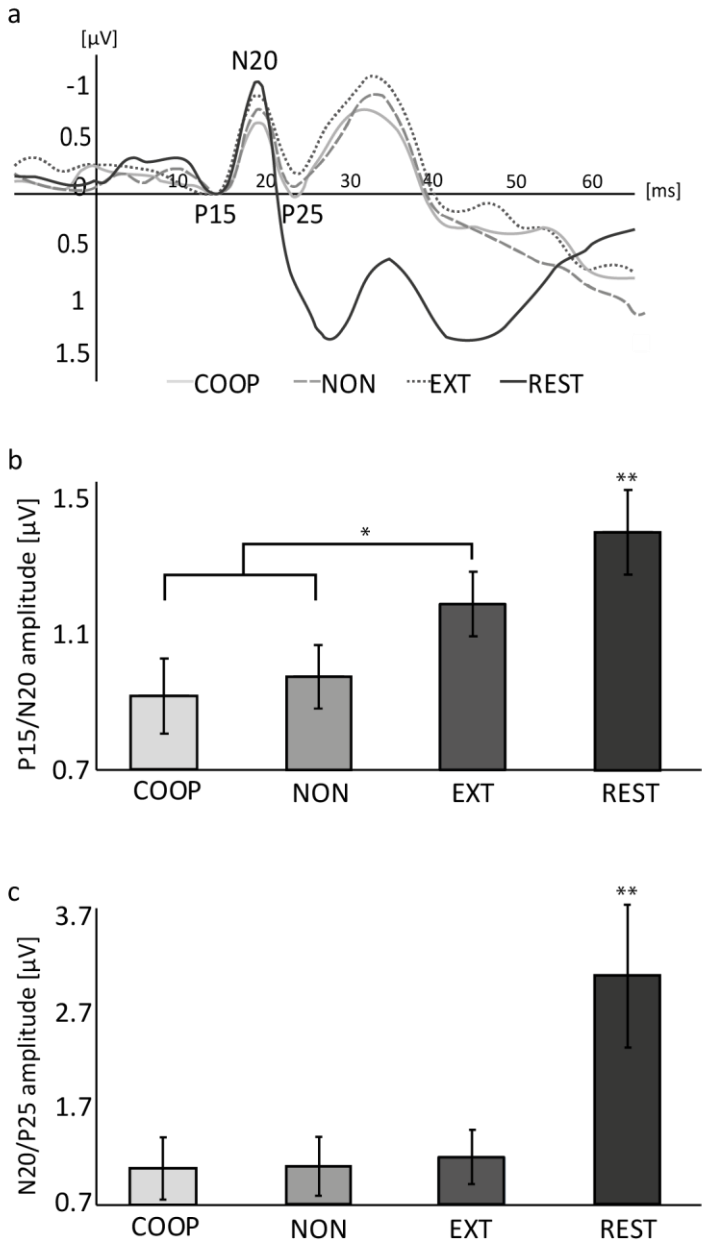


Figure 4.4: Experiment 2. a) Group averaged EEG-traces recorded from S1 area contralateral to PNS applied at 0ms. For illustration purpose, the P15 component of each condition was set to 0µV. b) At REST, P15/N20 amplitude was significantly larger compared to the movement conditions and was significantly smaller during COOP and NON compared to EXT. c) N20/P25 amplitude at REST was significantly larger than during movement. No differences were observed between movement tasks. Error bars represent standard error (SE). The large SE in c) is due to one outlier with fourfold higher amplitudes than the rest of the sample. *p<0.05.

4.4.3 Experiment 3 – Short afferent inhibition

Four participants had to be excluded due to technical issues. Data was analysed from 27 participants (mean age: 28 ± 5 y.; 14 women; 2 left-handed). We observed a significant main effect between the tasks ($F_{(2.4,58,4)} = 35.896$, $p < 0.01$). All movement tasks showed significantly less inhibition compared to REST (54.4 ± 5.5%; all $p < 0.01$) (Figure 4.5). SAI was task-specifically modulated as it was significantly smaller during COOP (-2.4 ± 3.9%; $t = 2.25$, $p = 0.01$) and NON (0.4 ± 4.1%; $t = 2.11$ $p = 0.04$) compared to EXT (9.4 ± 3.7%). No significant difference was seen between COOP and NON ($t = 0.54$, $p = 0.29$). To investigate the link between sensory input and M1 inhibition, we calculated the correlation between the SEP amplitude and SAI (Fig. 4.6). Technical issues affected SAI data of one participant that was included also in the SEP experiment. Therefore, the correlation was calculated for 13 participants. We observed a positive correlation between SEP amplitude and SAI ($r = 0.352$) that was significant ($p = 0.02$) indicating that a larger SEP amplitude induced a stronger inhibition of M1.

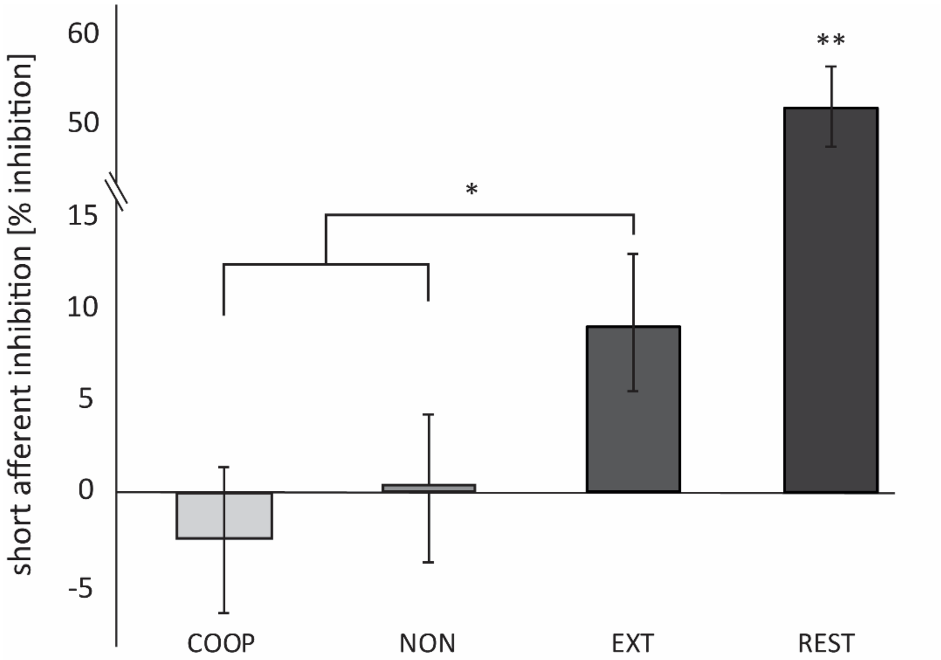


Figure 4.5: Experiment 3. SAI is expressed as the percentage difference between MEP_C and MEP_{NC}. Positive values indicate inhibition, negative values indicate facilitation. SAI was significantly smaller during COOP and NON compared to EXT. At REST, inhibition was significantly higher compared to the movement conditions. *$p < 0.05$. **$p < 0.01$.

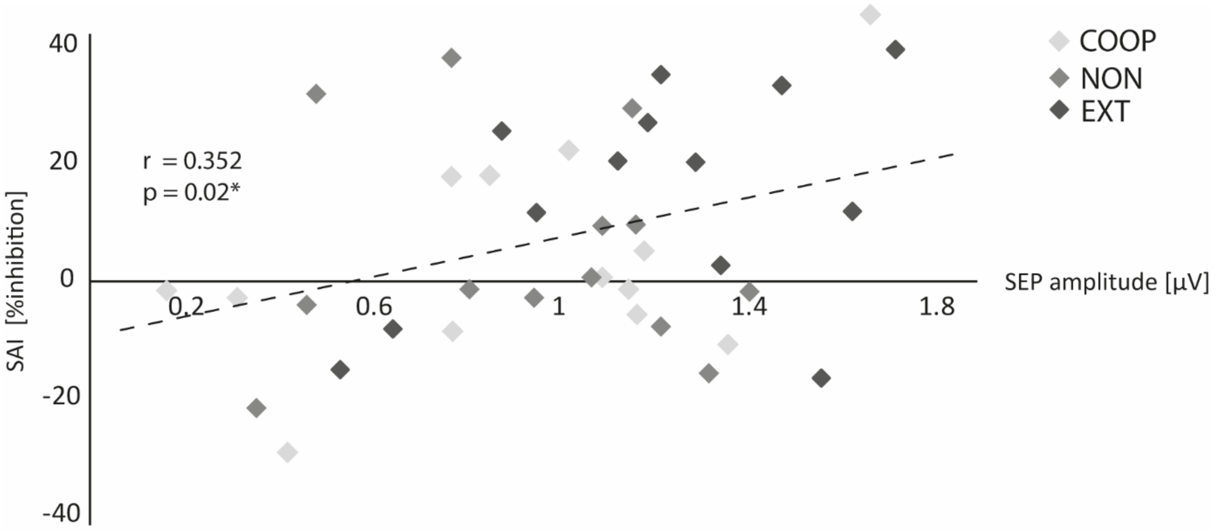


Figure 4.6: Relation between SEP and SAI. Sensory volley (SEP) and M1 inhibition (SAI) were significantly correlated i.e. the larger the SEP amplitude the more SAI. Symbols represent individual participants in each condition. The asterisk indicates a significant correlation (*p<0.05).

4.5 Discussion

In the present study, three object manipulation tasks with different levels of sensory feedback predictability were designed. The aim was to investigate how the modifications of internal and external sensory feedback influence the control of muscle activation and processing of sensory input. In three separate experiments, co-activation of forearm muscles, SEP amplitude and SAI were assessed. The main results revealed less co-activation in forearm muscles, smaller SEP amplitude of the P15/N20 complex and least M1 inhibition during the predictable coupling task compared to the uncoupled and unpredictable coupling task.

4.5.1 Integrated sensory feedback modulates co-activation

The sensorimotor system adapts muscle activations and force depending on the predictability of the environment (for review see Franklin & Wolpert, 2011). Increasing the instability or unpredictability of the environment by adding external disturbances has been shown to result in increased joint stiffness (Burdet et al., 2001; Hogan, 1984) induced by stronger co-activation of agonist and antagonist muscles stabilizing the corresponding joint (Carter et al., 1993; Finley et al., 2012; Hogan, 1984). This increase is suggested to be a strategy to be less susceptible and more ready for possible disturbances (Franklin and Wolpert, 2011). In line with these studies, we observed a modulation of co-activation as a function of predictability of the task. More specifically, significantly less co-activation was found in the predictable coupling task during which integrated sensory input between the two hands was received. Tactile information of the skin touching the object is crucial to control the manipulation of that object. During object interaction, grip force is finely adjusted to the load force to optimise friction between the object and the skin and thus providing a minimal safety margin (Johansson and Westling, 1988). This adjustment is controlled by the co-activation of hand and arm muscles (Johansson, 1991). Johansson & Westling reported an overshoot of grip force and stronger co-activation in forearm muscles as a response to unexpected weight changes of a manipulated object (Johansson and Westling, 1988). In another study by Blakemore and colleagues, participants had to pull an object up and down with the right hand to track a target sinusoidal load curve (Blakemore et al., 1998b). They showed that predictive grip force modulation of the right hand was most precise when the left hand supported the movements of the right hand indicating the highest predictability in this task. These results are in line with the present study showing weaker co-activation in the predictable coupling task compared to the unpredictable coupling task. The stronger co-activation might have been necessary to increase grip force for maintaining a higher safety margin to compensate for potentially unexpected behaviour of the object. The integrated tactile input during the predictable coupling task can be constantly anticipated requiring only a minimal safety margin. The integration of the tactile input from both sides of the body is suggested to take place in the secondary somatosensory cortex (S2) (Dietz et al., 2015; Disbrow et al., 2001; Simoes and Hari, 1999). This area was shown to be particularly important during coupled object manipulation (Dietz et al., 2015). We therefore propose that in the present study, co-activation was strongly reduced by the availability of integrated sensory feedback and the feed forward control during the predictable coupling task. In contrast, during the unpredictable coupling task, the movement cannot only be controlled by forward mechanisms but relies more on feedback control depending of the external influence. For optimal object control it is therefore likely that co-activation increases as a preparatory step to enhance the readiness for unexpected disturbances.

4.5.2 Sensory gating is modulated by predictability of the task

SEP amplitudes are reduced during concurrent tactile stimulation (Kakigi and Jones, 1985, 1986), passive (Abbruzzese et al., 1981; Rushton et al., 1981) and voluntary movement (Chéron and Borenstein, 1987; Papakostopoulos et al., 1975; Rushton et al., 1981) of the stimulated body part compared to SEPs elicited at rest. This sensory gating is thought to prevent an flooding of sensory information to the CNS by filtering irrelevant information (Chéron and Borenstein, 1987; Cromwell et al., 2008). We observed that both the P15/N20 and N20/P25 SEP amplitude were reduced in all movement tasks compared to rest which is in line with previous studies suggesting a general movement related gating of sensory input. In addition to the movement related gating, P15/N20 SEP amplitude was significantly reduced in the predictable compared to the unpredictable task. Sensory input is thought to be reduced depending on how accurate our internal forward models predict the future sensorimotor states (Blakemore et al., 1999; Wolpert et al., 1995). In the unpredictable coupling task in the present study, sensory feedback of the experimenter is less predictable leading to a greater discrepancy in the predicted and perceived sensorimotor state. This feedback-controlled movement depends on external sensory stimuli to maintain optimal motor control. Consequently, sensory input might be less strongly gated. In line with that, it has been shown that cutaneous reflex responses (Michel et al., 2008) and corticospinal excitability (Davare et al., 2019) are upregulated in “low-predictability” compared to “high-predictability” situations. We therefore suggest that the sensory system becomes generally more salient during the unpredictable coupling task to other incoming events thereby increasing the response of the MNS.

Interestingly, only P15/N20 amplitude but not the N20/P25 was modulated by the different tasks. The P15 peak is generated by activity of medial leminiscal afferents projecting to thalamic ventral posterolateral nucleus (Katayama and Tsubokawa, 1987; Stöhr and Riffel, 1982). In contrast, the N20/P25 represents the activity in cortical S1 areas after arrival of the afferent volley (Cruccu et al., 2008; Kany and Treede, 1997; Ruddy et al., 2016). This suggests that sensory information was specifically gated at subcortical sites depending on the predictability of the task. The involvement of subcortical sites in task-specific sensory gating was recently reported by Lei and colleagues who investigated SEPs in response to MNS during precision grip or power grip (Lei et al., 2018). In accordance to the present results, they reported N20/P25 and P15/N20 components to be generally reduced during both grips compared to rest. Further, the P15/N20 SEP amplitude was differently gated between grips. This supports our findings that in addition of a cortically mediated sensory reduction during movement compared to rest, subcortical centres are responsible for a task-specific gating sensory input.

4.5.3 Influence of sensory gating on M1 inhibition

In the present study, the amount of SAI positively correlated with the size of the SEP amplitude. This result is in line with previous studies which reported that SAI depends on the magnitude of the sensory volley (Bailey et al., 2016; Fischer and Orth, 2011). In these studies, however, stronger M1 inhibition was achieved by increasing the intensity of the peripheral stimulus. In contrast, the intensity of the MNS in the present study was kept constant for all tasks. The observed modulation of SAI in the present study presumably depended on the predictability related gating of SEP. Additional to the general reduction of SAI during movement compared to rest, SAI was specifically reduced in the predictable coupled and uncoupled task compared to the unpredictable coupling task paralleling the observed sensory gating. A higher salience of the sensory system in the unpredictable coupling task might have led to less sensory gating and, consequently in a stronger M1 inhibition. The neural pathways for the modulation of SAI are still not fully understood. SAI is generally thought to be modulated by inhibitory projections from S1 to M1 (Tokimura et al., 2000; Tsang et al., 2014) or from direct thalamo-cortical projections to M1 (Oliviero et al., 2005; Ruddy et al., 2016). In the present study, general reduction in SAI during movement compared to rest can be explained by the attenuated cortical N20/P25 SEP component. However, task-specific SAI modulation was only matched by the changes of the subcortical P15/N20 SEP component. We therefore provide supporting evidence that both cortical and subcortical sites are involved in the modulation of SAI whereas subcortical sites are specifically involved in modulating SAI between differently predictable movement tasks. These results provide novel information about the importance of subcortical sites in gating sensory information and their direct influence in the inhibition of motor output.

4.5.4 Conclusion

During object manipulation, prediction accuracy can be improved when both hands receive integrated sensory feedback over a shared object or decreased due to unpredictable sensory feedback from an external source. To sustain optimal motor control during the latter, movements rely on feedback control based on the sensory input from the external source since forward models are not accurate in predicting the future sensorimotor states. This seems to be compensated for by enhanced muscle co-activation of the limb to increase the readiness to react on possible external disturbances. Additionally, the sensory system increases its saliency with a reduced gating at subcortical sites allowing for enhanced processing of these external stimuli to update the current sensorimotor state. In contrast, availability of integrated sensory feedback from both hands allows for optimal forward control. Here, muscular co-activation is decreased and subcortical gating of external sensory input is enhanced thereby economizing sensorimotor resources. This study presents novel information in how the central nervous system adapts sensorimotor control in response to modifications in task predictability.

Chapter 5

Do it yourself: Providing intensive and effective home-based therapy of the upper limb for stroke survivors using ARCO

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(Under review, Journal of NeuroEngineering and Rehabilitation)

5.1 Abstract

Limited access to intensive and effective training especially after hospitalization complicates optimal stroke rehabilitation. Thus, novel therapy approaches are needed which can be self-administered in an unsupervised environment, as for example at the patient's home. The present study addressed the hypotheses that cooperative hand movement training using a novel device (ARCO) is (i) feasible for the application in the clinic and in an unsupervised home-based setting for mildly to severely affected chronic stroke patients and (ii) that it improves upper limb motor function. Seven chronic stroke participants (9-22 years after stroke) completed a 6-week training phase with ARCO, i.e. 2 weeks of supervised training at the hospital followed by 4 weeks of training at the participants' homes without supervision. Feasibility was evaluated with the Intrinsic Motivation Inventory (IMI). Training efficacy was assessed with Fugl-Meyer Upper Extremity score (FM-UE), Box and Block-Test (BBT) and Maximal Voluntary Contraction (MVC) of the wrist. Significant improvements were shown in the FM-UE ($p = 0.017$) and wrist extension MVC of the more affected limb ($p = 0.032$). BBT scores tended to increase ($p = 0.057$). The IMI score was high (median > 5.5) throughout the whole therapy period. Participant P5 had no voluntary wrist function prior to study onset (FM-UE wrist: 0, MVC wrist extension: 0 [Nm], BBT-score: 0) and regained some of it by the end (FM-UE wrist: 4, MVC wrist extension: 0.44Nm, BBT: 2). ARCO is feasible for intensive unsupervised home-based training and enhances upper limb function in chronic stroke patients. Notably, one participant regained some voluntary wrist movements during therapy despite a chronicity of over 17 years. Thus, ARCO might be a promising new self-administered therapy approach also feasible for patients with limited or no voluntary muscle activity in the more affected limb.

5.2 Introduction

Stroke is the leading cause of adult disability (Thrift et al., 2017). Patients often suffer from severe motor impairments in the upper limb, which affects quality of life and independence (Cauraugh et al., 2010; Dobkin, 2005; Langhorne et al., 2009). Although a recovery plateau is reported to be reached between the first three to six months after stroke (Byblow et al., 2015; Prabhakaran et al., 2008; Stinear et al., 2017) functional upper limb improvements might still occur after this period (Page et al., 2008; Whitall et al., 2000). Various unimanual and bimanual therapy approaches exist for post-stroke upper limb rehabilitation (Cauraugh et al., 2010; Luft et al., 2004; Sakzewski, 2012; Van Delden et al., 2012).

Cooperative hand movements are one specific sub-category of bimanual movements whereby one hand has to precisely counteract the force of the cooperating other limb. These hand movements are essential for many functionally meaningful activities of daily living (ADL), e.g. opening a bottle or igniting a matchstick. Recently, it has been shown that the neural control mechanisms for cooperative hand movements differ from other uni- and bimanual movements (Dietz et al., 2015; Schrafl-Altermatt and Dietz, 2014). Here, task-specific bilateral reflex responses in the forearms after unilateral medina nerve stimulation (Dietz et al., 2015) and an enhanced activation of ipsilateral S1 cortical areas compared to non-cooperative hand movements (Schrafl-Altermatt and Dietz 2014) were reported. These findings indicate an enhanced involvement of ipsilateral efferent and afferent pathways in the control of each hand during cooperative tasks. This behaviour has been shown to be partially preserved in chronic stroke subjects (Schrafl-Altermatt and Dietz, 2016a; Schrafl-Altermatt and Dietz 2016b). Thus, focused cooperative hand movement training might promote the inclusion of affected and unaffected afferent and efferent pathways on the control of the more affected arm, which might be beneficial for upper limb recovery. However, there is currently no training approach or device available focusing cooperative hand movements.

