Bimanual Coordination and Motor Learning in Children with Unilateral Motor Disorders

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Abbreviations

AD	**Ad**olescents
AH	**A**ffected **H**and
AHA	**A**ssisting **H**and **A**ssessment
AHC	**A**ffected **H**and **C**ondition (the condition of the bimanual box-opening task in which the affected hand performs the initial movement of the task)
ANOVA	**An**alysis **o**f **Va**riance
CC	**C**orpus **C**allosum
CHEQ	**C**hildren's **H**and-Use **E**xperience **Q**uestionnaire
CIMT	**C**onstraint**-I**nduced **M**ovement **T**herapy
cm	**C**enti**m**eters
CMCT	**C**entral **M**otor **C**onduction **T**ime
CMPP	**C**ortico**m**otor **P**rojection **P**atterns
CNS	**C**entral **N**ervous **S**ystem
CP	**C**erebral **P**alsy
CST	**C**ortico**s**pinal **T**ract
CV	**C**oefficient of **V**ariation
DD	**D**evelopmental **D**isregard
DOF	**D**egrees **o**f **F**reedom
DTI	**D**iffusion **T**ensor **I**maging
FA	**F**ractional **A**nisotropy
fMRI	**F**unctional **M**agnetic **R**esonance **I**maging
GMFCS	**G**ross **M**otor **F**unction **C**lassification **S**ystem
HABIT	**H**and**-A**rm **B**imanual **I**ntensive **T**herapy
HSS	**H**ope **S**cale **S**cores
Hz	**H**ert**z** (frequency)
ICF	**I**nternational **C**lassification of **F**unctioning, Disability and Health

IP	**I**nflection **P**oint (the value on the x-axis corresponding to the change of direction in the sigmoid function)
JTTHF	**J**ebsen-**T**aylor **T**est of **H**and **F**unction
LAH	**L**ess **A**ffected **H**and
LAHC	**L**ess **A**ffected **H**and **C**ondition (the condition of the bimanual box-opening task in which the less affected hand performs the initial movement)
m	**M**etres
MACS	**M**anual **A**bility **C**lassification **S**ystem
MEP	**M**otor **E**voked **P**otentials
MMs	**M**irror **M**ovements
MRI	**M**agnetic **R**esonance **I**maging
OC	**O**lder **C**hildren
RS	**R**adiological **S**core
s	**S**econds
TC	**T**emporal **C**oupling
TDC	**T**ypically **D**eveloping **C**hildren
TMS	**T**ranscranial **M**agnetic **S**timulation
TP	**T**otal **P**ath
TTD	**T**otal **T**ask **D**uration
uCP	**U**nilateral **C**erebral **P**alsy
YC	**Y**ounger **C**hildren

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Abstract

Introduction

Appropriate bimanual coordination is essential for many tasks in daily life. Children with unilateral cerebral palsy (uCP) however struggle with the execution of such tasks. Extensive research has been done investigating motor impairments on a functional level using standardized procedures. There is a lack of studies however looking at the specific problem of coordination of a bimanual task, especially with respect to the different underlying neuropathologies.

Aims & Methods

Within this thesis, kinematics of bimanual hand movement during a role differentiated bimanual box opening task in children with uCP, as well as in typically developing children (TDC) of similar ages, were investigated. The aims were: i) to identify behavioural changes in peak periods of development of the corpus callosum and areas of the prefrontal cortex, both of which are related to bimanual function in typically developing children; ii) to explore the relation between motor impairments of children with uCP and their bimanual coordination and iii) to investigate the impact of various underlying neuropathologies on bimanual coordination in children with uCP.

Results

For the first study, a total of 37 TDC between 5 and 16 years were included and allocated to their respective age-group: Young Children (YC: 5-6 years), Old Children (OC: 7-9 years) and Adolescents (AD: 10-16 years). The two older groups performed the task significantly faster than YC. Likewise, a trend (yet without reaching significance) towards a more ideal temporal sequencing was shown between YC and the two older groups. In contrast, spatial accuracy as expressed by the path length increased only in the AD group.