To optimize rehabilitation outcome, stroke patients need intensive and continuous therapy (Langhorne et al., 2011) which should optimally be maintained after hospitalization. However, the growing number of patients requiring rehabilitation after stroke causes an increasing socio-economic burden for healthcare systems and thus, optimal rehabilitation can often not be implemented, challenged by financial issues and restrictions in support (Page et al., 2004; Poli et al., 2013). Therefore, ARCO (COoperative Arm Rehabilitation) therapy has recently been developed as an unsupervised home-based training approach focusing on cooperative hand movements to improve upper limb recovery and accessibility of intensive therapy post-stroke. The ARCO device allows training of cooperative movements. One hand has to statically compensate the forces exerted by the other hand allowing a training of intensive, repetitive coordination patterns which are functionally relevant for ADL tasks. This unique characteristics of the ARCO therapy might allow even severely affected stroke survivors without any voluntary wrist movements to stabilize the device against movements of the less affected side. This setup makes use of the kinematic chain to induce activity in the severely impaired wrist. The present study addresses (i) whether ARCO therapy is feasible for an unsupervised home-based use for mildly to severely affected chronic stroke survivors, and (ii) whether it improves upper limb function in this cohort of participants.

5.3. Methods

5.3.1 Participants

For this study, eight chronic stroke patients (median time since stroke = 164 months) with unilateral upper limb impairment were recruited (see Table 5.1). The study was approved by the local ethic committee (Kantonale Ethikkommission Zürich; PB_2016-00229) and was performed according to the declaration of Helsinki. Participants provided written informed consent before study onset.

5.3.2 ARCO device

The ARCO device consists of two handles connected over a shoe-type brake (Fig. 5.1A). Rotational movement is transferred from one handle to the other such that one hand has to counteract the movements of the other hand to stabilize the device (Fig. 5.1B). Tightening or loosening the tuning wheel on the brake adjusts the force of the brake and thus the resistance

Table 5.1: Patient baseline characteristics

Patient	Age (y)	Sex	Months since CVI	Ipsilesional hemisphere	Stroke type	Site of CVI	Initial FM-Score	Training protocol
P1	61	m	162	left	haem.	basal-ganglia	52	FREE
P2	68	m	167	right	haem.	parietal-occipital	44	FREE
P3	40	m	179	left	haem.	basal-ganglia	26	FREE
P4	45	f	59	left	isc.	MCA	39	INST
P5	55	f	197	left	isc.	basal-ganglia	18	INST
P6	54	f	272	left	isc.	n.a	57	FREE
P7	66	m	47	left	isc.	MCA	35	INST
P8	52	m	113	right	haem.	tempo-parietal	41	INST

CVI = cerebro-vascular insult; isc. = ischaemic stroke; haem. = haemorrhagic stroke; MCA = middle cerebral artery; FM = Fugl-Meyer score;. INST = participants were instructed to train 4x/week and 25min/session; FREE = participants chose freely if, when and how much they wanted to train for counteractive rotation of the handles. Different handles, i.e. spindle, crank and nut (Figure 5.1A), can be easily attached and detached at one side of the ARCO to target different whole arm, wrist and finger actions by mimicking various cooperative ADL tasks. The “spindle” accessory (e.g. opening a bottle) is manipulated by wrist flexion/extension and whole hand flexion; the “nut” (e.g. screwing a nut onto a bolt) is mainly manipulated with combined finger and wrist supination/pronation and the “crank” (e.g. winding up a blind) with retraction/protraction of the shoulder and flexion/extension of elbow and wrist. The second handle of the ARCO is a fixed cylindrical handle (same shape as “spindle”) requiring static stabilization by activating the wrist extensor/flexor and hand flexor muscles irrespective of the kinematics of the moving limb. The ARCO is equipped with a potentiometer recording the relative position of the handles and a force sensor in the brake to record the movement resistance. These signals are transferred via Bluetooth to a laptop and used to control the six available exergames (programmed in house with Unity Technologies, San Francisco, CA, USA) presented on a laptop in front of the participants (Fig. 5.1B). Repeated back and forth rotations of the handles are used to induce left/right or up/down movements of virtual objects depending on the goal of the exergame. Every combination of exergame and accessory is possible. Stroke survivors often suffer from extensor weakness, which limits their ability for functional extension movements (Cauraugh et al., 2000). Thus, all exergames were programmed to focus on wrist extension rather than flexion. Since training documentation is crucial, especially when the training is performed at home without supervision, the ARCO software automatically records temporal (e.g. training date, training time), executive (e.g. choice of game, handle and moving hand) and dose (e.g. training duration, rotated distance (°), resistance) information to provide a detailed report about training content (Walker et al., 2017).

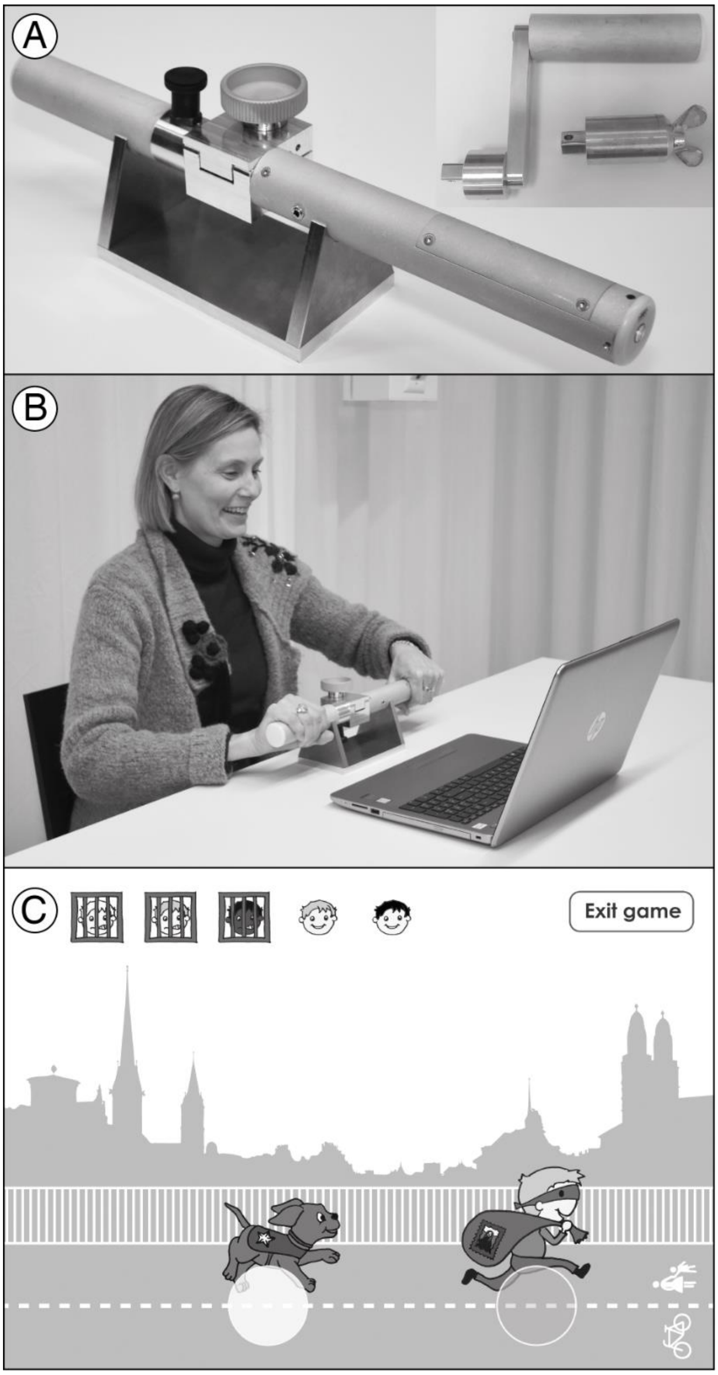

Figure 5.1: ARCO therapy essentials. A) The ARCO device with the “spindle” accessory attached (the accessories “crank” and “nut” are displayed on the right). The two handles are connected over a clutch, that is, rotational force applied to one handle is translated to the other handle. Three different accessories can serve to train a variety of ADL tasks. B) A participant manipulating the ARCO device. Repeated back and forth rotation of the accessory while stabilization of the second handle, is used to interact with exergames presented on a laptop in front of the participants. Exemplarily, repeated back rotation of the spindle (i.e. wrist extensions) induces rightwards movement of a dog to catch a thief displayed in panel C.

5.3.3 Study design

Participants trained for 2 weeks (4x/week and 25 minutes/session) at the hospital followed by 4 weeks of home-based training without supervision. For the home-based ARCO training, participants were randomly allocated to either of two groups: One group of participants (INST) was instructed to follow the same training protocol as during the first two weeks under supervision, while the second group (FREE) was instructed to use the device at their own discretion. Clinical outcomes were assessed twice with a one-week interval before therapy onset to assure stability without ARCO therapy (Pre1 & Pre2) and again after the six-week intervention (Post). Neurophysiological measures were performed during Pre2 and Post. Participants were visited on a weekly basis at their homes to verify their well-being and for conducting the Intrinsic Motivation Inventory (IMI, see below) and collection of training data. For ARCO therapy description, see supplements.

5.3.4 Outcomes

Feasibility

The primary outcome for feasibility was the Intrinsic Motivation Inventory (IMI). This questionnaire assesses the subjective experience and motivation of a given activity or instrument (McAuley et al., 1989) covering 5 question domains (see supplements) and was conducted once in the first two weeks of supervised training and weekly during home based training. Protocol compliance and training behaviour (i.e. use or non-use of the ARCO) was automatically recorded by the ARCO software and was also included as an outcome of feasibility. Pain and exhaustion were monitored after each training session on a 10-point scale (i.e. 1: no pain, 10: maximum imaginable pain; 1: no exhaustion, 10: maximal exhaustion).

Clinical assessments

Changes in motor impairment and function were assessed with the Fugl-Meyer Assessment of the Upper Extremity (FM-UE) (Fugl-Meyer et al., 1975) the Box and Block Test (BBT) (Mathiowetz et al., 1985) and the Cooperative Activity Stroke Assessment (CASA). CASA has recently been developed as a clinical assessment evaluating bilateral upper limb coordination. In this assessment, participants solve functionally relevant bimanual cooperative tasks of daily living scored on a quantitative (i.e. execution time) and qualitative (i.e. movement quality) scale. Tasks include opening a clip box, opening & closing of a zipper, opening a jam jar, opening a bottle and unscrewing a nut from a bolt (see supplements for assessment details). Maximal Voluntary Contraction (MVC) of wrist extension and flexion was determined as the highest of three maximal static wrist extension/flexion movements on the “spindle” accessory while the other handle was externally restricted by a torque sensor. Sensory impairment was measured with the Electrical Perception Threshold (EPT) (see supplements).

Neurophysiological outcomes

Neural adaptions of afferent sensory pathways were investigated by the ratio of somatosensory evoked potentials (SSEP) (amplitude of ipsilateral SSEP divided by amplitude of contralateral SSEP) recorded over bilateral S1 cortices. A higher ratio indicates a stronger involvement of ipsilateral afferent pathways. Further, the magnitude of reflex responses in the contralateral limb to unilateral electrical ulnar nerve stimulation was assessed. SSEPs on S1 cortices and reflex responses in the contralateral extensor carpi radialis muscle were elicited by unilateral ulnar nerve stimulations at the wrist of the more affected (MA) and less affected (LA) limb at rest and during cooperative hand movements (for details see supplements).

5.3.5. Statistical analysis

All statistical procedures were performed in SPSS (Version 23; IBM, Armonk, New York, USA). Since all data was not normally distributed, non-parametric statistics (i.e. Wilcoxon signed ranked tests) were used for outcome comparisons. Stability of clinical outcome measures prior to training was confirmed comparing Pre1 and Pre2. Influence of training was assessed by comparing Pre2 (referred to "Pre" onwards) and Post. One-sided Wilcoxon signed-ranked tests were used for clinical outcomes based on a strong a-priori hypothesis that ARCO therapy would lead to improvements in upper limb recovery. A p-value below 0.05 was considered significant. If not stated otherwise, values are given as median and interquartile range (IQR, 25th - 75th percentile).

5.4 Results

Participant characteristics are summarized in Table 1. One participant (P3) withdrew from the study after the second week of home-based training. This participant was on strong medication and reported that small discrepancies with the ARCO device (e.g. device not charged, delay in the Bluetooth-connection from the device to the laptop) lead to negative mood fluctuations. Thus, data was analyzed from seven participants (age: 57 ± 8 years; months since stroke: 162 ± 79, mean ± SD). All other participants were compliant to the protocol. Clinical outcome measures were not significantly different from Pre1 to Pre2 (FM-UE: $p = 0.58$; BBT: $p = 0.46$; CASA: $p = 0.25$). Participants reported no pain (0.0, 0 - 0.8) and training exhaustion to be optimal (5.0, 5.0 - 6.2). Participant P5 showed particularly interesting results, which are reported and discussed in addition to the general findings.

5.4.1 ARCO feasibility

IMI score (max. score = 7) across participants showed a high intrinsic motivation throughout the entire training period (week 2: 5.41, 5.19 – 6.31; week 6: 5.58, 5.31-6.04) (Fig. 5.2A).

Intrinsic motivation was high for every question domain (see Table 5.3 in supplements). Not only did all participants show protocol compliance, on median (IQR, 25th -75th percentile) participants in the FREE group (trainings per week: 6, 4 – 9.75; training duration per week: 133, 98-182 min) trained more often compared to the INST group (trainings per week: 4, 4 – 4: training duration per week: 100, 76 – 109 min) (Fig. 5.2B&C). None of the ARCO devices had to be replaced or required mechanical repair during home-based training. Three participants contacted the examiners because of a problem with the device, which could be solved via phone or an additional home visit in one of the cases. In the ARCO Evaluation Questionnaire, participants reflected the training as predominantly positive. It was easy to handle hardware (e.g. changing the accessories or resistance), software and interface, and independent use was possible for all participants.

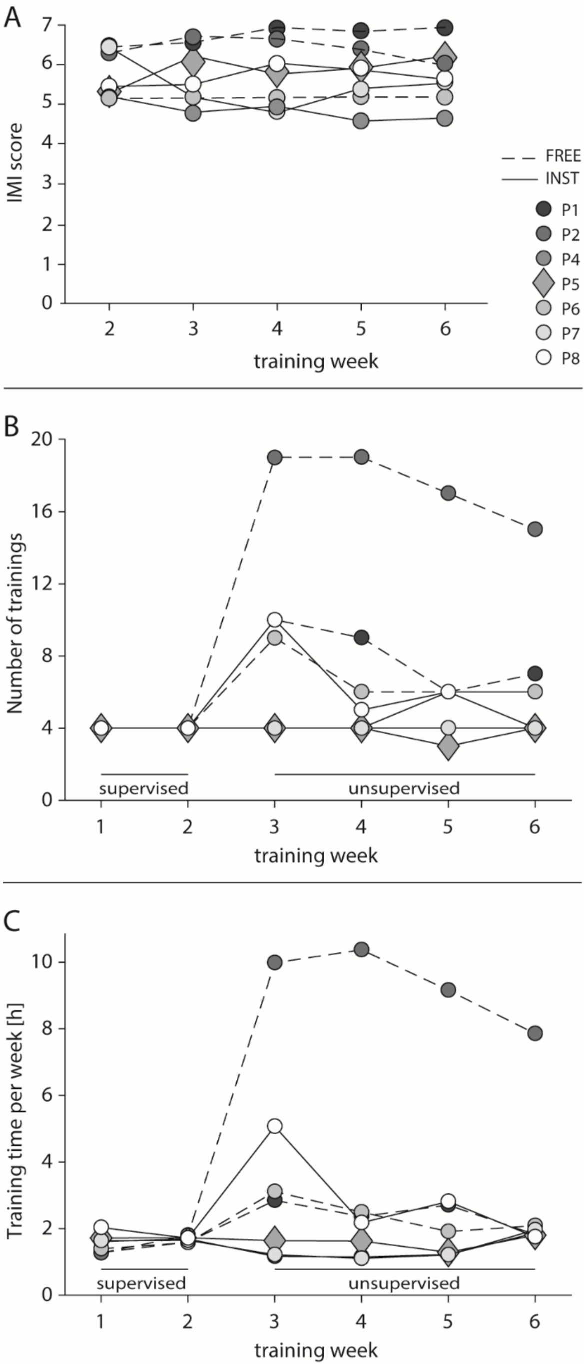

Figure 5.2: Feasibility of ARCO therapy. A) IMI (Intrinsic Motivation Inventory) scores per every week and patient. B) Number of trainings performed by every participant each week. Participants of the INST group were compliant to the protocol. Participants of the FREE group conducted more trainings than those of the INST group. C) Training time in hours per week. Only the actual movement time is included here, while the time to change settings in the software, start a new game, change the accessory of the ARCO device etc. is not included but was part of the perceived training session duration for the participants. While the FREE group trained for a longer duration, the INST group trained about 100 minutes per week. Dashed lines indicate participants in the FREE group (i.e. no training instructions for unsupervised training) while solid lines represent participants of the INST group (i.e. instructed to train 4x a week for 25min).

5.4.2 Clinical outcomes

Significant improvements were observed in the FM-UE score (Pre: 41, 37 - 48; Post 43, 38.5 - 49.59; p = 0.017) and in the CASA score (Pre: 39, 35.5 - 42; Post: 42, 37-44.5; p = 0.013). BBT scores increased (Pre: 13, 12.5 - 33; Post: 21, 15 - 37.5; p = 0.057) approaching significance (Fig. 5.3A). Wrist extension force increased in both the MA and LA limb. The increase was significant for the MA limb (p = 0.032) (Fig. 5.3B). Sensory impairment, measured as EPT was significantly improved for the index finger on the MA hand (Pre: 3.50, 1.90 - 2.29 mA; Post: 2.77, 2.08 - 3.43 mA; p = 0.04) but not for the 5th digit and the thenar eminence. No changes in sensory perception were observed for the LA hand.

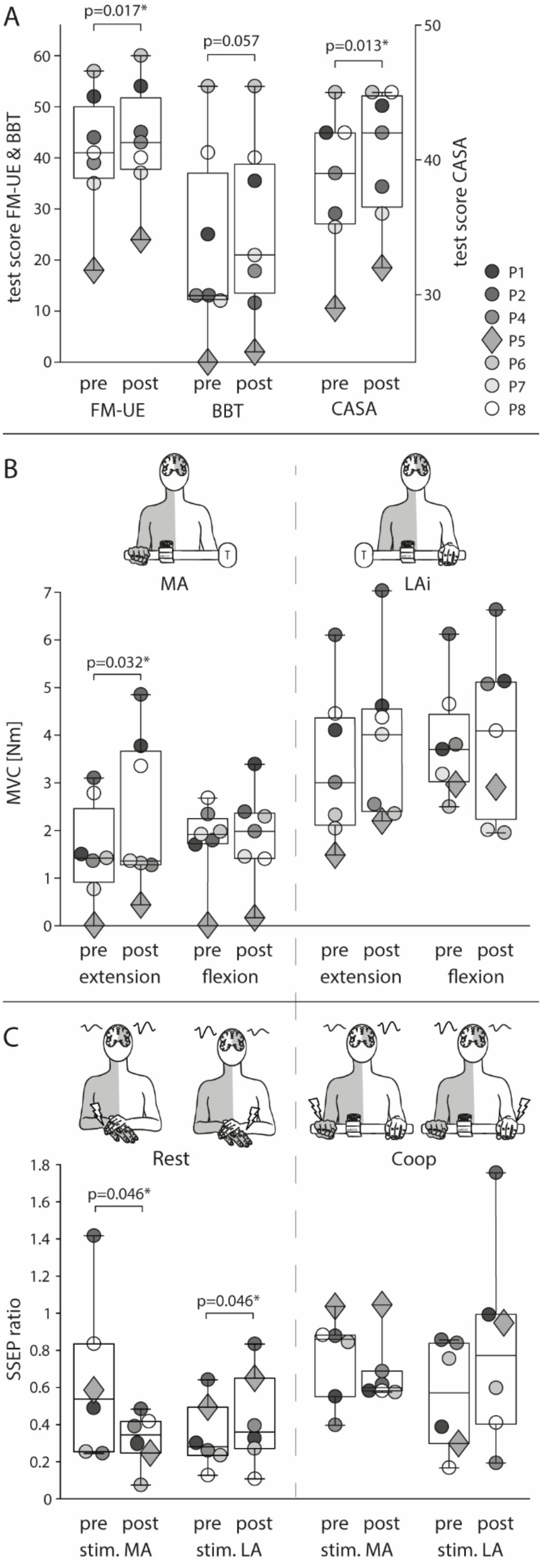

Figure 5.3. Changes in clinical outcomes before and after 6 weeks of ARCO therapy. A) Significant improvements occurred in the Fugl-Meyer Upper Limb Score (FM-UE) and Cooperative Activity Stroke Assessment (CASA) while the Box and Block Test (BBT) approached significance. Note that P5 increased in the BBT from 0 to 2. B) Static Maximal Voluntary Contraction (MVC) was recorded from unilateral wrist extension or flexion of both limbs performed with the “spindle” accessory. Note that P5 could not perform wrist extension or flexion prior to therapy

and recovered some voluntary movement during therapy. C) Changes in SSEP amplitude ratio (ipsilateral amplitude divided by contralateral amplitude) elicited with ulnar nerve stimulation at rest or during cooperative hand movements. After ARCO therapy most participants show a decreased SSEP ratio when elicited at the MA limb. In contrast, SSEP amplitude ratio increased in most participants after the therapy when elicited at the LA limb. Effects are similar and consistent in almost all participants during rest or during cooperative hand movements. Asterisks indicate significant differences ($p < 0.05$). MA = more affected limb; LA = less affected limb.

5.4.3 Case analysis: Participant P5

One participant (P5) showed particularly interesting results in response to ARCO therapy. This participant had the lowest clinical scores of all trained participants prior to therapy (Fig. 5.3A & B). P5 showed no voluntary wrist movement and scored 0 in the BBT. A magnetic resonance image and patient characteristics are presented in Figure 5.4. After the training, this participant could voluntary extend (MVC: 0.44 Nm) and flex (MVC: 0.17 Nm) the wrist of the MA limb, scored 2 in the BBT and increased from 0 to 4 points in the FM-UE wrist category. The change of the total FM-UE was clinically significant (6 points). Although severely impaired, this participant managed the handling of the ARCO device including software, game control, hardware, and independent detachment/attachment of the available accessories.

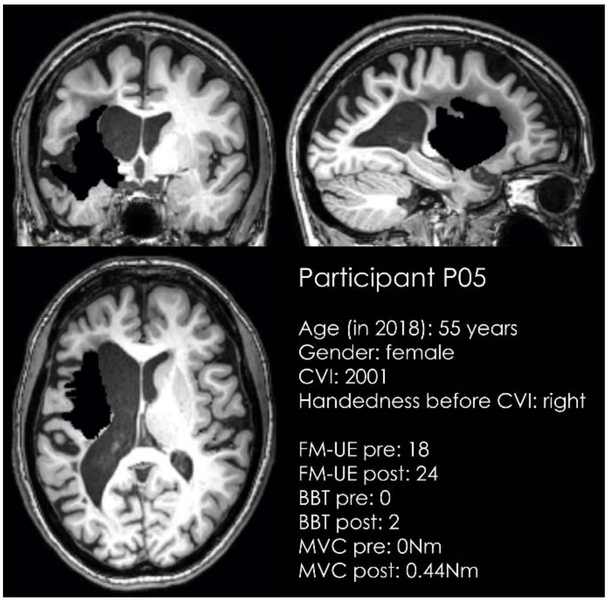

Figure 5.4: Participant P5. T1 weighted magnet resonance image and clinical characteristics. The image illustrates a large lesion spreading over the basal ganglia and an enlargement of the lateral ventricle. This participant showed the lowest clinical scores before therapy (i.e. FM-UE score, BBT score) and could not voluntarily extend the affected wrist. Despite the major damage and impairment, the participant was able to train with the device and upper limb function improved. Note that the stroke incident of this patient occurred in 2000 while this image was taken in 2018

after the therapy period of the present study. Maximal Voluntary Contraction (MVC) is referred to wrist extension of the more affected limb.

5.4.4 Neurophysiological outcomes

Due to a technical error, the SSEP data of P6 had to be discarded. After the therapy, SSEP ratio decreased after stimulation of the MA limb, in contrast to an increase in SSEP ratio after stimulation of the LA limb for both rest and cooperative hand movement conditions. This behaviour was consistent in all participants except for P4 and significant at rest (Stim. MA limb, $p = 0.046$; Stim. LA limb, $p = 0.046$, Table 5.2). Contralateral reflex responses could be evoked in three of the seven participants. The magnitude of contralateral reflex responses in these three participants tended to increase in the MA wrist extensor (i.e. after stimulation of the LA limb) while they decreased in the LA wrist extensor (i.e. after stimulation of the MA limb) (see Fig. 5.5 in online supplements).

Table 5.2: SSEP amplitude ratio

		SSEP ratio	
Stim. MA limb		Pre	Post
	Rest	0.53 (0.31-0.77)	0.34 (0.26-0.41)*
	Coop	0.86 (0.62-0.88)	0.60 (0.58-0.66)
Stim LA limb			
	Rest	0.28 (0.24-0.44)	0.36 (0.28-0.58)*
	Coop	0.57 (0.32-0.81)	0.77 (0.45-0.98)

SSEP ratio is calculated as absolute ipsilateral/contralateral SSEP peak to peak amplitude. MA = more affected; LA = less affected; SSEP = Somatosensory evoked potential. Asterisks indicate significant difference from Pre to Post ($p<0.05$). Values are given as median (1st quartile – 3rd quartile)

5.5 Discussion

The present pilot study addressed the feasibility and efficacy of home-based ARCO therapy in chronic stroke survivors. The main findings of the study were that 6 weeks of cooperative hand movement training with the ARCO device (i) was safe and feasible to be applied in an unsupervised home-based setting in all participants, (ii) significantly improved upper limb function, and (iii) allowed a severely affected patient (chronicity over 17 years) to regain some voluntary wrist movement in the more affected limb.

5.5.1 ARCO feasibility

ARCO was safe, feasible and well accepted by the participants. Median IMI scores were high not only at the beginning (week 2: 5.41) but also throughout the whole therapy period (week 6: 5.58). Similar scores were achieved in other studies using virtual-reality based interactive tabletop- (Beursgens et al., 2012; Jacobs et al., 2013), telerehabilitation- (Lloréns et al., 2015) or robot-assisted (Nijenhuis et al., 2015) devices aiming for self-administered therapy. High intrinsic motivation for the domains “Importance/Effort” and “Value/Usefulness” (Table 5.3 in supplements) indicated that participants subjectively perceived ARCO therapy as beneficial and important to improve their upper limb function. This finding is supported by the training behaviour. Participants in the INST group followed the protocol as recommended. Notably, participants without dose recommendations (i.e. FREE group) showed a higher training dose during home-based training. This suggests a strong intention to train with the ARCO device especially when participants are allowed to train on their own discretion. The self-administered training dose in the present study was similar (Nijenhuis et al., 2015) or higher (Sivan et al., 2014) compared to other studies presenting home-based training approaches for a similar period. Besides motivating exergames, participants reported the ARCO device’s hardware and software to be simple and intuitive. This likely contributed to the good feasibility and intention to train reported here. Home-based ARCO therapy was also feasible and safe to be used for P5 without external support suggesting it to be applicable also in severely affected patients.

It has been proposed that (robotic-) assistive devices might lead to a better outcome than conventional therapy (Housman et al., 2009; Klamroth-Marganska et al., 2014), which might be not always accessible, difficult in self-administration or coupled with high costs, especially after hospitalization. Therefore, the simple application of ARCO therapy might have the potential to reduce costs and increase accessibility of therapy.

5.5.2 Improvements in upper limb function

Optimal responsiveness to treatment is expected to occur in the first 3-6 months after stoke before recovery plateaus (Prabhakaran et al., 2008; Stinear, 2017). However, there may be still some motor recovery occurring beyond this period (Lohse et al., 2014; Page et al., 2008; Sun et al., 2018; Whitall et al., 2000). ARCO therapy lead to significant improvements in upper limb impairment and function as measured with FM-UE, CASA, and extensor MVC of the MA limb despite a median time post-stroke of 13.5 years. The median increase in FM-UE score was significant but rather small (i.e. 2 points). Van den Lee et al. reported similarly changes in the FM-UE score (1.2 points) in chronic stroke participants (median 3.6 years) using a six times higher training dose as in the present study (Van Der Lee et al., 2001). Studies using robot assisted therapies achieved slightly higher FM-UE changes, i.e. 3.3 points in chronic stroke participants (average chronicity 2.3 years) (Fasoli et al., 2004) or 3.4 points (Klamroth-Marganska et al., 2014) which were statistically significant compared to conventional therapy. Especially severely affected patients might benefit from such robot-assisted therapies since the weight support offers training of the more affected limb with high intensity and dose even with minimal residual function (Housman et al., 2009). However, robot-assisted therapy may significantly improve motor impairment, but not force (Klamroth-Marganska et al., 2014; Mehrholz et al., 2012). We are able to show significant improvements both in impairment and voluntary force in the present study, which might be of considerable functional advantage. However, neither the above mentioned nor the present study showed average FM-UE changes in the range considered as clinically meaningful (4.25-7.25) (Page et al., 2012), which indicates a generally limited recovery potential in the late phase of stroke.

Positive transfer effects in clinical assessments for unilateral impairment and function (i.e. FM-UE, BBT, MVC) occurred in the present study despite ARCO therapy being performed with bilateral movements. This suggests that task-specific training with the ARCO induces general transfer and non-task-specific effects. These motor improvements were accompanied by improvements in sensory impairment. We could show that the EPT of the index finger was significantly lower after ARCO therapy. Either hand, irrespective of moving or stabilizing, received continuous haptic feedback over the kinematic chain during ARCO therapy. This continuous cooperative “sensation” might be crucial in the precise control of force generation of either hand in solving cooperative tasks (Thomas et al., 2018) and might explain the improvements in sensory perception shown here.

5.5.3 Case study P5

The results of one participant (P5) were of particular interest. P5 showed considerable flexor-spasticity and no voluntary movement in the wrist and finger joints prior to training. The distal MA limb was therefore only able to statically compensate the forces from the LA moving limb during therapy. This participant was able to voluntarily move the MA wrist and fingers at the end of the study, could grasp and lift two wooden blocks over an obstacle in 60 seconds (BBT-score) and increased from 0 to 4 points in the wrist category of the FM-UE score. These improvements in function occurred despite an almost solely static activation of the MA limb during therapy. P5 improved 6 points in the FM-UE surpassing the suggested minimal clinical difference of the FM-UE (Page et al., 2012). Upper limb recovery, especially for P5, might be attributed to the unique functionality of the ARCO device. ARCO transfers the rotation applied from one hand to its cooperating partner, which compensates with the same force expenditure by stabilization of the handle. This provides a considerable advantage: Dependent on the severity of stroke, the moving limb can be either the MA or LA limb. This has also allowed P5 (without voluntary movement in the MA distal limb) to train a functionally relevant bilateral cooperative task where both hands are proposed to constantly utilize the specific neural mechanisms underlying cooperative hand movements (Dietz and Schrafl-Altermatt, 2016). This functionality might allow the ARCO device to be used by a greater range of patients than other therapies. For example, constraint Induced Movement Therapy (CIMT) is thought to be one of the most effective treatments in stroke rehabilitation, however patients need a certain degree of voluntary movement as a prerequisite, e.g. 10°-20° of active voluntary wrist extension (Baldwin et al., 2018; Barzel et al., 2015; Page et al., 2008) or 10° active extension of the thumb and two other digits (Barzel et al., 2015; Kwakkel et al., 2016). Similarly, in studies presenting therapies using robot-assisted devices, participants were required to move the wrist by at least 15° (Sivan et al., 2014) or 15° active elbow-flexion and finger flexion (Nijenhuis et al., 2015), respectively, for inclusion. In contrast, ARCO therapy might be applied and achievable for patients with minimal upper limb and no wrist function.

5.5.4 Neurophysiological findings

After ARCO therapy, SSEP amplitude ratio was decreased when the MA limb was stimulated while it increased with stimulation of the LA limb (Fig 5.3C). This indicates that the more affected hemisphere becomes more involved in processing of sensory input with ARCO therapy. This could suggest that the afferent pathways show a rebalancing of sensory input processing in favor of the more affected hemisphere. Similarly, the contralateral reflex responses seemed to be decreased after training in the LA limb and increased in the MA limb. A rebalancing of efferent output in favor of the MA limb could be also speculated here.

It is known that the underlying basis of bilateral movement training is to utilize the intact hemisphere and pathways via callosal connections to support the activation of the MA hemisphere promoting intra- and interhemispheric rebalancing of excitation and inhibition (Cauraugh et al., 2010; Cauraugh and Summers, 2005; Luft et al., 2004; Stinear et al., 2008). Cooperative hand movement training in the present study might have caused similar effects leading to the rebalancing of sensory afferent input and efferent output in favor of the ipsilesional structures.

5.5.5 Limitations

The main limitation of this pilot study is the small sample and a missing control group. The stable pre-measurements separated by one week and the chronicity of the participants (median 162 months) indicate that the positive outcomes after ARCO therapy are to be ascribed to spontaneous neurobiological recovery (Langhorne et al., 2011). However, we cannot exclude the possibility that other unimanual or bimanual non-cooperative movement training would have caused similar functional or neurophysiological effects. Although most clinical outcomes were statistically significant, they failed to reach clinical significance.

Unfortunately, this seems to be a rather general limitation for most chronic stroke survivors than due to the choice of intervention or dose. Because of the sample size, findings have to be interpreted with caution and are not necessarily generalizable. We are not yet able to report a “severity threshold”, that is, a specific patient profile suitable or not suitable for ARCO therapy. Further, all participants in the present study were in a chronic phase after stroke, thus efficacy and feasibility of ARCO therapy early after stroke (i.e. acute or subacute phase) and its integration in clinical daily routine has yet to be elucidated.

5.6 Conclusion

One of the main goals of stroke rehabilitation is the improvement of upper limb function and impairment, however, growing number of patients and insufficient accessibility limit optimal recovery. With ARCO therapy and the unique functionality of the ARCO device, we present a novel approach focusing on functionally relevant cooperative hand movements, which could be performed by all participants not only in the hospital but also without therapeutic surveillance at their homes. Besides general positive effects, one severely affected patient regained some voluntary wrist and finger movement despite being chronic since over 17 years. We report ARCO therapy to be feasible, safe and efficient for promoting upper limb recovery. It might thus be a promising and easily accessible therapy approach in stroke rehabilitation for a broad range of stroke phenotypes. In the future, controlled clinical trials are needed to elucidate the efficacy and feasibility of ARCO therapy in a larger population including different stroke phases and severities.

5.7 Supplements

5.7.1 Supplemental Methods

ARCO therapy

Participants were familiarized with the ARCO device, software interface and how to control the exergames during the first training session. The therapists had to consider aspects of the participants’ individual level of functional impairment for constructing the training protocol, including: (1) Can the more affected limb (MA) be used as the active limb? (2) If yes, which accessories can be used by the MA limb? And (3) for how long are participants able to use the MA hand as the moving or static hand during a session? Use of the MA limb as the moving limb was encouraged, however, moving and stabilizing limb could be switched in case of e.g. fatigue or pain. The specific neural coupling mechanisms during cooperative hand movements have been shown to be robust and insensitive to changes in movement velocity or resistance (Thomas et al., 2018), thus resistance of the ARCO was set individually for every participant and adapted to be reported as an optimal training intensity by the participant. The desired movement execution for each accessory was shown to the participants by therapists during the initial two supervised training weeks. During the unsupervised home-based therapy period, tutorial videos occurring prior to the start of each exergame helped the participants for a correct movement execution. Additionally, movement execution was controlled during weekly visits by the therapists.

Electrical perception threshold

Electrical stimulation (biphasic pulse of 0.2ms duration with a frequency of 3.1Hz) was applied at the skin of thenar eminence, the index finger and the pinky finger of both the affected and unaffected limb through self-adhesive surface electrodes (Ambu® A/S Neuroline 700, Denmark) with a Keypoint® DantecTM G4 (Neurolite, Belp, Switzerland). Stimulation intensity was stepwise increased by 0.1 mA starting at 0 mA with a frequency of ~1Hz until the participant subjectively reported perception of the stimulus. This was repeated three times to validate the correct threshold.

Neurophysiological assessments

To assess the EMG reflex activity in the contralateral limb (schematic drawing in Fig. 5.5) and to evoke somatosensory evoked potentials (SSEP), 15 electrical stimulations were applied at the ulnar nerve of the wrist via a Keypoint® DantecTM G4 (Neurolite, Belp, Switzerland) through self-adhesive surface electrodes (Ambu® A/S Neuroline 700, Denmark). The stimulation electrodes were placed on the ulnar nerve at the wrist (2cm inter-electrode distance, cathode proximal). The stimulations were triggered randomly between 3-8s at rest or during cooperative hand movements. Participants performed cooperative hand movements with bilateral anti-phasic wrist extension/flexion movements in supine position using the “spindle” accessory. Stimulation intensity was calculated as the sum of the sensory threshold (i.e. minimal intensity at which the participant perceived the stimulus) and the motor threshold (i.e. intensity of the first visible twitch of the abductor digiti minimi). The stimulation consisted of a train of four biphasic pulses of 1ms duration separated by 2ms. EMG reflex activity of the ECR muscle of both upper limbs (Noraxon, Scottsdale, AZ, USA) were recorded with hydrogel surface electrodes (KendallTM H124SG, 2,4cm diameter) sampled (1500Hz) and band-pass filtered (10-10.000Hz). The magnitude of the contralateral reflex response was quantified as the reflex to background ratio. After rectification of the EMG signal, the root mean square (RMS) was calculated in the time window 75ms-135ms after stimulation onset, which includes the main components of the contralateral reflex response (i.e. N2/P2 amplitude) (Dietz et al., 2015). It was then normalized to the background RMS EMG -30ms to -10ms prior to stimulation. SSEPs were recorded (DantecTMKeypoint® G4, Neurolite, Switzerland) via needle electrodes (Spes Medica, 12mm, Genoa, Italy) placed on the scalp on the locations of C3 and C4 and referenced to Fz with 24kHz and filtered (band-pass: 3Hz-500Hz,band-stop 45-55Hz). N20/P25 SSEP peak –to peak amplitude was automatically calculated as the difference of the minimum between 17ms and 23ms (N20) and the maximum between 21ms and 29ms (P25) however, every trace was visually verified and time-adjusted if necessary. For the SSEP ratio, the ipsilateral SSEP amplitude was divided by the contralateral SSEP amplitude.

5.7.2 Supplemental Results

Intrinsic Motivation Inventory (IMI)

We show high values for each of the question domains throughout the therapy period (Table. 5.3). High ratings were achieved especially for the domains “Effort/Importance” and “Value/Usefulness”.

Table 5.3 Intrinsic Motivation Inventory (IMI) scores for the different question domains

	training week				
IMI domain	2	3	4	5	6
Interest/ Enjoyment	6.5 (5.8-6.7)	6.5 (6.1-6.8)	6.2 (5.7-6.5)	6.5 (6.5-6.8)	6.5 (5.8-6.8)
Competence	6.0 (5.1-6.3)	5.3 (5.0-6.1)	5.0 (4.3-6.3)	4.6 (4.3-6.1)	5.3 (4.8-6.3)
Effort/Importance	6.6 (6.0-6-8)	6.8 (5.8-6.9)	6.8 (5.7-7.0)	7.0 (5.4-7.0)	6.8 (6.1-7.0)
Value/Usefulness	6.6 (5.4-7)	5.8 (5.5-6.4)	6.0 (5.5-6.6)	6.6 (5.5-7.0)	6,5 (5.6-7.0)
Pressure/Tension	4.0 (3-5.75)	4.5 (3.0-5.5)	6.0 (4.0-6.5)	4.5 (3.5-5.7)	4.5 (3.0-5.7)

Values are given as median (1st quartile-3 quartile). The maximum score of the IMI is 7.