For the second study, a total of 37 children with uCP between 7 and 17 years were included. Children presented manual impairments between levels I and III (according to the Manual Ability Classification System). It could be shown that task duration increased and spatial accuracy decreased with increasing levels of impairment, especially in children with higher levels of impairment (level III). Furthermore it could be shown that a subgroup of children experienced an involuntary interference when moving their affected hand, limiting the use of their less affected hand.

The third study utilised a multiple case study involving nine children diagnosed with uCP with neuroimaging and neurophysiological data. The children were found to have various neuropathological patterns resulting in different forms and severities of motor impairments. It could be shown that grey-matter lesions had the most severe impact on manual abilities.

Conclusion

In TDC, performance of bimanual hand movements was temporally related to peak developmental periods of the corpus callosum, emphasizing the importance of interhemispheric exchange of information for bimanual coordination. In children with uCP, bimanual performance was related to the level of impairment of the affected hand. In addition it was found however that some children show excessive bimanual interference when using their affected hand in a bimanual task which limits the functionality of the less affected hand, possibly related to i) ipsilateral corticomotor projection patterns from the less affected hemisphere to the affected hand or ii) lack of suppression of interhemispheric crosstalk. It could also be shown that the various neuropathologies can affect bimanual motor control differently. Detailed diagnosis of the neuropathology and motor impairment are thus essential for the planning of tailored therapy interventions.

1 Introduction

With the development of the upright posture, the use of hands for the manipulation of objects has become of great importance to humans. Many activities in daily life depend on our manual abilities. Most tasks require the coordinated use of both hands at the same time (bimanual coordination) along with the disparate or role-differentiated use of the two hands. Cutting with a knife for example requires one hand for stabilising and gripping an object while the other hand grips and manipulates the knife. A high level of spatiotemporal cooperation between the hands is essential in order to successfully complete most of these tasks.

Cerebral palsy (CP) is a group of common non-progressive disorders with pathological characteristics of the motor areas in the central nervous system (CNS) that originates congenitally or during early infancy. Unilateral CP (uCP) denotes a subgroup of these children, in which neural impairments are predominantly located in one hemisphere with few or no pathologies found in the other. In general, motor skills are thus also impaired predominantly unilaterally (contralateral to the side of the affected hemisphere). About 1/3 of all children with CP are affected by such unilateral motor disorders (Arnfield, Guzzetta, & Boyd, 2013). Children with uCP usually perform unimanual tasks using their less affected hand (LAH) which thus becomes their dominant hand. Using the affected hand (AH) is often avoided due to high attentional demands (Houwink, Aarts, Geurts, & Steenbergen, 2011). As such, tasks that require the use of both hands at the same time are often avoided or strategies are sought in order to address these problems with the use of only one hand, e.g. opening a bottle by fixing it between the legs (Sköld, Josephsson, & Eliasson, 2004).

Therapy interventions based on principles of motor learning have become increasingly popular in recent years and were designed with the purpose of improving the skills of the AH and developing bimanual skills in children with uCP (Sakzewski, Gordon, & Eliasson, 2014). Such therapy interventions have generally been shown to be very effective in improving uni- and bimanual functions on group level (Novak et al., 2013). The outcome measures however mostly focus on the skills of the AH during the performance of uni- or bimanual tasks and less on the actual spatiotemporal cooperation between the hands. This thesis thus focuses on the movement kinematics during a functional bimanual box-opening task that requires role disparate actions each hand.

The aims of this dissertation are:

1. To investigate coordinative aspects of hand movement during a role differentiated bimanual movement task typically developing children; contrasting different age groups attributed to characteristic developmental changes of structures that are of importance for bimanual movement tasks (i.e. the corpus callosum and the prefrontal cortex)

2. To investigate bimanual coordination in children with uCP and compare performance across different levels of impairment as well as to relate outcomes with standardized measures of uni- and bimanual function

3. To explore the relation of neuropathological characteristics as identified in neuroimaging and bimanual movement skills in children with uCP

The overall aim of this research project was to develop a better and more individualised understanding of the implications of uCP (in its various forms) on bimanual coordination which might help to develop more individually tailored therapy interventions for children with uCP in the future.

2 Aspects of Motor Control and Learning and the Special Case of Bimanual Coordination

The field of studies investigating the emergence and control of coordinated movement patterns in humans and animals is a composite of different disciplines including physiology, psychology, neurology or even physics. One of the most influential scholars in the recent history of movement science was the Russian physiologist Nikolai Bernstein. Many of the modern theories are based on the principles and problems formulated by him. In his seminal work, which is considered to be one of the cornerstones of movement sciences, he defines motor coordination as:

> *"…the process of mastering redundant degrees of freedom of the moving organ, in other words the conversion to a controllable system. More briefly, coordination is the organization of the control of the motor apparatus."* (Bernstein, 1967, p. 127)

The term *degrees of freedom(DOF)* refers to the complexity of the structures involved in the movement control found on very different levels, such as body segments, joints, muscles, neurones, etc. If these are integrated into a complex movement that involves the control of multiple segments, the number of DOF increases considerably. The different systems of the CNS involved in (sensory-) motor control are described in the following section. Furthermore, theoretical concepts explaining the emergence of coordinated movement patterns (i.e. motor control are learning) are presented in the second and third part in combination with empirical evidence.

2.1 Central Sensory and Motor Systems

The human body consists of multiple organs that provide afferent information about various properties of the body itself. Information about force being applied to muscles or tendons for example is collected by the proprioceptive receptors, information about angular acceleration and the orientation of the head in the earth's gravitational field by the vestibular system, whereas information about the environmental context is collected by the visual system. On the other hand, muscles are the only organs that transform the efferent sets of information from the nervous system in order to produce movement so that the body can interact with its environment. In between, complex connections between the different sensory and motor systems of the CNS mediate the information returned by the sensors and generate an adequate output.

2.1.1 **Spinal Control of Movement**

The spinal cord is the (hierarchically) lowest place where afferent and efferent information is wired up in order to generate a motor output. The lower motor neurons, i.e. motor neurons that innervate the somatic muscles directly, are located in the ventral horn of the spinal cord. At the same time, afferent information from the somatic sensory receptors is fed back into the dorsal horn. In addition, the input from higher motor areas is interconnected here. The conversion of the afferent input into an efferent output at the spinal cord is called a spinal reflex and can either be i) monosynaptic, i.e. one afferent neuron feeds information from the receptor to the motor neuron in a direct manner or ii) polysynaptic, i.e. afferent signals are connected by one or more interneurons enabling signal modulation. Since the work of Sherrington published over 100 years ago (Burke, 2006; Sherrington, 1906), we know that reflexes are not just a simple stimulus response arc from receptor to effector, but rather integrate information from different receptors, as well as descending information from higher regions in order to produce an adequate and quick response to perturbations of the system.

Spinal control of movement is a necessary part in order to maintain the stability of the movement output in the case of perturbations of the system, for example in the case of reflexes (O. K. Andersen, 2007; Sandrini et al., 2005). Even self-contained rhythmic movement patterns can be generated in the spinal cord, such as for example in the case of the central pattern generators (Forssberg, Grillner, Halbertsma, & Rossignol, 1980; MacKay-Lyons, 2002). Nevertheless, highly skilled, more complex behaviour, integrating inputs from many different sources, e.g. visual, proprioceptive or vestibular, and producing a finely attuned motor output is only achieved with the inclusion of higher brain areas.

2.1.2 **Brain Control of Movement**

The spinal cord, in addition to its contribution to the regulation of movement, carries large axons that transport information from the periphery to the CNS and vice versa. Efferent motor commands from higher-order motor areas are being sent downstream, primarily via the corticospinal (or pyramidal) tract (CST). One important feature of the CST and of the sensory pathways is the crossover (decussation) of axons originating from the left hemisphere to the right side of the spinal cord and vice versa inside the medulla. Interestingly however, a small share of the CST fibres do not decussate. These ipsilateral connections can lead to the activation of muscles on both sides of the body from one hemisphere (bilateral activation). This type of phenomenon can be particularly found in young infants and usually disappears with continuing maturation (Eyre, Taylor, Villagra, Smith, & Miller, 2001).