Neurophysiological outcomes

Contralateral reflex responses could be evoked in three of seven participants. The magnitude of reflex responses of these three participants tended to increase in the MA wrist extensor (i.e. after stimulation of the LA) while they decreased in the LA wrist extensor (i.e. after stimulation of the MA) (Fig.5.5).

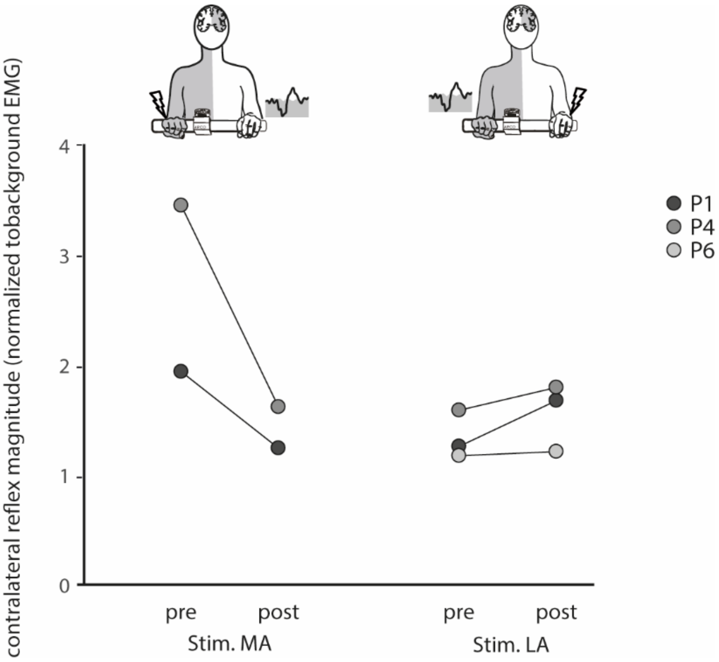

Figure 5.5: Magnitude of reflex responses in the extensor carpi radialis muscle contralateral to the site of stimulation. Stimulation of the MA limb leads to a contralateral reflex response in the LA limb and vice versa. Contralateral reflexes could only bilaterally be evoked in P1 and P4, and in P6 after stimulation of the LA limb. The y-axis represents normalized values, that is, absolute reflex magnitude was normalized to background muscle activity prior to stimulation.

Chapter 6

General Discussion

The main objective of this thesis was to evaluate whether cooperative hand movements and their underlying neural control have the potential for an evidence based therapy approach in stroke rehabilitation. To address this, we first conducted studies to gain a better understanding of the sensorimotor control of cooperative hand movements. From these studies and previous research, a novel scientific based therapy approach focussing on cooperative hand movements was developed and evaluated for its feasibility and efficacy to improve upper limb function in chronic stroke survivors. In the following section, the findings of each chapter will be summarized and briefly discussed. Additionally, limitations of the thesis and implications for future research will be addressed.

6.1 Neural coupling is modulated by the disturbance of sensory perception

In chapter 2, we investigated the influence of unimanual sensory deprivation using an ischemic nerve block (INB) on the neural coupling mechanism. During INB, we observed that contralateral reflexes (i.e. reflexes in the limb contralateral to the side of stimulation) were enhanced at the sensory-deprived side and reduced at the non-deprived side. This might be explained by an imbalance in the interhemispheric coupling of S2 since this area is known to integrate shared afferent input from both hands (Disbrow et al., 2001) and plays an important role in the neural coupling during cooperative hand movements (Dietz et al., 2015). Thus, the mismatch of the afferent input could lead to a biased interhemispheric balance (Hari et al., 1998) resulting in an imbalance in the contralateral reflex output. Actually, we hypothesized a reduction of contralateral reflexes in both arms based on the enhanced influence of ipsilateral afferent pathways during cooperative tasks (Schrafl-Altermatt and Dietz, 2014), that is, a reduced afference would affect both hemispheres similarly. Instead, such a sensory deficit seems to induce an interhemispheric disbalance leading to an unequal output of contralateral reflexes in favour of the sensory deprived limb. Therefore, the neural coupling may serve as a compensatory mechanism by enhancing the output to the sensory impaired side. Similarly, such a compensatory role could be also observed in chapter 3 of the present thesis where the neural coupling was suggested to serve as a mechanism to match forces between the two limbs to maintain cooperative task success.

We further observed that despite unilateral sensory deprivation, clear contralateral reflex responses were observed in both the right and left limbs. This might indicate that afferent feedback about the cooperative action from the non-deprived hand is processed and integrated in both hemispheres sufficiently to generally preserve the functional coupling.

The structures responsible for the generation and transmission of the contralateral reflex are still not known. This question cannot confidently be answered with this present study. But the fact that INB only induced modulations in the contralateral but not in the ipsilateral reflexes indicate different pathways for their transmission and might allow further speculation in the processing of the contralateral reflexes and where modulations might have occurred.

One possibility might be that the sensory input from the stimulation is transmitted to the contralateral hemisphere and is integrated over the corpus callosum to the ipsilateral hemisphere releasing the reflex response to the contralateral limb. In this scenario, modulation of transcallosal excitability due to INB would only affect the contralateral but not the ipsilateral reflex. However, this possibility is unlikely since ipsi- and contralateral reflexes occur with a similar latency (Dietz et al., 2015) and callosal transmission would delay the response for at least 8ms (Cracco et al., 1989). Alternatively, the stimulation might be processed in the ipsilateral hemisphere via direct ipsilateral afferent pathways (Noachtar et al., 1997) releasing the response to the contralateral limb since an enhanced involvement of these pathways was observed during cooperative tasks (Schrafl-Altermatt and Dietz, 2014). Direct ipsilateral afferent projections, which are not involved in the transmission of the ipsilateral reflex, might be affected by INB modulating only the contralateral reflex. Another possibility might be that the stimulation is transmitted to the contralateral hemisphere releasing the response to the ipsilateral limb via ipsilateral efferent pathways. These can involve the uncrossed corticospinal tract (Welniarz et al., 2017) or the cortico-reticulospinal tract (Baker, 2011). This would involve an efferent route for the contralateral reflex not involved in the processing of the ipsilateral reflex where a modulation due to INB might have occurred. Lastly, since both ipsilateral afferent and efferent pathways might be involved in the contralateral reflex, it cannot be excluded that its processing (and its modulation during INB) involves a combination of these pathways.

6.2 Effect of different movement demands on the neural coupling

In chapter 3, we investigated whether modifications in movement demands (i.e. velocity and resistance) influences the neural coupling observed during cooperative hand movements. We demonstrated that not only reflexes at the ipsilateral but also those at the contralateral side of stimulation linearly increased with muscle pre-activation associated with increasing movement velocity and resistance. In previous studies, this automatic scaling was only investigated and observed for reflex activity ipsilateral to the side of stimulation and was suggested to compensate for mechanical disturbances of the limb (Marsden et al., 1972; Marsden et al., 1976; Pruszynski et al., 2009). We could show that this scaling of reflex activity also applies to reflexes at the contralateral side of stimulation. This indicates that unilateral disturbances are rapidly compensated at both limbs to precisely match forces exerted from both limbs.

Therefore, the neural coupling mechanism might have an important functional role that serves to maintain task success since any force differences between the limbs would interfere with solving cooperative tasks. Such a functional role of bilateral corrective responses to unilateral perturbation to maintain the task goal is supported by previous work. For example, it was shown that when independent cursors had to be moved to a target by each arm, unilateral perturbations were only corrected by the perturbed arm. In contrast, moving a single cursor with both arms, the same perturbation elicited corrective movements also in the unperturbed arm (Diedrichsen, 2007). Using a similar task, another study observed bilateral reflexes in the upper limbs during unilateral perturbation only in the shared cursor condition (Mutha and Sainburg, 2009). This underlines that to maintain task success, which is dependent on both arms, bilateral corrective adaptions are required.

Further, we observed that clear contralateral reflex responses occurred irrespective of the movement demand suggesting the neural coupling to be a robust mechanism that seems to be not limited to a certain movement velocity or resistance. This finding could have important implications for the use of cooperative hand movements in stroke rehabilitation. It is known that hemiparesis after stroke strongly limits force (Lodha et al., 2010) and movement velocity (Cirstea and Levin, 2000) of the affected limb. Therefore, patients with such limitations in movement capacity might still benefit from the neural coupling supporting the control of the affected limb.

6.3 Integrated sensory feedback during cooperative hand movements influences sensorimotor control

In chapter 4, we investigated how differences in the predictability of sensory feedback between bimanual object manipulation tasks modulates muscular activations and the processing of external sensory input. We could demonstrate that co-activation was strongly reduced during the cooperative task. Increasing co-activation is thought to be a strategy to enhance the readiness to compensate unpredictable external events for example by increasing joint stiffness (Burdet et al., 2001; Franklin and Wolpert, 2011) or grip force to an object (Johansson, 1991). Thus, the reduced co-activation during cooperative tasks is associated with the availability of the integrated sensory feedback from both hands that can be accurately predicted by internal forward models. In contrast, the task in which unpredictable sensory feedback was perceived causes a constant mismatch between the predicted and perceived sensory feedback. This task cannot only be controlled by forward mechanisms, thus, co-activation might be increased for a higher readiness for external disturbances. Further, we observed that besides a general sensory gating (i.e. reduction of SEP amplitude) during movement compared to rest, SEP amplitudes were task specifically reduced between the tasks which was most pronounced during the cooperative task. It is known that our brain uses internal forward models to predict future sensorimotor states and attenuates the sensory consequences from our own actions as they can be accurately predicted (Blakemore et al., 1999; Wolpert et al., 1995). However, this attenuation of self-generated input seems to be different to sensory gating which reflects a general reduction of any incoming external stimuli depending on the current motor behaviour (Brown et al., 2013; Lei et al., 2018; Rushton et al., 1981). In fact, in the present study, sensory gating was investigated by assessing changes in SEP amplitude, that is, a response to a stimulus evoked from an equally unpredictable external source. As for the co-activation, the reduced SEP amplitudes during cooperative tasks might be explained with the strong predictive forward control due to the availability of the integrated feedback of both hands which is accurately predictable. The maintenance of such control is less dependent on other sensory input, thus, the salience for external sensory information might be decreased leading to a stronger gating of incoming external inputs. We further observed that only the subcortical SEP component was modulated between tasks, thus, a task-specific gating of sensory input is suggested to occur at subcortical sites.

Together, these findings suggest that the sensorimotor control during cooperative tasks is more efficient compared to non-cooperative tasks since co-activation and the salience for external sensory input is reduced due to availability of well predictable integrated feedback of both hands. This might have implications for stroke rehabilitation. Co-activation is associated with spasticity of the affected limb (Hu et al., 2013; Ohn et al., 2013) and a higher motor effort (Franklin et al., 2008; Franklin and Wolpert, 2011). Therefore, training cooperative tasks might contribute to a reduction of spasticity and delay the accumulation of fatigue.

A question that might arise in this study is the relation between the behaviour of co-activation and sensory gating. We could not find a correlation between these two (data not shown) indicating that co-activation and sensory gating might not be directly linked. However, they were both similarly modified by the predictability of the task. Therefore, they might represent two “sides of the same coin” that are similarly adjusted by the CNS depending on the predictability of the task and might reflect the efficiency of the current sensorimotor control.

6.4 Integration of cooperative hand movements in stroke rehabilitation

The findings of the present thesis together with those of previous research support a beneficial use of cooperative hand movements in stroke. Therefore, in chapter 5, we developed a novel therapy approach focussing on cooperative hand movements and evaluated its feasibility and efficacy to improve upper limb function in stroke survivors. Chronic stroke survivors performed ARCO therapy for 2 weeks in a clinical setting followed by four weeks unsupervised at home. IMI scores revealed a strong intrinsic motivation and intention to train similar to those observed in other self-administrable home-based therapies (Lloréns et al., 2015; Nijenhuis et al., 2015) indicating a good feasibility of ARCO. Scores of all clinical assessments (i.e., FM-UL, CASA, BBT) and affected wrist extension MVC increased. We further observed that after therapy, the SEP amplitude ratio (ipsilateral/contralateral amplitude) increased after stimulation of the non-affected limb but was reduced after stimulation of the affected limb. Similarly, contralateral reflex responses increased in the affected limb while they decreased in the non-affected limb. The neurophysiological findings suggest a rebalancing of ipsilateral afferent input and efferent output in favour of the affected structures which might underlie the functional improvements of the affected limb (Cauraugh et al., 2010; Stinear et al., 2014). The more severely affected participants did not show contralateral reflex responses which is in line with previous findings (Schrafl-Altermatt and Dietz, 2016a). Yet, these patients showed functional improvements after the therapy. Thus, the presence of contralateral reflex responses as part of the neural coupling might have a supportive role, but is not the exclusive mechanism leading to improvements in upper limb function shown here. Vast research has shown the beneficial effects of bimanual movement training for improving upper limb function (Cauraugh et al., 2010; Luft et al., 2004; Summers et al., 2007). Therefore, the bimanual motor training in our therapy per se likely contributed to the observed improvements. One participant had a strong flexor spasticity prior to therapy and showed no voluntary wrist extension. After therapy, wrist movement slightly recovered and clinical scores improved clinically meaningful (Page et al., 2012). These results might be interesting when we consider our findings in chapter 4 where we could show that muscular co-activation is strongly reduced during the performance of cooperative tasks. It is known that co-activation is associated with the degree of spasticity in stroke patients (Hu et al., 2013; Ohn et al., 2013). Thus, it might be speculated that less co-activation and, consequently, a more discrete activation of agonist muscles during the training of cooperative tasks could have influenced a reduction of spasticity. This might have contributed to the meaningful functional improvements of this patient regarding clinical scores and slight voluntary wrist movement. The results of this patient further show that ARCO might have functional advantages compared to other therapies such as CIMT or some robot-assisted therapies which require a certain residual wrist function (Baldwin et al., 2018; Page et al., 2008; Sivan et al., 2014).

Together, we observed that ARCO therapy is efficient in improving upper limb function, is feasible to be applied in a broad range of stroke phenotypes, and targets intrinsic motivation and self-administration as key aspects for optimal therapy (Bermúdez i Badia and Cameirão, 2012; O'Brien et al., 2019; Saywell et al., 2017). The self-administrative nature of ARCO therapy allows its application not only at home but might be also feasible during hospitalization in the patient’s room. This could provide a possibility for the patients to train in addition to the standard therapy sessions advancing accessibility.

6.5 Limitations

In the first part of the study, we investigated the sensorimotor control of cooperative hand movements and underlined their potential benefit for stroke rehabilitation. However, these studies were carried out in healthy individuals, thus, the findings are not necessarily generalizable to a neurologically impaired population. For example, robust occurrence of contralateral reflexes was demonstrated in healthy individuals (Dietz et al., 2015) while these reflexes are usually not observable in severely affected stroke patients (Schrafl-Altermatt and Dietz, 2016a). We could demonstrate that the contralateral reflexes are robust even when movements are performed with low velocity and resistance. However, severely affected stroke patients, likely showing such a limited movement behaviour, might not profit from this robustness since this functional coupling of the upper limbs might not be present after all.

The newly developed ARCO therapy may be promising to advance stroke rehabilitation as it was shown to be easily accessible, feasible and effective to improve upper limb function. However, several points should be considered. First, the small sample size limits the study in generalization of the results. Second, the sample included only participants in a chronic stage. Effects might have been stronger in acute or subacute patients since neuroplasticity is most prominent early after stroke (Byblow et al., 2015; Langhorne et al., 2011). Third, clinical and neurophysiological assessments were only performed before and directly after the therapy. A follow-up investigation of the outcomes could give additional information about the long-term effects of our therapy. Lastly, the lack of a control group does not allow us to conclude that the results are specific for cooperative hand movement therapy. It might be that unimanual- or bimanual non-cooperative training would have caused similar changes in functional or neurophysiological behaviour.

6.6 Conclusion

The task-specific neural coupling during cooperative hand movements seems to have a functional role as a robust mechanism to compensate disturbances by matching the performance of both upper limbs to maintain task success. This mechanism is preserved even with sensory impairments and low muscular-pre activity. Further, cooperative tasks seem to underlie an efficient forward motor control by which muscular co-activation and the processing of external sensory input is reduced associated with the well predictable integrated sensory feedback of both hands. This reduced co-activation and the robustness of the neural coupling support previous studies in the notion that a training of cooperative hand movements might have beneficial effects in improving the function of the upper limb. Consequently, a novel therapeutic approach based on cooperative hand movements and their underlying neural control was developed that was feasible and efficient to improve upper limb function in stroke survivors. Together, the present thesis contributes to the understanding of sensorimotor control during cooperative hand movements and provides a promising scientific-based approach with a potential for further use in stroke rehabilitation.

6.7 Future considerations

We gained further insight into the sensorimotor control during cooperative hand movements supporting their potential for stroke survivors. However, many aspects of these movements regarding their control and optimal use for therapy are still not fully understood which leaves several avenues for future research.

6.7.1 Cooperative tasks: One concept, different coordination modes

In the present thesis, cooperative hand movements were investigated as reciprocal tasks analogous to opening a bottle, igniting a match or slicing bread where forces of one hand have to be precisely counteracted by the cooperating hand for task success. However, other situations in daily live require both hands to work cooperatively in a symmetrical coordination (e.g., lifting a box) in which homologous muscles are engaged in parallel (Kantak et al., 2017). Symmetrical movements seem to be the default operation mode of the central nervous system (CNS) for the upper limbs as they are easier and stable to perform (Banerjee et al., 2012; Kelso, 1984; Meyer-Lindenberg et al., 2002; Swinnen and Wenderoth, 2004). Behavioural differences might occur from interfering high- or low-level neural crosstalk (Cauraugh and Summers, 2005; Swinnen, 2002). For example, each limb might receive signals from each hemisphere via contralateral and ipsilateral pathways whose signals are congruent during symmetric tasks but can be conflicting in asymmetric tasks due to non-homologous muscle activation (Cattaert et al., 1999; Maki et al., 2008). It is therefore conceivable that a more synchronized motor output during symmetric cooperative tasks might lead to an even stronger reduction of co-activation as that observed in the present thesis during asymmetric cooperative tasks. Further, it has been shown that ipsilateral MEPs in the contracting biceps brachii muscle were increased during concurrent activation of the contralateral triceps muscle but were decreased during synchronous activation of bilateral biceps muscles (Tazoe and Perez, 2014). Given the assumed involvement of ipsilateral efferent pathways in the processing of the contralateral reflex during cooperative tasks (Dietz et al., 2015), it might be speculated that this reflex response is reduced during symmetric cooperative tasks. In contrast, recent results of our group (unpublished) show that ipsilateral MEPs in the wrist extensor were not different during symmetric and asymmetric cooperative tasks. Future studies could evaluate the influence of the coordination mode on the reflex behaviour during cooperative hand movements.

Further, investigations in this framework might also have clinical implications. Unilateral stroke may lead to hyperexcitability of the contralesional hemisphere resulting in increased transcallosal inhibition of the ipsilesional hemisphere (Murase et al., 2004; Ward and Cohen, 2004). Bimanual symmetric movement therapy is thought to increase the coupling between hemispheres and increase their synchronization (Cauraugh and Summers, 2005; Luft et al., 2004). Accordingly, symmetrical movements are assumed to rebalance inter- and intra-hemispheric inhibition to facilitate activity of the damaged hemisphere promoting upper limb recovery. In the present thesis we demonstrate a rebalancing of afferent input and efferent output in favour of the affected structures. However, it would be interesting to investigate if this effect is stronger after symmetric cooperative hand movement training.

6.7.2 Neural pathways involved in cooperative hand movement control

The neural pathways involved in the control of cooperative hand movements are still unclear. However, ipsilateral efferent pathways are assumed to play an important role. This notion is based on similar latencies of ipsi- and contralateral reflex responses as observed in previous studies (Dietz et al., 2015), and on recent results of our group (unpublished) demonstrating enhanced iMEPs during cooperative compared to non-cooperative hand movements. Supporting evidence could be gained by investigating ipsilateral cortico-muscular coherence which might be enhanced during cooperative tasks.