Penfield and Brodley (1937) discovered with their pioneering work on the human brain that the cortical areas around the central sulcus hold the somatic motor (primary motor cortex, or rostral to the central sulcus) and sensory (primary somatosensory cortex, caudal to the central sulcus) representations of the human body. One of the best known models of the human motor cortex, the homunculus (see Fig. 2.1), showcases the results of their discovery. Motor responses can be directly elicited from the primary motor cortex, as well as from the areas located anteriorly to it, i.e. premotor- and supplementary motor area. The latter two areas seem to be involved in more complex movement patterns (Graziano, Taylor, Moore, & Cooke, 2002). The prefrontal cortex, which is located even further rostral, is involved in the performance of movements that require abstract thinking and anticipation of consequences, and it also plays a key role in response inhibition (Rae, Hughes, Anderson, & Rowe, 2015).

Fig. 2.1 Motor Homunculus. A cross section of a hemisphere of the central nervous system including the parts of the body that correspond (i.e. are being controlled) to the specific part of the primary motor cortex (reprinted from "The Cerebral Cortex of Man" by Penfield & Rasmussen, 1950)

Additional structures that are involved in the execution of movement and acquisition of motor skills are the basal ganglia and the cerebellum. The basal ganglia are involved in a loop originating in the cortex and concluding in the supplementary motor area. These structures seemed to be particularly involved in the selection and initiation of volitional movements (Nagano-Saito, Martinu, & Monchi, 2014). Disorders of the basal ganglia, such as Parkinson's or Huntington's disease, are thus often characterised by abnormal activation patterns, such as bradykinesia, i.e. slowness, akinesia, i.e. difficulty of movement initiation, or hyperkinesia, i.e. increased activation (J. Park, 2016). The function of the cerebellum on the other hand is to produce a coordinated flow of movement (e.g. movement sequence) and to modulate motor commands by integrating motor and sensory information (Manto et al., 2012).

2.2 Motor Control: Principles and Theoretical Concepts

A key feature associated with skilled movement is that performance needs to be very stable, while at the same time the movement needs to be variable and to adjust to all sorts of perturbations or changes in the environmental or internal structure[1]. For example, the output of a reaching movement will be very similar, regardless of whether the person stands upright or lies on their back. Yet the gravitational forces exerted on the arm are very different in both cases without however requiring any alteration of the motor command in a conscious state. Bernstein first proposed an investigation of how the motor system manages to control the various parts of the body that are involved in movement without consciously controlling them. The *degrees of freedom problem* (Bernstein, 1967) became one of the basic questions in the studies of motor control. In the following subsection, theoretical concepts of motor control are presented together with the underlying behavioural principles and experimental results that support or refute those concepts.

2.2.1 Movement Control: An Open- or Closed-Loop Process?

Firstly, it is important to consider by which systems and through which processes movement is controlled. Two different strands of models emerged based on control theory models in order to address this question: feedforward or open-loop in contrast to feedback or closed-loop models of motor control.

Open-Loop Perspective on Motor Control

Open-loop models of motor control examine the emergence of movement exclusive of any sensory input to correct the movement during the execution. Those models do not blank out and dismiss the existence of sensory mechanisms, yet propose that the execution of a (volitional) movement should be organised centrally in its entirety, e.g. in the form of a generalised motor program (Schmidt, 1975), prior to the execution of an action and not modified due to any feedback during the movement execution. Rapid movements, such as the jab of a boxer for example, are executed in a timeframe that seems to be too short for feedback correction mechanisms. Deafferentation, i.e. the sectioning of the dorsal root and

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[1] The human body is a system that is not in thermodynamic equilibrium and thus undergoes constant changes in its internal structure (e.g. weight increase or loss due to anabolic or katabolic processes)

thus the interruption of proprioceptive feedback, has often been used to study the impact of feedback (or rather the absence thereof) on movement execution. Even in the absence of visual feedback, deafferented monkeys are still able to perform simple reaching and pointing movements, nonetheless with reduced accuracy (Taub, Goldberg, & Taub, 1975). In humans, neuropathy of the sensory nerves can lead to chronic deafferentation. Individuals with this disorder are able to perform laboratory reaching tasks (such as Fitts' tasks) similarly to healthy controls, particularly in the presence of visual feedback (Medina, Jax, & Coslett, 2009), thus supporting the idea of a pre-programmed motor command. However, movements that involve constant levels of muscle contraction (Rothwell et al., 1982) or continuous movements without visual feedback (Medina et al., 2009) can barely be coordinated in a precise manner in the absence of feedback.