One pathway of the CNS for ipsilateral control involves the corticospinal tract via uncrossed axons projecting to the spinal cord (Welniarz et al., 2017) or over its axons recrossing at spinal level (Rosenzweig et al., 2009). Ipsilateral CST fibres are mainly involved in the control of axial and proximal muscles but have a minor role for the distal upper limb (Soteropoulos et al., 2011; Ziemann et al., 1999). In contrast, the reticulospinal tract, originating in the brainstem, is bilaterally organized also providing input to ipsilateral distal muscles (Baker, 2011; Soteropoulos et al., 2011) suggesting this tract as a likely candidate for ipsilateral efferent cooperative hand movement control. Future investigations may use startle reflexes since they are thought to arise from the reticular formation in the brainstem activating descending reticulospinal fibers (Grosse and Brown, 2003; Rothwell, 2006). Coherence of homologous upper limb muscles during startle reflex activity was shown to peak in the range between 10-20Hz. Since cortical drive synchronizes with muscles at higher frequencies this peak in coherence is assumed to be associated with reticulospinal drive (Grosse and Brown, 2003). It is conceivable that the startle reflex magnitude and its oscillating activity might be differently modulated during cooperative tasks which could provide novel insights into the pathways controlling these movements.

6.7.3 Further evaluation of ARCO therapy in stroke rehabilitation

The strongest capacity for functional reorganization of the CNS, and consequently optimal responsiveness to treatment, is known to take place in the acute and subacute stage, that is, within the first 3-6 months post stroke (Prabhakaran et al., 2008; Stinear, 2017). Although some recovery was reported to occur in the chronic (> 6 months) stage (Fasoli et al., 2004;

Klamroth-Marganska et al., 2014; Page et al., 2008), clinically significant improvements in function and impairment are difficult to achieve. In the present thesis, ARCO was only tested in chronic individuals, thus, we suggest its application and evaluation in an earlier stage post stroke.

The response to treatment can be highly variable in stroke survivors depending on the lesion size and location, integrity of cortico-cortical and corticospinal pathways, and initial impairment (Byblow et al., 2015; Langhorne et al., 2009). Thus, investigating ARCO therapy in a heterogeneous sample regarding the aforementioned factors could specify patients that respond best to the therapy. Regarding the importance of S2 areas for the neural coupling mechanism during cooperative tasks (Dietz et al., 2015) and the thalamus as the relay station for afferent input (Alitto and Usrey, 2003), ARCO therapy might be less effective in patients with lesions in those areas. Thus, future research should evaluate the effect of ARCO therapy in a larger sample including different patient subgroups; particularly regarding time after stroke, lesion characteristics, and residual sensorimotor function. Lastly, a randomized-controlled design would be the preferable choice to distinguish therapy-specific effects on sensorimotor function and neural reorganization.

6.7.4 ARCO therapy in other neurological diseases

ARCO was developed for the application in stroke patients to restore upper limb function based on the beneficial neural control of cooperative hand movements observed in previous studies and in the present thesis. Upper limb impairment is not exclusive for stroke, but is also prominent in other neurological diseases such as Multiple Sclerosis (MS) (Cattaneo et al., 2017; Spooren et al., 2012), Parkinson’s Disease (PD) (Agostino et al., 1998; Ponsen et al., 2008), and incomplete Spinal Cord Injury (iSCI) at cervical level (Cortes et al., 2013; Snoek et al., 2004). Recently, preserved contralateral reflex responses were observed even in severely affected iSCI (Scharfenberger et al., 2018). Thus, the enhanced bilateral organization of afferent and efferent pathways and the efficient motor control during cooperative hand movements (i.e., reduced co-activation) might be preserved not only in stroke but also in patients with other neurological diseases. The application of ARCO therapy might be of particular interest in patients with unilateral cerebral palsy (CP) in which damage of the CNS can occur shortly after birth or even prenatally (Krigger, 2006). CNS damage in this early stage leads to strong reorganization or rewiring of the sensorimotor system favouring ipsilateral control from the non-affected hemisphere as shown in enhanced mirror movements and ipsilateral MEPs in the affected limb (Jaspers et al., 2016). Based on the strong ipsilateral control during cooperative tasks and our observations that these are performed with reduced co-activation, ARCO therapy could optimize motor function in this patient population.

Therefore, an interesting question that remains is whether the application of cooperative hand movement training has the potential to be effective in promoting upper limb recovery not only in stroke but also in other neurological diseases.

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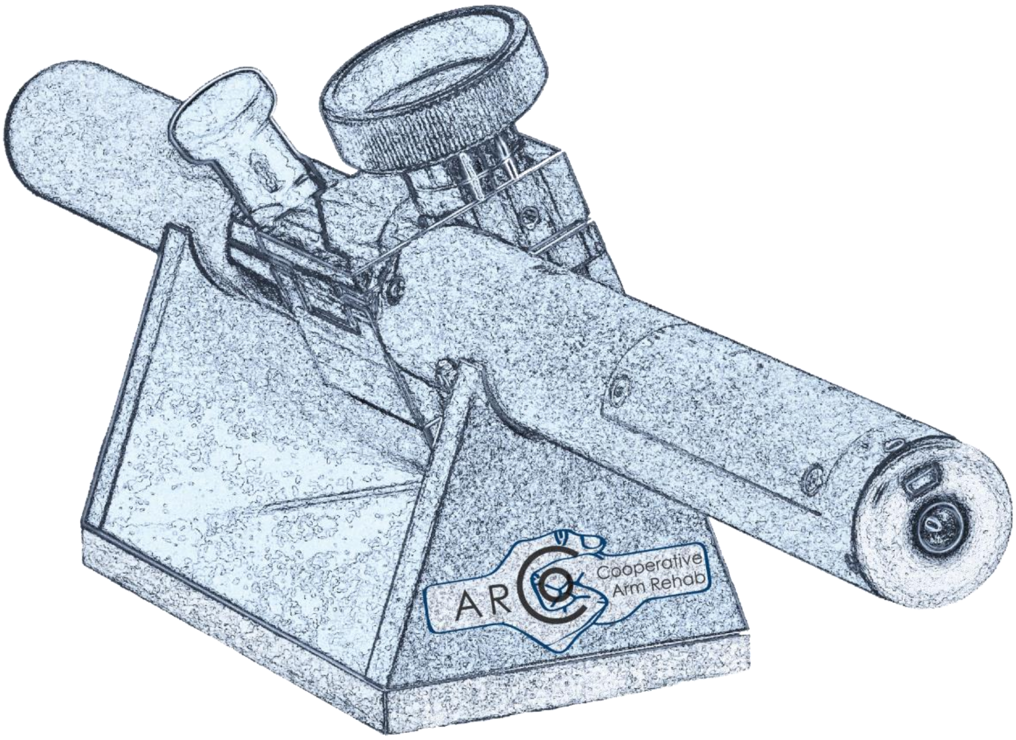
Glossary

ADL	Activities of Daily Living
ANOVA	Analysis Of Variance
ARCO	Cooperative Arm Rehabilitation
AUC	Area Under the Curve
CASA	Cooperative Activity Stroke Assessment
CIMT	Constraint Induced Movement Therapy
CNS	Central Nervous System
COOP	Predictable coupling condition
CP	Cerebral Palsy
CST	Corticospinal Tract
CVI	Cerebro-vascular Insult
EEG	Electroencephalography
EMG	Electromyography
EPT	Electrical Perception Threshold
Exergames	Virtual games designed to support exercise
EXT	Unpredictable coupling condition
FM-UE	Fugl-Meyer Assessment of the Upper Limb
FREE	Participant group free to choose their training group
HAEM	Haemorrhagic Stroke
ICA	Independent Component Analysis
IMI	Intrinsic Motivation Inventory
INB	Ischaemic Nerve Block
INST	Participant group instructed for specific therapy dose
ISC	Ischaemic Stroke
M1	Primary Motor Cortex
MCA	Middle Cerebral Artery
MEP	Motor Evoked Potential
MNS	Median Nerve Stimulation
MS	Multiple Sclerosis
fMRI	Functional Magnetic Resonance Imaging
MT	Motor Threshold
MVC	Maximal Voluntary Contraction
N2	Long latency negative peak
N20	First negative peak of cortical SEP component
NON	Uncoupled condition

P15	Positive peak of subcortical SEP component
P2	Long latency positive peak
P25	First positive peak of cortical SEP component
PD	Parkinson’s Disease
PMC	Premotor Cortex
PT	Perceptual Threshold
REST	Resting Condition
RMS	Root Mean Square
S1	Primary Somatosensory Cortex
S2	Secondary Somatosensory Cortex
SAI	Short Afferent Inhibition
SEP/SSEP	Somatosensory Evoked Potential
SI	Stimulation Intensity
SMA	Supplementary Motor Cortex
SCI	Spinal Cord Injury
STG	Superior Temporal Gyrus
VS	Vibration Sensation
TMS	Transcranial Magnetic Stimulatio

Appendix

ARCO
User Manual

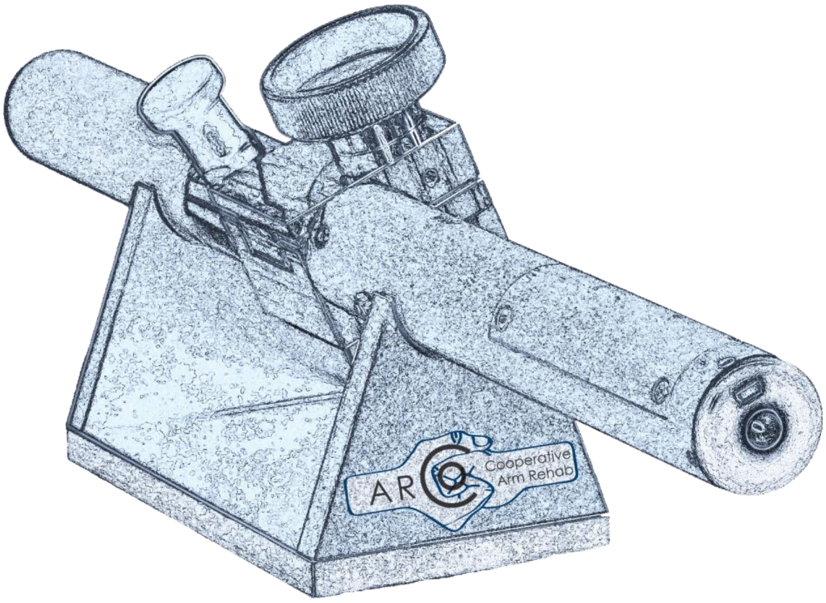


Lieber ARCO Benutzer, liebe ARCO Benutzerin

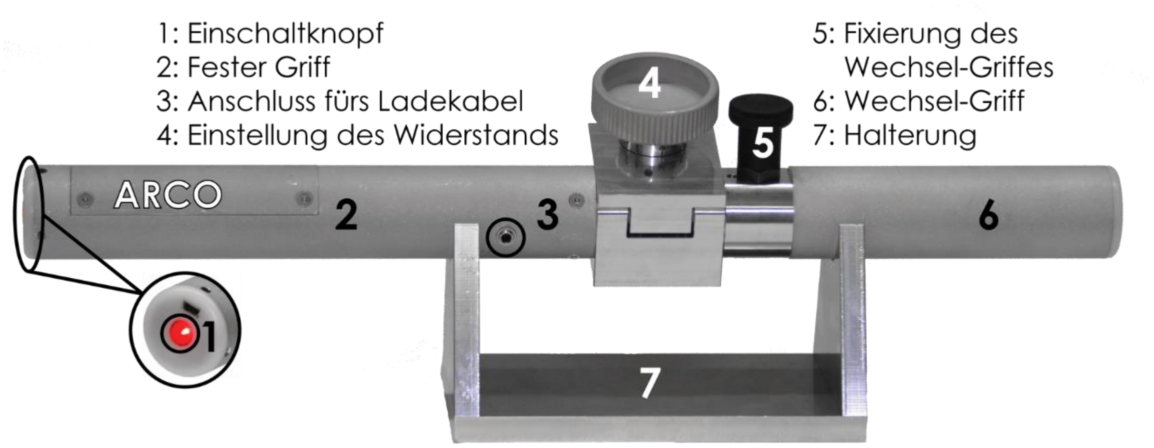
Dieses Handbuch enthält alle wichtigen Informationen zum Gebrauch des ARCO Gerätes und der Bedienung des Laptops und der Spiele. Lesen Sie es bitte vor dem ersten Gebrauch gut durch.

Häufig auftretende Fragen und Antworten sind in Kapitel 5 zu finden. Falls Sie weitere Fragen haben, wenden Sie sich bitte an das ARCO Team. Die Kontaktangaben sind auf Seite 38 zu finden.

Viel Spass und Erfolg beim ARCO Training!



Kurzanleitung



Laden Sie vor dem ersten Gebrauch den ARCO mit dem mitgelieferten Ladegerät vollständig auf (ca. 60min).
Schalten Sie ARCO ein, indem Sie den Einschaltknopf gedrückt halten (ca. 3sek) bis der er rot leuchtet.

Starten Sie den Computer und öffnen Sie die Software durch Doppelklick auf das ARCO-Symbol.

Wählen Sie Ihren Spieler-Name in der Liste an. Wählen Sie das gewünschte Spiel aus und befolgen Sie die angezeigten Anweisungen.

Viel Spass und Erfolg!

Laptop

Der ARCO kann mit zwei verschiedenen Laptop-Modellen benutzt werden. Überprüfen Sie, welchen Laptop Sie benutzen und entnehmen Sie dann die entsprechenden Informationen von Modell HP oder Model Acer.

Laptop-Modell HP

1: Windows-Symbol
2: Einschaltknopf
3: Anschluss fürs Ladekabel
4: Touchpad

5: f6 🔈⊘ : Ein- / Ausschalten des Tons
f7 🔈– : Ton leiser stellen
f8 🔈+ : Ton lauter stellen
6: ARCO-Symbol

Laptop-Modell Acer

1: Windows-Symbol
2: Einschaltknopf
3: Anschluss fürs Ladekabel
4: Touchpad

5: Fn+∇ 🔈+ : Ton leiser stellen
Fn+∆ 🔈- : Ton lauter stellen
6: ARCO-Symbol

Akku aufladen

Stecken Sie das Ladekabel in die markierte Öffnung (Laptop-Bild: 3) und schliessen Sie das Kabel ans Stromnetz an.

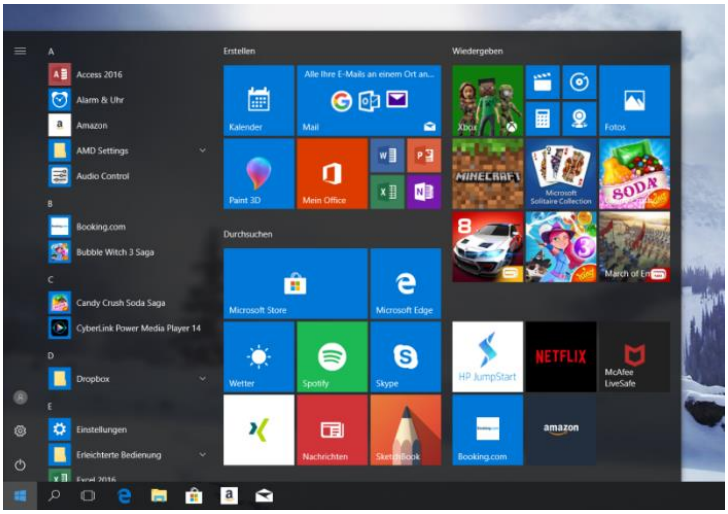
Maus

Stecken Sie die Maus an der markierten Stelle ein. Nutzen sie zum Klicken die linke Maus-Taste. Alternativ zur Maus kann auch das Touchpad (Laptop-Bild: 4) benutzt werden.

Ein- und Ausschalten des Laptops

Drücken sie zum Einschalten des Laptops den Startknopf (Laptop-Bild: 2) und warten Sie, bis der Laptop gestartet hat. In der Desktop-Ansicht des Laptops können Sie nun das ARCO-Symbol (Laptop-Bild: 6) sehen.

Führen Sie folgende Schritte aus, um den Laptop herunterzufahren:



Schritt1:

Klicken Sie mit dem Pfeil auf das Windows-Symbol (Laptop-Bild: 1) so dass folgendes Fenster zu sehen ist.

Schritt 2:

Klicken Sie mit dem Pfeil auf das Power-Symbol (im Bild blau umkreist), welches sich nun direkt über dem Windows-Symbol befindet

Schritt 3:

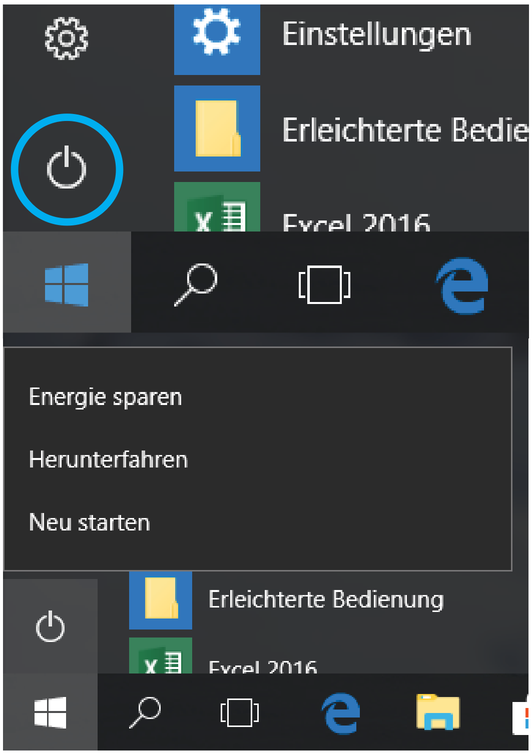
Eine Menu-Liste erscheint über dem Power-Symbol.

Schritt 4:

Klicken Sie mit dem Pfeil auf „Herunterfahren“ und warten Sie, bis der Bildschirm komplett schwarz ist.

Schritt 5:

Sie können nun den Laptop zuklappen



Lautstärke regulieren

Die Spiele enthalten Musik und akustische Effekte. Stellen Sie daher den Ton am Laptop in einer angenehmen Lautstärke ein. Die Spiele können aber auch ohne Ton gespielt werden.

Die Lautstärke des Laptops regulieren Sie durch Drücken von f6, f7 oder f8 beim Modell HP oder Fn+Pfeil hoch oder Fn+Pfeil runter beim Modell Acer (Laptop-Bild: 5).

Wenn Sie den Ton des Laptops ein- oder ausstellen möchten, drücken Sie f6 beim Modell HP oder oder Fn+f8 beim Modell Acer.

Zum Reduzieren der Lautstärke drücken Sie f7 beim Modell HP oder Fn+Pfeil beim Modell Acer runter (so oft, bis die gewünschte Lautstärke erreicht ist).

Zum Erhöhen der Lautstärke drücken Sie f8 beim Modell HP oder Fn+Pfeil hoch beim Modell Acer (so oft, bis die gewünschte Lautstärke erreicht ist).

Benutzerregeln

Der mit ARCO mitgelieferte Laptop ist ausschliesslich zur Anwendung der ARCO-Software für das Training mit ARCO vorgesehen.

Es ist nicht gestattet, den Laptop anderswertig einzusetzen.

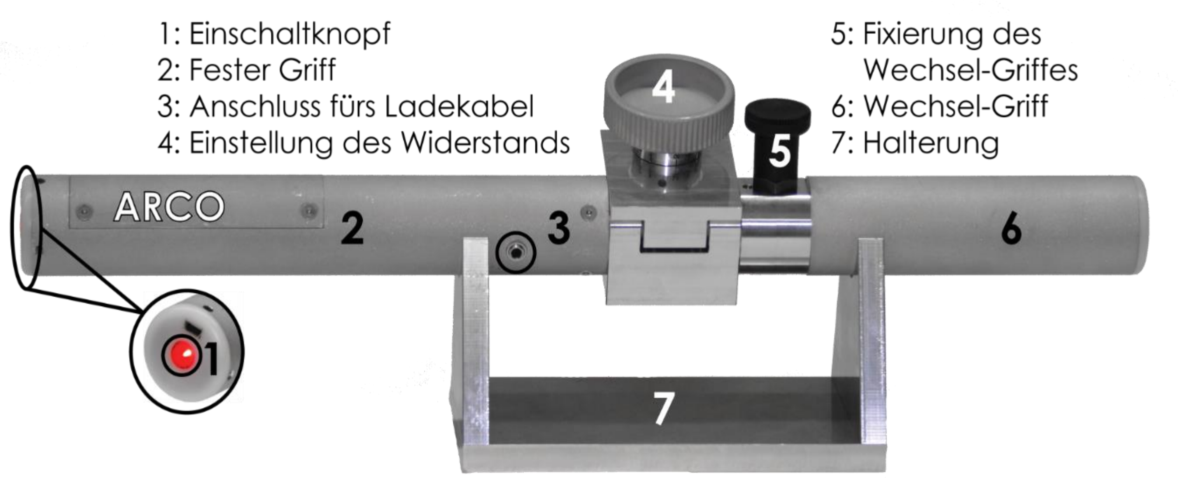
Bitte unterlassen Sie jegliche Veränderungen der Einstellungen und benutzen Sie ausser der

ARCO-Software keine Programme.

Lassen Sie bitte die Internetverbindung ausgeschaltet.

Das Nicht-Einhalten dieser Vorschriften kann zu unwiderruflichen Beschädigungen der ARCO-Software führen.

ARCO



Akku aufladen

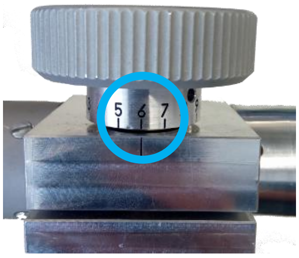
Stecken Sie das Ladekabel in die markierte Öffnung (ARCO-Bild: 3) und schliessen Sie das Kabel ans Stromnetz an. Training mit ARCO ist auch bei eingestecktem Ladekabel möglich.

Einschalten des ARCOs

Schalten Sie ARCO ein, indem Sie den Einschaltknopf (ARCO-Bild: 1) gedrückt halten (ca. 3sek) bis der er rot leuchtet.

Widerstand

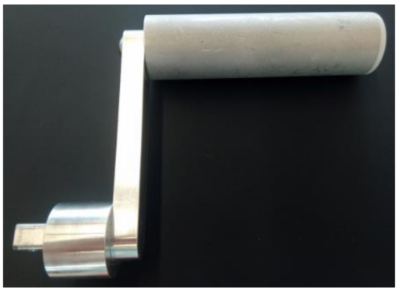
Um den Widerstand für die Rotation des Wechsel-Griffes einzustellen, drehen Sie am Einstellungsrad (ARCO-Bild: 4). Je höher die Zahl beim Markierungsstrich, desto grösser der Widerstand.



Wechselgriffe

Zum Training mit ARCO stehen Ihnen verschiedene Wechselgriffe (ARCO-Bild: 6) zur Verfügung.


Spindel


Kurbel


Mutter

Austauschen der Wechselgriffe

Schritt 1: Ziehen Sie den schwarzen Fixierhebel (ARCO-Bild: 5) nach aussen.

Schritt 2: Drehen Sie ihn leicht, so dass er in dieser entriegelten Position bleibt.

Schritt 3: Ziehen sie den Wechselgriff raus und ersetzen Sie ihn durch den gewünschten Griff.

Schritt 4: Drehen Sie den schwarzen Fixierhebel wieder leicht zurück. Er fällt automatisch etwas nach innen und fixiert den Wechselgriff.

Halterung

Der ARCO kann frei in der Luft gehalten werden während des Trainings, oder zur Gewichtsentlastung in die Halterung (ARCO-Bild: 7) gelegt werden. Zur besseren Stabilisierung können Sie den ARCO in der Halterung mit einem Klettverschluss leicht befestigen (Wichtig: ziehen Sie diesen nicht zu fest an!).

Software

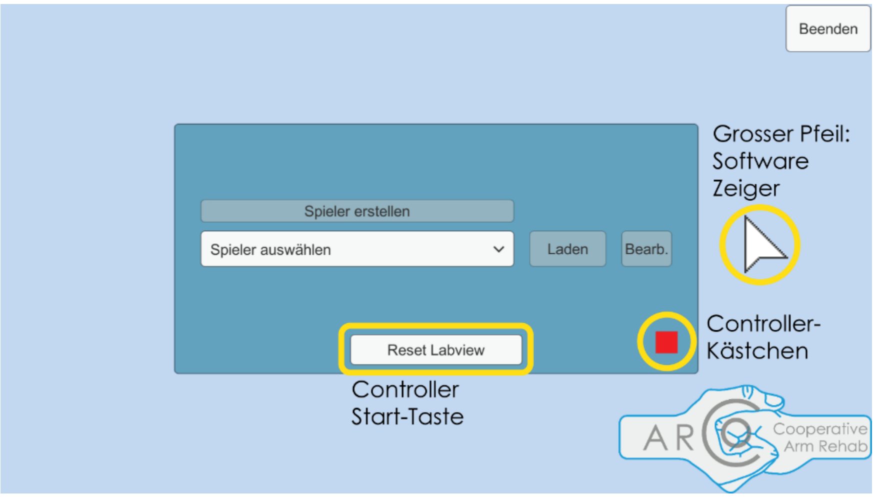
Starten der Software

Für einen Reibungslosen Spielstart ist es besser, wenn der ARCO eingeschaltet ist bevor der Laptop gestartet wird.

Doppelklicken Sie zum Öffnen der Software das ARCO-Symbol.

ARCO

Nun sehen sie folgenden Startbildschirm:



Grosser Pfeil: Software Zeiger

Controller-Kästchen

Controller Start-Taste

Schritt 1:

Warten Sie, bis das ARCO-Controller-Fenster kurz erscheint und wieder verschwindet.

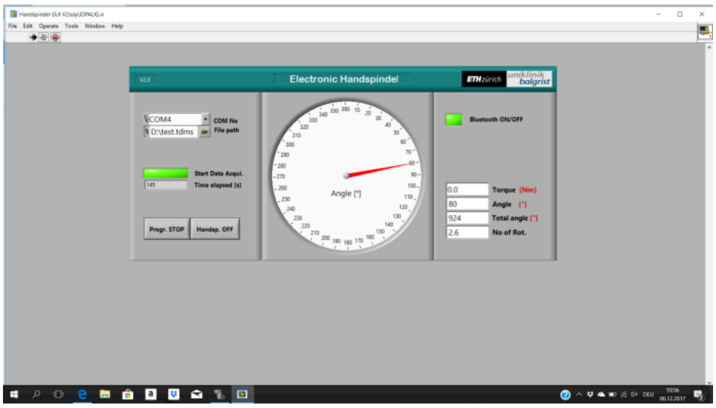
Schritt 2:

Drücken Sie einmal die linke Maustaste, um den grossen Pfeil in der Software als Zeiger zu aktivieren.

Schritt 3:

Überprüfen Sie, ob das Controller-Kästchen grün ist.

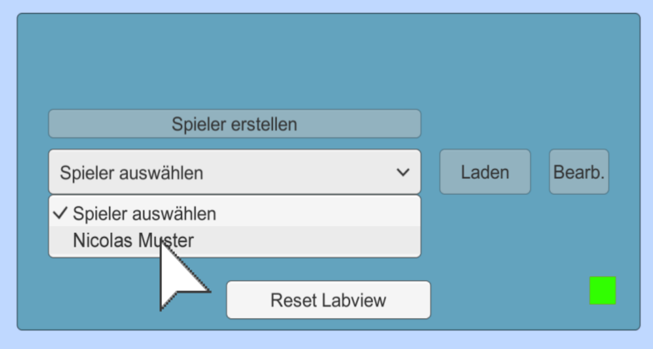
- ➔ Wenn ja: Weiter zu Schritt 4
- ➔ Wenn nein: Klicken Sie auf die Controller Start-Taste (Reset Labview) und wiederholen Sie die Schritte 1-3



COM4 COM No
D:\test.tdms File path
145 Time elapsed [s]
0.0 Torque [Nm]
80 Angle [°]
924 Total angle [°]
2.6 No of Rot.

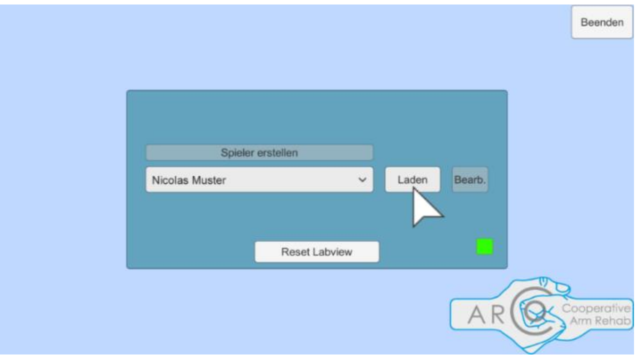
Schritt 4:

Klicken Sie auf „Spieler auswählen“ und wählen Sie Ihren Benutzernamen in der nun sichtbaren Liste an.



Schritt 5:

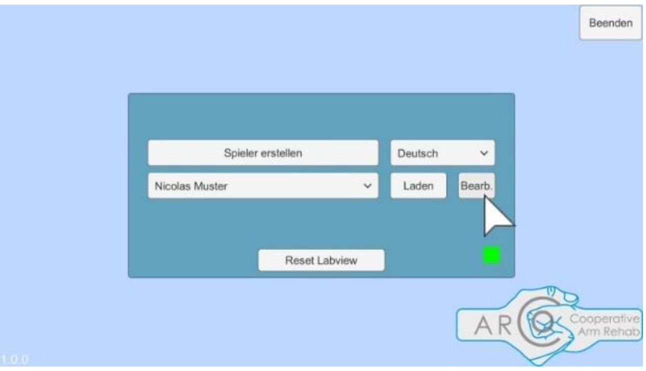
Klicken Sie auf „Laden“ um zur Spiel-Auswahl zu gelangen. Wenn Sie einen neuen Spieler/Patient anlegen möchten, klicken sie auf „Spieler erstellen



Nicolas Muster

Spieler erstellen und Bearbeiten

Um einen neuen Spieler zu erstellen, klicken Sie im Startbildschirm auf „Spieler erstellen“. Um Einstellungen eines bereits erstellten Spielers zu bearbeiten klicken Sie auf „Bearb.“. In diesem Menü stehen verschiedene Funktionen zur Auswahl, welche im Folgenden erklärt werden.



Nicolas Muster

Visual Screen Perception and attention Assessment (ViSPA)

ViSPA testet Ihre Fähigkeit, den gesamten Bildschirm des Laptops wahrzunehmen und stellt fest, ob die Spiele gespielt werden können. Klicken Sie dazu auf „ViSPA“ und folgen Sie den Anweisungen.

Nicolas Muster

Geburtsdatum: 10 10 1967

☐ Zeitbegrenzung [s] Seconds

☑ linke Hand ☑ rechte Hand

MVC	Links	Rechts
Spindel	0.0	0.0
Kurbel	0.0	0.0
Mutter	0.0	0.0

ROM [°]	Links	Rechts
Spindel	45	45
Kurbel	180	180
Mutter	90	90

Maximalkraft

Der ARCO ermöglicht die individuelle Einstellung der Maximalkraft für die rechte und linke Hand und für jeden Griff.

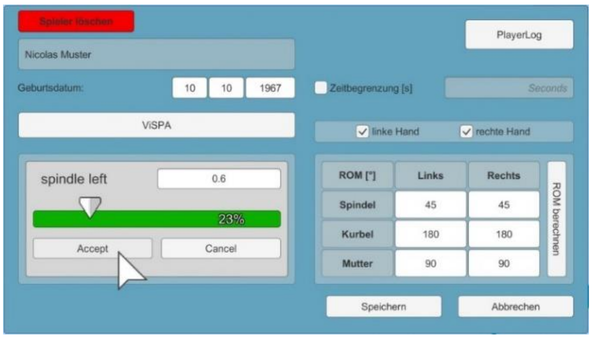
Klicken Sie auf das Feld des Griffes/Hand von welchem Sie die Maximalkraft einstellen möchten.

Für das Beispiel „Spindel links“, bringen Sie den Griff „Spindel“ an den ARCO an und greifen den Spindel-Girff mit der linken Hand. Erhöhen Sie nun den Widerstand des ARCO (s. Kapitel 3.3) schrittweise, bis Sie entweder (1) den Griff mit der linken Hand nicht mehr nach Hinten drehen können (während die rechte Hand den anderen Griff festhält) oder (2) bei zurückdrehen des Griffes mit der linken Hand, der Griff mit der rechten Hand nichtmehr festhalten können. Klicken Sie auf „akzeptieren“ um die die Kraft zu speichern und fahren Sie mit den anderen Griffen/ der anderen Hand fort.

Nicolas Muster
Geburtsdatum: 10 10 1967
☐ Zeitbegrenzung [s] Seconds
☑ linke Hand ☑ rechte Hand

MVC	Links	Rechts
Spindel	0.0	0.0
Kurbel	0.0	0.0
Mutter	0.0	0.0

ROM [°]	Links	Rechts
Spindel	45	45
Kurbel	180	180
Mutter	90	90



Nicolas Muster
Geburtsdatum: 10 10 1967
☐ Zeitbegrenzung [s] Seconds
☑ linke Hand ☑ rechte Hand

spindle left 0.6
23%

ROM [°]	Links	Rechts
Spindel	45	45
Kurbel	180	180
Mutter	90	90

☑ Gravitation
Schwierigkeit: 1
0%

Die derzeitige Krafteinstellung, je nach eingestelltem Griff wird vor jedem Spielstart dargestellt und zeigt Ihnen auf wieviel Prozent Ihrer Maximalkraft der ARCO im Moment eingestellt ist.

Bewegungsumfang (ROM)

Nicolas Muster
Geburtsdatum: 10 10 1967
☐ Zeitbegrenzung [s] Seconds
☑ linke Hand ☑ rechte Hand

MVC	Links	Rechts
Spindel	0.5	0.0
Kurbel	0.0	0.0
Mutter	0.0	0.0

ROM [°]	Links	Rechts
Spindel	45	45
Kurbel	180	180
Mutter	90	90

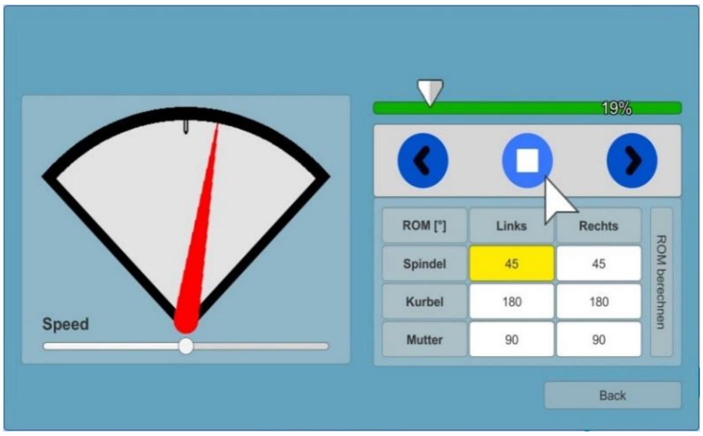
Die Spiele der ARCO Software werden über die Bewegung der Griffe gesteuert. Die Empfindlichkeit der Spiele ist zunächst für jeden Spieler gleich Eingestellt.

Jedoch kann je nach der Fähigkeit mit der Sie ihren Arm Ihre Hand oder Ihre Finger bewegen können, die Empfindlichkeit der Spiele angepasst werden. Dies ermöglicht ein problemloses Spielen selbst mit sehr kleinem Bewegungsumfang des Armes, der Hand oder der Finger.

Klicken Sie dazu im Menü auf „ROM berechnen“.

Klicken Sie nun auf die entsprechende Einstellung, für welche Sie den Bewegungsumfang einstellen möchten. Bringen Sie den entsprechenden Griff an den ARCO an und erhöhen Sie den Widerstand auf mindestens 15% (grüner Balken).

Klicken Sie auf ▶ um die Messung zu starten.



ROM [°]	Links	Rechts
Spindel	45	45
Kurbel	180	180
Mutter	90	90

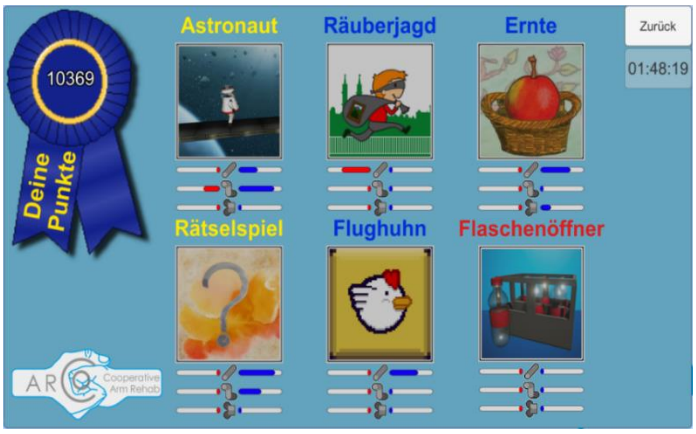
Drehen Sie den Griff mit der entsprechenden Hand vor- und zurück im gleichen Rhythmus wie vom roten Pfeil vorgegeben und dies, solange bis die Berechnung abgeschlossen ist. Versuchen Sie dabei jede Bewegung mit dem für Sie größtmöglichen Bewegungsausmaß wie möglich zu durchzuführen. Falls Ihnen der Rhythmus zu schnell ist, können Sie diesen mit dem Balken darunter anpassen. Verschieben Sie den Regler nach links um zu verlangsamen oder nach rechts um den Rhythmus zu beschleunigen.

Die Einstellung des ROM muss nicht zwingend vorgenommen werden, sondern lediglich wenn Ihnen ein Spiel nicht sensitiv genug auf Ihre Bewegungen reagiert.

Spiel-Auswahl

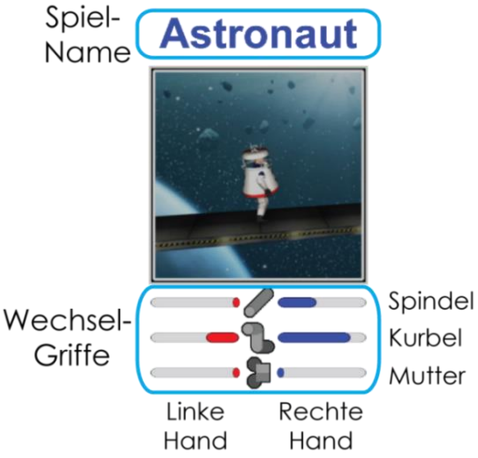
Punkte-Schleife:

Hier können Sie Ihre aktuelle Gesamtpunktzahl sehen. Wenn Sie die Software zum ersten Mal benutzen und somit noch keine Punkte erzielt haben, ist diese Schleife noch nicht zu sehen. Je fleissiger Sie trainieren, desto höher wird Ihre Punktzahl.



Spiele:

Alle Ihnen zur Verfügung stehenden Spiele sind hier mit einem kleinen Bild dargestellt. Über dem Bild steht der Spiel-Name- Unter dem Bild sind die für dieses Spiel für Sie freigeschalteten Wechselgriffe abgebildet mit Indikatoren, die anzeigen, welche Hand mit welchem Griff wie lange trainiert hat.



Zurück-Knopf:

Durch Anklicken dieses Knopfes kommen Sie zurück zum Startbildschirm.

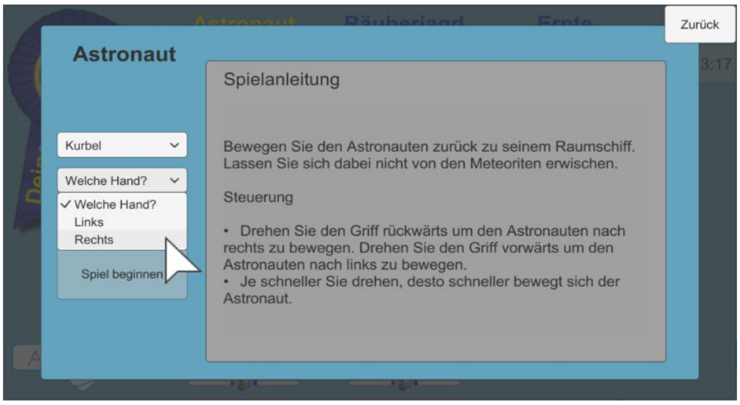
Zeit:

Hier sehen Sie, wie viel Zeit seit dem Starten der Software bereits vergangen ist.

Spiel starten

Schritt 1:

Klicken Sie auf das Bild des gewünschten Spiels um das Spiel-Start-Fenser zu öffnen. Sie sehen links die Griff- und Hand-Auswahl, rechts eine kurze Spielanleitung.



Spielanleitung

Bewegen Sie den Astronauten zurück zu seinem Raumschiff. Lassen Sie sich dabei nicht von den Meteoriten erwischen.