Closed-Loop Perspective on Motor Control

A closed-loop perspective on motor control highlights the importance of sensory or feedback mechanisms (e.g. from proprioceptors) for the execution of movements. The important feature is a reference mechanism that compares the actual movement with the desired goal. The executive level receives information about any misalignment so that executive parameters can be adjusted.

Reflex loops are examples of closed-loop motor control mechanisms. Merton (1953) hypothesized that the reflective properties of the muscles (i.e. the gamma-loop) act as a servo mechanism that guides the muscle to its required force. Muscle spindles can detect sudden changes to the length of a muscle fibre which results in a tonic stretch reflex. In order to keep the muscle spindles sensitive to these changes, intrafusal muscle fibres (i.e. inside the muscle spindle) being activated simultaneously with the surrounding (extrafusal) muscle fibers. This mechanism can indeed help to make compensatory alterations in muscle stiffness (Houk, 1979). Experimental findings however rather seem to dismiss the hypothesis that the gamma-loop is used to drive the muscle to its desired state (Houk, 1979; McIntyre & Bizzi, 1993).

The idea of a servo-mechanism being used as a motor control structure has been enhanced by others under the term equilibrium point hypothesis (McIntyre & Bizzi, 1993). Fifty years ago, Feldman proposed his equilibrium-point hypothesis or lambda (λ) model for motor control (Feldman & Levin, 2009), a concept that incorporates feedback as the control mechanism for movement. A central point of this hypothesis is that a movement result, such as a tonic stretch reflex threshold (λ) contains the parameter for movement execution and movement is subsequently produced via spinal circuitry in order to reach that threshold. Thus, scaled up to the volitional motor control, movements are coordinated by a constant ratio in order to balance the relative differences in position, force and goal outcome. In this context, motor impairments, such as spasticity, can lead to discrepancies in λ and thus to an abnormal movement behaviour (Levin & Feldman, 1994). The equilibrium point hypothesis seems like an elegant way to model simple movements involving a small number of DOF based on spinal circuits. This mechanical perspective however blanks out all the supraspinal areas of the motor system and the dynamic interaction of the different systems (Sainburg, 2015).

2.2.2 **Perception and Action**

Theories which include feedback mechanisms (such as the λ model) often assume that movement is not controlled by a single structure responsible for the generation of certain movements (i.e. the brain), but is rather self-organised at different levels of the motor system. Instead of being planned or programmed, movement is assumed to result as a direct consequence of information, such as sensory information about the body's state, implicit knowledge about the biomechanical structures, information about the environment and or cognitive information about the manner in which a movement should be executed.

The Ecological Perception Action Theory (Turvey & Kugler, 1984) states that movement is generated as a direct consequence of environmental perception. Gibson (1958) first hypothesised that visual perception is directly linked to motor actions. Turvey and Kugler (1984) then further developed their ecological approach to perception and action. From their point of view, an abstract Cartesian control mechanism (e.g. a motor program) needs to be rejected in favour of information-guided motor control.

The existence of two different streams of visual processing, a ventral and a dorsal stream, support the assumption of a perception (i.e. vison) guided motor control (Lee & van Donkelaar, 2002). While the ventral stream processes information about the general attributes of the visualized objects, the dorsal stream processes information that are of importance for the interaction with them. The dissociation between the two streams becomes evident for example when one of them is impaired. Brain injured individuals with lesions in the parietal lobe (dorsal stream) can show signs of optic ataxia, a disorder in which visually guided movement is impaired, however objects can still be recognized normally (Pisella et al., 2009). Visual agnosia on the other hand which results from damage in the parietal lobe (ventral stream) results in an impaired object recognition while at the same time visually guided movements seem to be unaffected (Milner et al., 1991).

2.2.3 Self-Organized Motor Control under Principles of Dynamical Systems (Synergetics)

The Dynamical Systems Theory is a field of Mathematics that describes the behaviour of complex nonlinear systems. The theory of Synergetics, developed by Hermann Haken (1988), uses principles stipulated by the dynamical systems theory in order to explain the self-organized emergence of coordinated (movement) patterns in nature. Such self-organizing dynamical systems can be found in a variety of domains, such as physics (e.g. laser) biology (e.g. in morphogenesis) or sociology and economics (e.g. the formation of a public opinion) (Haken, 2004). In the case of motor control, the Theory of Synergetics (Haken, Kelso, & Bunz, 1985) provides a framework to study the formation of (macroscopic) movement patterns under presumptions of nonlinear self-organisation of the microscopic subsystems with its multiple DOF (Kelso & Schöner, 1988). The theory provides the advantage of explaining variability and stability (in the case of movement patterns) and thus provides a possible answer to Bernstein's degrees of freedom problem (Bernstein, 1967; Van Emmerik, Rosenstein, Mcdermott, & Hamill, 2004).