Steuerung

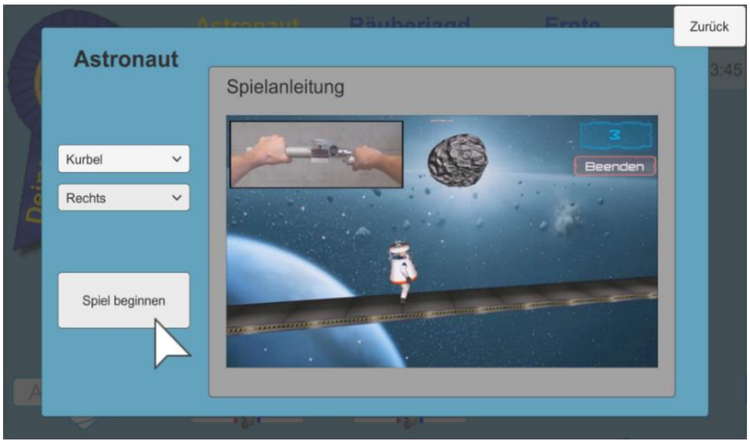
- Drehen Sie den Griff rückwärts um den Astronauten nach rechts zu bewegen. Drehen Sie den Griff vorwärts um den Astronauten nach links zu bewegen.
- Je schneller Sie drehen, desto schneller bewegt sich der Astronaut.

Schritt 2:

Klicken Sie auf „Griff auswählen“ und wählen Sie den Wechselgriff aus, den Sie zum Trainieren benutzen möchten. Falls dieser Griff noch nicht am ARCO angebracht ist, wechseln Sie die Griffe gemäss Anleitung.

Schritt 3:

Klicken Sie auf „Welche Hand?“ und wählen Sie die Hand aus, die den Wechselgriff bewegen soll. Es erscheint nun ein Anleitungs-Video, indem sie sehen, welche Bewegung auszuführen ist.



Schritt 4:

Klicken Sie auf „Spiel beginnen“.

Spiele

Astronaut

Ziel des Spiels:

Helfen Sie dem Astronauten, sein Raumschiff wiederzufinden. Achten Sie dabei darauf, dass er nicht von Meteoriten getroffen wird oder vom Weg abkommt.

Einstellungen:

Schwierigkeit: 5

Highscore: 0

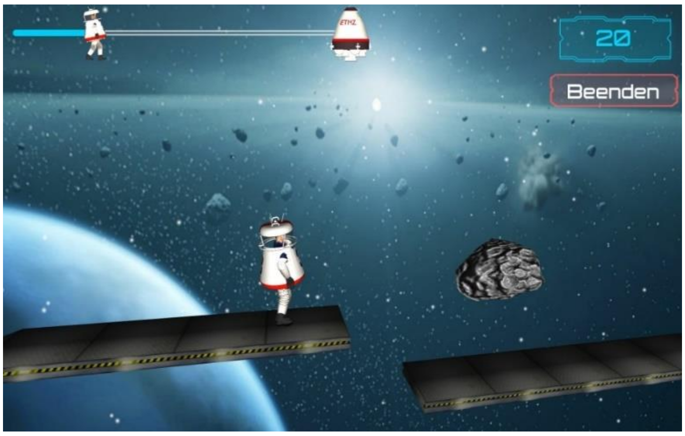
Spielzeit: 00 h 00 min

Falls Sie das Spiel mit der gewählten Hand und dem eingestellten Griff bereits gespielt haben, sind der aktuelle Highscore und die bereits gespielte Gesamtzeit angezeigt. In dem Fall ist auch die letzt-gespielte Schwierigkeit eingestellt, ansonsten ist die Markierung auf Schwierigkeit 1 eingestellt. Verändern Sie gegebenenfalls die Schwierigkeit für das Spiel durch gleichzeitiges Anklicken und Verschieben der Markierung. Je höher die Schwierigkeit gesetzt wird, desto öfter müssen Sie Meteoriten ausweichen und schwieriger wird der Weg zum Raumschiff. Der grüne Balken gibt an, wie gross der aktuelle Widerstand von ARCO ist. Ein Wert von 10% würde bedeuten, dass der Widerstand aktuell 10% ihrer Maximalkraft beträgt.

Je höher die gewählte Schwierigkeit und der Widerstand, desto mehr Punkte.

Verändern Sie gegebenenfalls die Schwierigkeit für das Spiel durch gleichzeitiges Anklicken und Verschieben der Markierung. Je höher die Schwierigkeit gesetzt wird, desto öfter müssen Sie Meteoriten ausweichen und schwieriger wird der Weg zum Raumschiff.
Der grüne Balken gibt an, wie gross der aktuelle Widerstand von ARCO ist. Ein Wert von 10% würde bedeuten, dass der Widerstand aktuell 10% ihrer Maximalkraft beträgt.
Je höher die gewählte Schwierigkeit und der Widerstand, desto mehr Punkte.
Klicken Sie anschliessend auf „Spiel beginnen“.

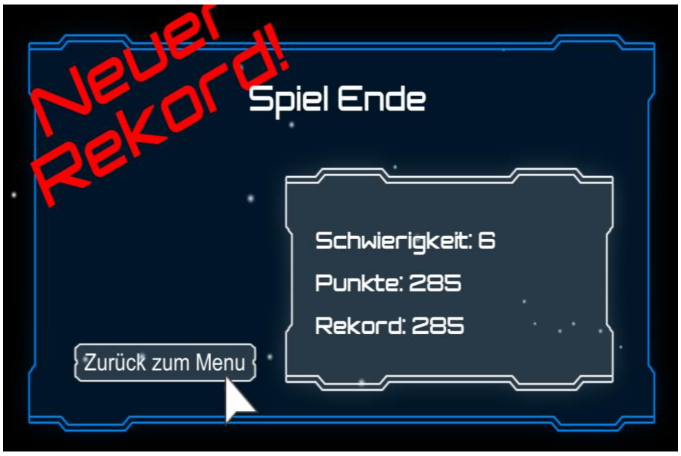
Spiel:



Das Spiel verfügt über 4 Levels. In jedem Level muss der Astronaut im Weltall zu seinem Raumschiff bewegt werden. Immer wieder kommen Meteoriten von oben oder unten. Wenn der Astronaut von einem Meteoriten getroffen wird, wird er an den Start des aktuellen Levels zurückgesetzt. Zudem ist der Weg nicht immer durchgehend. Es müssen Lücken übersprungen und bewegliche Weg-Teile passiert werden. Der Astronaut darf dabei nicht vom Weg runterfallen, sonst muss er zurück zum Level-Start. Durch Aufwärtsbewegung des ARCO-Wechsel-Griffs bewegt sich der Astronaut vorwärts, durch Abwärtsbewegung rückwärts.
Je weiter der Astronaut auf seinem Weg vorankommt, desto mehr Punkte erhalten Sie. Diese sind oben rechts in blau angezeigt. Wie weit der Weg zum Raumschiff noch ist, können sie am Fortschrittsbalken oben links erkennen. Wenn das Raumschiff erreicht ist, fliegt der Astronaut ins nächste Level.

Ende des Spiels:

Am Ende des 4. Levels endet das Spiel automatisch. Wenn Sie es vorher beenden möchten, klicken sie oben rechts unter dem Punktestand auf „Beenden“.
Über „Zurück zum Menu“ kommen Sie wieder zum Einstellungs-Fenster. Sie können nun die Schwierigkeit anpassen und das Spiel wieder starten, oder über „Beenden“ zurück zur Spiel-Auswahl gelangen.


Neuer Rekord!
Spiel Ende
Schwierigkeit: 6
Punkte: 285
Rekord: 285

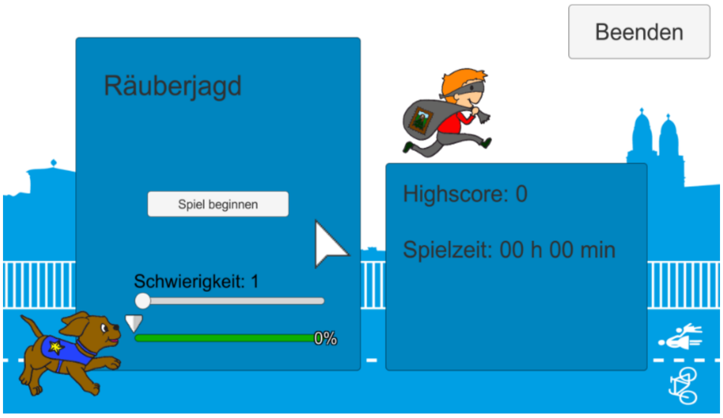
Räuberjagd

Ziel des Spiels:

Helfen Sie, unsere Städte von Räubern zu befreien. Fangen sie mit dem Polizeihund alle Räuber und bringen Sie sie hinter Gitter.

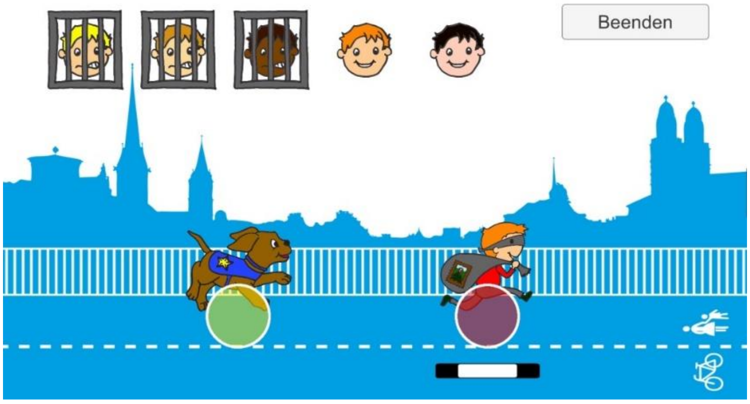
Einstellungen:

Falls Sie das Spiel mit der gewählten Hand und dem eingestellten Griff bereits gespielt haben, sind der aktuelle Highscore und die bereits gespielte Gesamtzeit angezeigt. In dem Fall ist auch die letzt-gespielte Schwierigkeit eingestellt, ansonsten ist die Markierung auf Schwierigkeit 1 eingestellt. Verändern Sie gegebenenfalls die Schwierigkeit für das Spiel durch gleichzeitiges Anklicken und Verschieben der Markierung. Je höher die Schwierigkeit gesetzt wird, desto kleiner sind die Kreise vom Polizeihund und Räuber.
Der grüne Balken gibt an, wie gross der aktuelle Widerstand von ARCO ist. Ein Wert von 10% würde bedeuten, dass der Widerstand aktuell 10% ihrer Maximalkraft beträgt.
Je höher die gewählte Schwierigkeit und der Widerstand, desto mehr Punkte.
Klicken Sie anschliessend auf „Spiel beginnen“.



Schwierigkeit: 1
0%
Highscore: 0
Spielzeit: 00 h 00 min

Spiel:



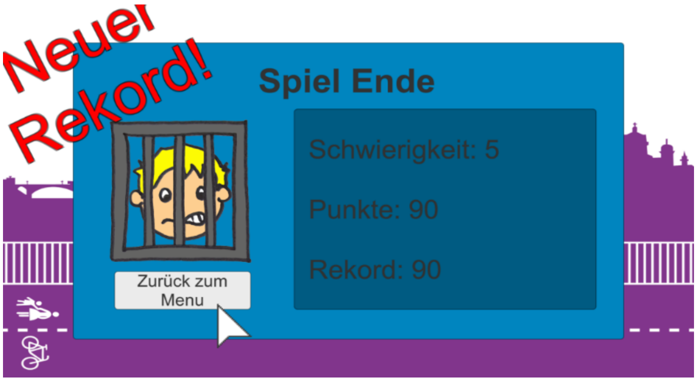
Das Spiel verfügt über 8 Levels. In jedem Level muss der Polizeihund in einer Stadt jeweils 5 Räuber fangen und hinter Gitter bringen. Die Räuber werden mit jedem Level schneller.

Durch Aufwärtsbewegung des ARCO-Wechsel-Griffs bewegt sich der Polizeihund nach rechts, durch Abwärtsbewegung nach links.

Der Hund hat einen gelben Kreis und der Räuber einen roten. Um der Räuber zu schnappen, müssen diese Kreise möglichst oft und lange überlappen. Unter den Räubern ist jeweils der Energie-Balken des Räubers zu sehen. Der weisse Bereich wir kleiner, wenn die Kreise von Hund und Räuber überlappen. Wenn der weisse Balken ganz weg ist, ist der Räuber geschnappt und kommt hinter Gitter.

Wie viele Räuber in der aktuellen Stadt noch zu fangen sind, können Sie an der Grafik über der Stadt erkennen. Wenn alle Räuber in der Stadt hinter Gitter sind, kommen Sie automatisch in die nächste Stadt.

Ende des Spiels:



Schwierigkeit: 5

Punkte: 90

Rekord: 90

Am Ende des 8. Levels endet das Spiel automatisch. Wenn Sie es vorher beenden möchten, klicken sie oben rechts unter dem Punktestand auf „Beenden“.

Über „Zurück zum Menu“ kommen Sie wieder zum Einstellungs-Fenster. Sie können nun die Schwierigkeit anpassen und das Spiel wieder starten, oder über „Beenden“ zurück zur Spiel-Auswahl gelangen.

Ernte

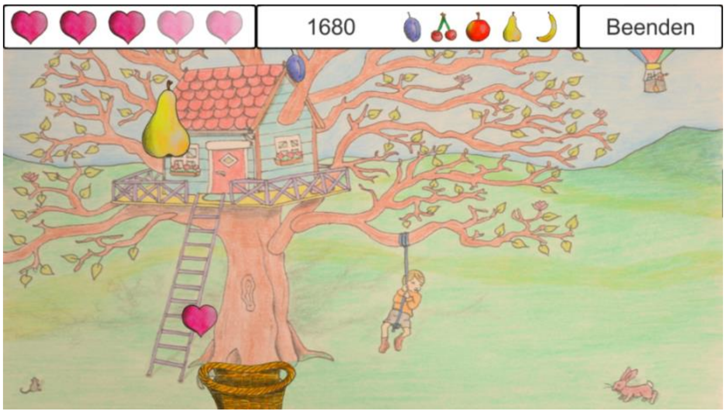
Ziel des Spiels:

Sammeln Sie so viele Früchte wie möglich ein, ohne dass diese auf den Boden fallen.

Einstellungen:

Falls Sie das Spiel mit der gewählten Hand und dem eingestellten Griff bereits gespielt haben, sind der aktuelle Highscore und die bereits gespielte Gesamtzeit angezeigt. In dem Fall ist auch die zuletzt-gespielte Schwierigkeit eingestellt, ansonsten ist die Markierung auf Schwierigkeit 1 eingestellt. Verändern Sie gegebenenfalls die Schwierigkeit für das Spiel durch gleichzeitiges Anklicken und Verschieben der Markierung. Je höher die Schwierigkeit gesetzt wird, desto langsamer bewegt sich der Korb.
Der grüne Balken gibt an, wie gross der aktuelle Widerstand von ARCO ist. Ein Wert von 10% würde bedeuten, dass der Widerstand aktuell 10% ihrer Maximalkraft beträgt.
Je höher die gewählte Schwierigkeit und der Widerstand, desto mehr Punkte.
Klicken Sie anschliessend auf „Spiel beginnen“.

Spiel:



Im Spiel kommen verschieden grosse Früchte von oben herunter, verteilt über die ganze Breite des Bildschirms. Diese müssen mit dem Früchtekorb eingefangen werden, und zwar so, dass sie komplett im Korb landen. Bei grossen Früchten muss dementsprechend der Korb sehr genau unter die Früchte platziert werden, dass diese hineinfallen. Wenn der Korb nicht ganz am richtigen Ort ist bleibt die Frucht vor dem Korb, so dass Sie gut erkennen können, ob es richtig war oder nicht.
Wenn eine Frucht nicht im Korb landet, so kostet dies ein Leben. Sie haben zu Beginn des Spieles 5 Leben, dargestellt mit den 5 Herzen oben links. Verlieren Sie ein Leben, verblasst eins der Herzen. Wenn Sie Glück haben, kommt im weiteren Spielverlauf irgendwann

anstelle einer Frucht ein Herz. Wenn Sie dieses einfangen, haben Sie wieder ein Leben mehr. Durch Aufwärtsbewegung des ARCO-Wechsel-Griffs bewegt sich der Korb nach rechts, durch Abwärtsbewegung nach links.

Ende des Spiels:

Spiel Ende

Punkte: 1704

Rekord: 1704

Schwierigkeit: 4

Das Spiel endet automatisch, wenn Sie kein Leben mehr haben. Wenn Sie es vorher beenden möchten, klicken sie oben rechts unter dem Punktestand auf „Beenden“.
Über „Zurück zum Menu“ kommen Sie wieder zum Einstellungs-Fenster. Sie können nun die Schwierigkeit anpassen und das Spiel wieder starten, oder über „Beenden“ zurück zur Spiel-Auswahl gelangen.

Rätselspiel

Ziel des Spiels:

Testen Sie ihr Wissen in verschiedenen Themenbereichen und beantworten Sie möglichst viele Fragen richtig.

Einstellungen:

Frageniveau: 1

Schwierigkeit: 1

Highscore: 0

Spielzeit: 00 h 00 min

Falls Sie das Spiel mit der gewählten Hand und dem eingestellten Griff bereits gespielt haben, sind der aktuelle Highscore und die bereits gespielte Gesamtzeit angezeigt. In dem Fall ist auch die letzt-gespielte Schwierigkeit eingestellt, ansonsten ist die Markierung auf Schwierigkeit 1 eingestellt. Klicken Sie auf „Wähle eine Kategorie“ und wählen Sie die gewünschte Frage-Kategorie aus der Liste aus. Stellen Sie bei „Frageniveau“ das gewünschte Start-Niveau der Fragen ein. Das Niveau wird während des Spieles automatisch an Ihre Leistungen angepasst.

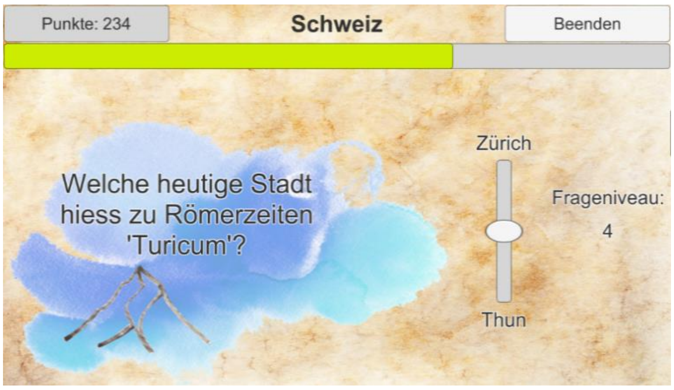
Verändern Sie gegebenenfalls die Schwierigkeit für das Spiel durch gleichzeitiges Anklicken und Verschieben der Markierung. Je höher die Schwierigkeit gesetzt wird, desto mehr müssen Sie den Griff bewegen um zur Antwort zu kommen.

Der grüne Balken gibt an, wie gross der aktuelle Widerstand von ARCO ist. Ein Wert von 10% würde bedeuten, dass der Widerstand aktuell 10% ihrer Maximalkraft beträgt.

Je höher die gewählte Schwierigkeit, das Fragenniveau und der Widerstand, desto mehr Punkte. Klicken Sie anschliessend auf „Spiel beginnen“.

Spiel:

Zur gewählten Themen-Kategorie werden Ihnen Fragen gestellt. Rechts davon bekommen Sie jeweils zwei Antwort-Möglichkeiten, eine oben und eine unten. Bewegen Sie die Ellipse in der Mitte des Antwortbalkens zu der Ihrer Meinung nach richtigen Antwort. Überlegen Sie nicht zu lange; wenn der Zeitbalken oben abgelaufen ist, verschwindet die Frage!



Punkte: 234

Schweiz

Welche heutige Stadt hiess zu Römerzeiten 'Turicum'?

Zürich

Thun

Frageniveau: 4

Durch Rückwärtsbewegung des ARCO-Wechsel-Griffs bewegt sich die Ellipse nach oben, durch Vorwärtsbewegung nach unten. Oben links sind die gesammelten Punkte angezeigt. In der Mitte können Sie sehen, welche Kategorie Sie zurzeit spielen. Rechts neben dem Antwortbalken ist das aktuelle Frageniveau angezeigt.

Ende des Spiels:

Wenn Sie das Spiel beenden wollen, klicken sie oben rechts unter dem Punktestand auf „Beenden“.

Über „Zurück zum Menu“ kommen Sie wieder zum Einstellungs-Fenster. Sie können nun die Kategorie ändern, das Start-Niveau neu bestimmen und / oder die Schwierigkeit anpassen und das Spiel wieder starten, oder über „Beenden“ zurück zur Spiel-Auswahl gelangen.

Spiel Ende

Schwierigkeit: 5

Punkte: 1552

Rekord: 1552

Flughuhn

Ziel des Spiels:

Fliegen Sie mit dem Flughuhn sicher durch die Hindernisse ohne dabei auf den Boden zu fallen.

Einstellungen:

☑ Gravitation
Schwierigkeit: 1
0%
Highscore: 0
Spielzeit: 00 h 00 min

☑ Gravitation
Schwierigkeit: 1

Falls Sie das Spiel mit der gewählten Hand und dem eingestellten Griff bereits gespielt haben, sind der aktuelle Highscore und die bereits gespielte Gesamtzeit angezeigt. In dem Fall ist auch die letzt-gespielte Schwierigkeit eingestellt, ansonsten ist die Markierung auf Schwierigkeit 1 eingestellt.

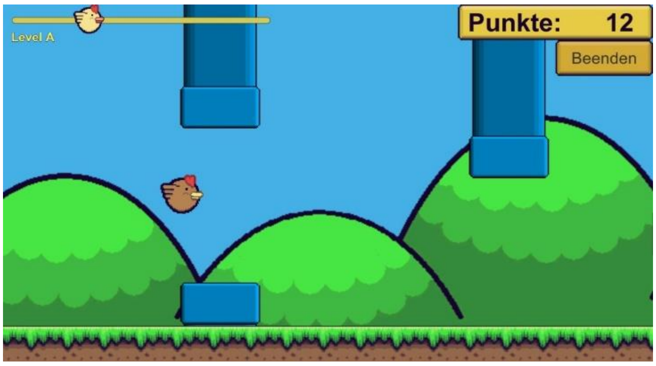
Entscheiden Sie, ob sie mit Gravitation (Häkchen gesetzt) oder ohne (kein Häkchen) spielen möchten. Die Gravitation bewirkt, dass das Huhn konstant etwas nach unten fällt und somit auch am ARCO gedreht werden muss, um das Huhn auf gleicher Höhe zu halten. Dies intensiviert die Trainingseinheit. Verändern Sie gegebenenfalls die Schwierigkeit für das Spiel durch gleichzeitiges Anklicken und Verschieben der Markierung. Je höher die Schwierigkeit gesetzt wird, desto mehr Hindernissen müssen Sie ausweichen.

Der grüne Balken gibt an, wie gross der aktuelle Widerstand von ARCO ist. Ein Wert von 10% würde bedeuten, dass der Widerstand aktuell 10% ihrer Maximalkraft beträgt.

Je höher die gewählte Schwierigkeit und der Widerstand, desto mehr Punkte.

Klicken Sie anschliessend auf „Spiel beginnen“.

Spiel:



Punkte: 12

Das Spiel besteht aus 5 Levels mit immer kleineren Lücken in den Hindernissen. Durch Aufwärtsbewegung des ARCO-Wechsel-Griffs bewegt sich das Flughuhn nach oben, durch Abwärtsbewegung nach unten. Wenn das Huhn in ein Hindernis fliegt oder auf den Boden fällt, geht es zurück an den Start des aktuellen Levels. Wie weit es noch bis zum nächsten Level ist, ist aus der Grafik oben links ersichtlich. Je mehr Hindernisse durchflogen werden, desto mehr Punkte erzielen Sie im Spiel. Die gesammelten Punkte sind oben rechts angezeigt.

Ende des Spiels:

Schwierigkeit: 4

Punkte: 356

Rekord: 356

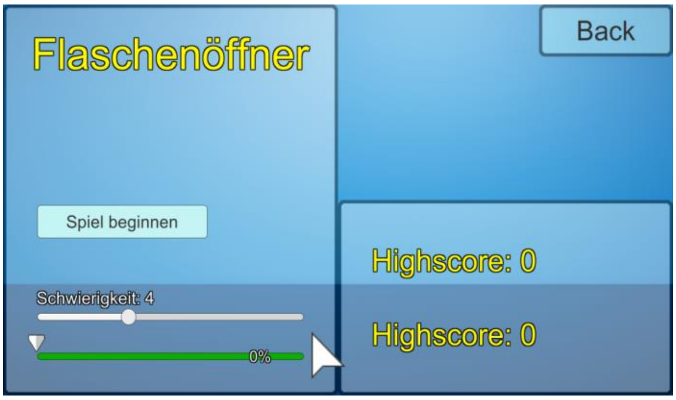
Am Ende des 8. Levels endet das Spiel automatisch. Wenn Sie es vorher beenden möchten, klicken sie oben rechts unter dem Punktestand auf „Beenden“. Über „Zurück zum Menu“ kommen Sie wieder zum Einstellungs-Fenster. Sie können nun die Schwierigkeit anpassen und das Spiel wieder starten, oder über „Beenden“ zurück zur Spiel-Auswahl gelangen.

Flaschenöffnen

Ziel des Spiels:

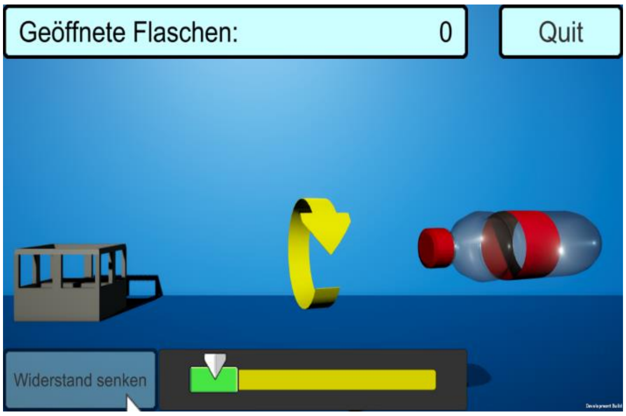
Öffnen sie so viele Flaschen wie möglich.

Einstellungen:



Falls Sie das Spiel mit der gewählten Hand und dem eingestellten Griff bereits gespielt haben, sind der aktuelle Highscore und die bereits gespielte Gesamtzeit angezeigt.
In dem Fall ist auch die letzt-gespielte Schwierigkeit eingestellt, ansonsten ist die Markierung auf Schwierigkeit 1 eingestellt. Verändern Sie gegebenenfalls die Schwierigkeit für das Spiel durch gleichzeitiges Anklicken und Verschieben der Markierung. Je höher die Schwierigkeit gesetzt wird, desto mehr müssen Sie den Griff bewegen um zur Antwort zu kommen. Der grüne Balken gibt an, wie gross der aktuelle Widerstand von ARCO ist. Ein Wert von 10% würde bedeuten, dass der Widerstand aktuell 10% ihrer Maximalkraft beträgt. Je höher die gewählte Schwierigkeit, das Fragenniveau und der Widerstand, desto mehr Punkte. Klicken Sie anschliessend auf „Spiel beginnen“.

Spiel:

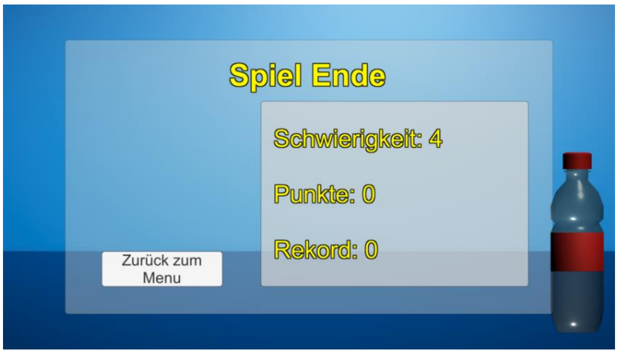


Bei diesem Spiel ist die Aufgabe Flaschen durch zurückdrehen des Griffes zu öffnen. Am unteren Bildschirmrand ist der Widerstandsbereich des ARCO eingeblendet. Der aktuelle Widerstand von ARCO (durch den Pfeil gekennzeichnet) muss sich innerhalb des grünen Bereichs befinden bevor die Flasche geöffnet werden kann.
Je mehr Flaschen geöffnet werden, desto weiter nach rechts wird sich der grüne Bereich bewegen. Erhöhen Sie also den Widerstand von ARCO, sodass der Pfeil stets im grünen Bereich liegt. Den Widerstand stellen Sie ein in dem Sie das Rad zwischen den Griffen in Uhrzeigersinn drehen. Je höher die Schwierigkeit vor Spielbeginn gesetzt wurde und je mehr Flaschen geöffnet werden, desto höher die Punktzahl. Wird der Widerstand mit der

Zeit zu hoch, können Sie den grünen Bereich auch durch ein Klicken auf „Widerstand senken“ verringern.

Ende des Spiels:

Das Spiel endet, wenn der Widerstand so schwer wird, dass Sie den Griff nicht mehr bewegen können. Falls Sie das Spiel vorher beenden möchten, klicken sie oben rechts unter dem Punktestand auf „Beenden“. Über „Zurück zum Menu“ kommen Sie wieder zum Einstellungs-Fenster. Sie können nun die Schwierigkeit anpassen und das Spiel wieder starten, oder über „Beenden“ zurück zur Spiel-Auswahl gelangen.


Spiel Ende

Schwierigkeit: 4

Punkte: 0

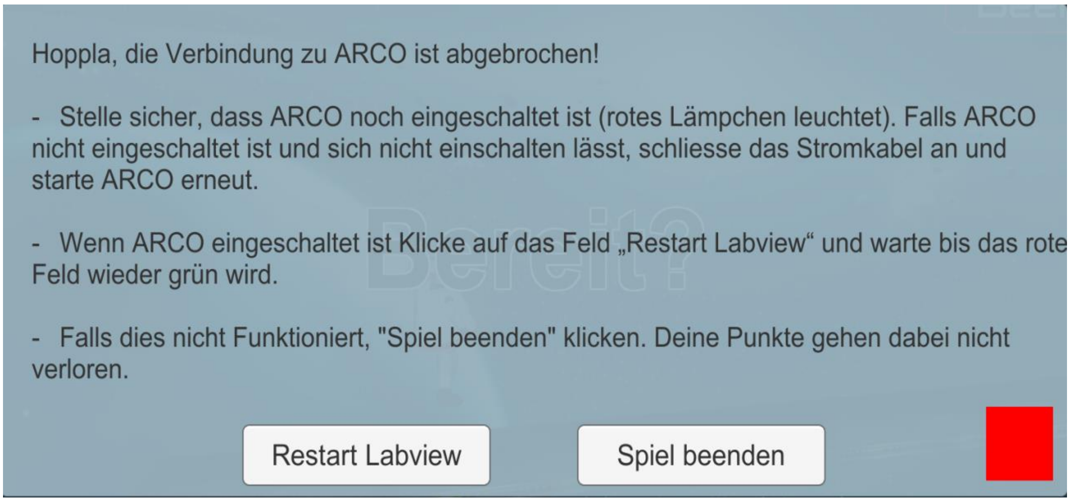
Rekord: 0

Beenden der Software

Klicken Sie im Spiele-Auswahl-Fenster auf „Zurück“ um wieder zum Startbildschirm mit der Spielerwahl zu gelangen.
Klicken Sie da auf „Beenden“.
ARCO stellt automatisch ab. Falls Sie also doch noch weiterspielen wollen und die Software wieder starten wollen, müssen Sie zuerst ARCO wieder einschalten. Ansonsten können Sie nun den Laptop abstellen. Vergessen Sie nicht, den Akku von ARCO wieder zu laden, damit er für die nächste Trainingseinheit wieder bereit ist!

Fehlermeldung

Sollte die Verbindung zwischen Software und ARCO plötzlich abbrechen, wird in der Software eine Fehlermeldung angezeigt. Befolgen Sie die Anweisungen der Fehlermeldung um die Verbindung zwischen ARCO und Laptop wieder herzustellen.



Hoppla, die Verbindung zu ARCO ist abgebrochen!

- Stelle sicher, dass ARCO noch eingeschaltet ist (rotes Lämpchen leuchtet). Falls ARCO nicht eingeschaltet ist und sich nicht einschalten lässt, schliesse das Stromkabel an und starte ARCO erneut.

- Wenn ARCO eingeschaltet ist Klicke auf das Feld „Restart Labview“ und warte bis das rote Feld wieder grün wird.

- Falls dies nicht Funktioniert, "Spiel beenden" klicken. Deine Punkte gehen dabei nicht verloren.

Zeitbasierte Trainingseinheiten

Mit dieser Funktion können Sie ein Zeitlimit für begonnene Spiele einstellen. Wenn Sie als Beispiel „300“ in das Feld eintragen, Endet jedes Spiel automatisch nach 5 Minuten. Die kann dazu dienen, das Training besser zu kontrollieren.

Nicolas Muster

Geburtsdatum: 10 10 1967

☑ Zeitbegrenzung [s] Seconds

☑ linke Hand ☑ rechte Hand

MVC	Links	Rechts
Spindel	0.5	0.0
Kurbel	0.0	0.0
Mutter	0.0	0.0

ROM [°]	Links	Rechts
Spindel	45	45
Kurbel	180	180
Mutter	90	90

Aufzeichnung der Trainingsdaten

Die Software speichert all Ihre Trainingsdaten ab. Das Beinhaltet zum einen gespielte Spiele mit Griff, Hand, Dauer, Schwierigkeit und erreichter Punktzahl, zum anderen Daten vom ARCO wie eingestellter Widerstand, Anzahl ausgeführter Rotationen und Geschwindigkeit der Rotationen. Diese Daten werden verwendet um das Training zu verfolgen. Die ARCO-Forschungsgruppe kann die Daten in anonymisierter Version für Sie auswerten.

Fragen und Antworten

Allgemeines

Befolgen Sie beim Gebrauch von ARCO die Gebrauchsanweisung um Fehler möglichst zu vermeiden. Häufige Fragen die auftauchen können sind im Folgenden aufgelistet und mögliche Lösungen dafür aufgezeigt. Falls eine Frage auftaucht, die sich mit diesen Massnahmen nicht lösen lässt, kontaktieren Sie bitte das ARCO-Team.

ARCO

Wieso lässt sich ARCO nicht einschalten?

- Der Akku ist leer. Laden Sie den Akku gemäss Anweisungen auf. Sie können auch bei eingestecktem Ladekabel trainieren.

Laptop

Wieso lässt sich der Laptop nicht starten?

- Der Akku ist leer. Laden Sie den Akku gemäss Anweisungen auf. Sie können auch bei eingestecktem Ladekabel trainieren.

Wieso reagiert der eingeschaltete Laptop nicht (Bewegen der Maus führt nicht zu Bewegung des Pfeils)?

- Stellen Sie sicher, dass die Maus richtig eingesteckt ist. Reagiert der Laptop trotzdem nicht, ziehen Sie die Maus raus und versuchen Sie, den Pfeil mit dem Touchpad zu steuern. Wenn es immer noch nicht geht, stellen Sie den Laptop forciert aus indem Sie den Einschaltknopf solange gedrückt halten, bis der Bildschirm schwarz ist. Schalten Sie anschliessend den Laptop wieder normal ein.

Software

Wieso wird das Controller-Kästchen nicht grün, obwohl die Anweisungen in Kapitel 4.1 befolgt wurden?

- Die Verbindung zwischen ARCO und Laptop ist unterbrochen.
  Stellen Sie sicher, dass ARCO eingeschaltet ist (rotes Lämpchen leuchtet).
  Beenden Sie die Software und schalten Sie den Laptop normal aus und wieder ein. Öffnen Sie die Software erneut.

Wieso reagieren die Spiele nicht auf den ARCO und / oder es erscheint eine Fehlermeldung?

- Die Verbindung zwischen ARCO und Laptop ist unterbrochen.
  Beenden Sie die Software und schalten Sie den Laptop normal aus. Schalten Sie zuerst ARCO und dann den Laptop wieder ein. Öffnen Sie die Software erneut.

Wieso reagieren die Spiele nicht so wie erwartet (Bewegung in die falsche Richtung oder falsche Art der Bewegung)?

- Im Spiel-Start-Fenster wurde der falsche Griff und / oder die falsche Hand angewählt. Beenden Sie das Spiel, gehen Sie zurück zum Spiel-Start-Fenster und wählen Sie den aktuellen Wechsel-Griff und die Hand, die diesen Griff bedient aus. Starten Sie das Spiel erneut.

Kontakt

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Curriculum Vitae

Personal information

First name:	Felix Alexander
Last name:	Thomas
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Place of birth:	Schwäbisch Hall
Nationality:	German
Email:	felix.alexander.thomas@gmail.com
Tel:	+49 176 707 213 49

Educational background

Dec 2016 - May 2020	Ph.D., ETH Zürich Neural Control of Movement Lab Neuroscience & Neurorehabilitation
Dec 2016 – May 2020	International PhD Program in Neuroscience Neuroscience Center Zürich (ZNZ) University Zürich & ETH Zürich
Oct 2014- Nov 2016	M.Sc., University of Konstanz Major: Movement & Training Science final grade: 1,4
Oct 2009 - Oct 2013	B.A., University of Konstanz Major: Movement Science final grade: 1,4

Core competencies

Application of various neuroscientific methods to measure brain/muscle signals in healthy individuals and neurologically impaired patients; Data management (processing and analysis); Good presentation skills; Fluent in oral and written English and German; Writing of scientific manuscripts

Occupational Career

September 2015 - December 2015	Internship in the NCM-Lab (Neural Control of Movement Lab) at the ETH Zürich
2014-2016	Research assistant and member of the Sensorimotor Performance Lab (http://www.spl.uni-konstanz.de)
April 2013- June 2013	Internship at the RehaFit GmbH as a sports therapist
2012-2013	Employee at the „Akademie für Sport und Gesundheit“ • Support • Online-marketing
2012-2015	Exercise instructor for the youngsters gymnastics at the University of Konstanz
2010-2015	Promotion activity at Eventpromotions Konstanz, Spörrer, Schuhwerk GmbH • Promotion of different products • Hosting • Logistics

Teaching activity

2017 – 2019	Master of Science Course at the ETH Zürich: *“Methods and Concepts in Human Systems Neuroscience and Motor Control”*
2016-2019	Supervision of students from ETH Zürich, Bachelor and Master level

Awards

June 2018	Investigator Award 2018 at the 4th Congress of the European Academy of Neurology (Lisbon)

List of Publications

Thomas FA., Dietz V., Scharfenberger T., Schrafl-Altermatt M. *Cooperative hand movements: effect of a reduced afference on the neural coupling mechanism (2018). 2018;29(8):650-4.*NeuroReport

Thomas FA., Dietz V., Schrafl-Altermatt M., *Automatic gain control of neural coupling during cooperative hand movements (2018)*. *2018;8(1):5959.*Sci.Rep.

Bächinger M., Lehner R., **Thomas FA**., Hanimann S., Balsters JH., Wenderoth N (2019) *Human motor fatigability as evoked by repetitive movements results from a gradual breakdown of surround inhibition.* 10.7554/eLife.46750. eLife

Giboin LS., Weiss B., **Thomas FA**., Gruber M.*, Neuroplasticity following short-term strength training occurs at supraspinal level and is specific for the trained task (2018). Acta physiologica 222, e12998.*

Congress talks

October 2019

European Congress of Neurorehabilitation, (Budapest, Hungary), *"Development and Validation of the Cooperative Activity Stroke Assessment (CASA)"*

August 2018

Hand and Brain Technology, (Ascona, Switzerland), *"Importance of Somatosensory Behaviour during Cooperative Hand Movements and their Application in Stroke Rehabilitation"*

June 2018

European Academy of Neurology, (Lisbon, Portugal), *"Efficacy and Feasibility of Home-Based Cooperative Hand Movement Training in Chronic Stroke Patients"*

February 2018

10th annual SGS/4s Conference (Magglingen, Switzerland), *"Cooperative Hand Movements: Automatic gain control of neural coupling"*

February 2016

8th annual SGS/4s Conference (Bern, Switzerland), *"Contributions of Peripheral and Central Mechanisms to Performance Reductions during Finger Tapping Tasks"*

Further training

Peripheral Nerve Stimulation (PNS) of upper and lower extremity, Transcranial Magnetic Stimulation (TMS), Electromyography (EMG) of upper and lower extremity, Electroencephalography (EEG)