Order and Control Parameters in Synergetics

The Synergetics theory consists of two important concepts, namely the order and control parameters (Kelso & Schöner, 1988). Order parameters are macroscopic quantities of the systems ordered state. In human gait for example there are typically at least two ordered states that show qualitative differences on a macroscopic level, walking and running (Diedrich & Warren, 1995). Control parameters are, on the other hand, quantities that can be changed continuously and which can at some point induce a bifurcation that leads the system away from its ordered state towards another (i.e. walking speed in the example of gait). Changes in the control parameter thus automatically guide the motor system from ordered to chaotic states and back.. The principle by which ordered states emerge is referred to as enslaving (Kelso & Schöner, 1988). The basic proposition is that only a limited number of order parameters contain the necessary information pertaining to the general movement pattern. All components of the motor system are then enslaved in order to maintain the ordered state. The principles of such dynamical systems have often been researched on continuous cyclical movement patterns, yet to a lesser extent on discrete actions.

Synergetics and Bernstein's Degrees of Freedom Problem

The basic assumption of Bernstein's key problem of motor control, the DOF problem (Bernstein, 1967), is derived from the field of physics. DOF are independent parameters that define the state of the system[2]. In the view of a (human) motor system, DOF are all the different independent parameters that determine the movement. These parameters can, for example, be broken down to single neurons or motor units which have to act in synergy to create coordinated movements. The key question for Bernstein was how a central control structure is able to control all the single DOF (e.g. every motor unit or neuron resp.) without exceeding the information-processing capacities. The assumption of the motor system possessing self-organizing properties provides a possible solution to this problem. According to this theory, the DOF are controlled by the so-called slaving principle (Kelso & Schöner, 1988). That is, the state of a (motor) system is governed by a few collective variables (i.e. order parameter). The order parameters act as attractors. When the system is near such an attractor, the components of the system are enslaved to work in the respective fashion. The usually sudden and nonlinear changes from one ordered state to another are termed bifurcation (Kelso & Schöner, 1988).

The Formation of Coordinative Structures or Synergies

Human movement is typically not the result of a single but rather of multiple DOF acting together in a coordinated fashion. Such task dependent functional interactions have been termed coordinative structures (Turvey, 1990; Van Emmerik et al., 2004). Extensive research has been done around the coordinated interaction between muscles, i.e. muscle synergies (Tresch & Jarc, 2009; Turvey, 2007). In their classical definition, a synergist is a muscle that works together with an agonist in a similar direction at the same joint. Synergies are task dependent (in certain aspects invariant) combinations of muscle activations that lead to a functional goal (in which case also antagonistic muscles can form a synergy) (Turvey, 2007). d'Avella, Saltiel & Bizzi (2003) for example, identified three different muscle synergies in the leg muscles of a frog during kicking. These synergies are

[2] In thermodynamics for example the state of a matter is determined by two degrees of freedom, temperature and pressure of the environment

characterised by some invariance in the temporal sequencing of the muscle activations and do correspond with qualitatively different behaviours (i.e. on a kinematic level).

2.2.4 **Variability and Stability**

Variability and stability are important aspects of skilled movement. It is essential to clarify these terms in the context of motor control theories since they can be easily misunderstood. Highly skilled movement patterns are characterised by an exceptional stability. The better the movement is controlled, the less it gets affected by any unexpected perturbations or changes in the environmental structure. Most humans can for example perform multiple (distracting) activities whilst walking or walk on different (even unknown) surfaces without affecting the stability of their general movement pattern. On the other hand, repetitive movements with the same goal can be highly variable within an individual, particularly when looking at highly automated movements. Bernstein (1967) demonstrated this phenomenon with the example of a blacksmith hitting an anvil with his hammer. The primary movement goal (i.e. hitting the anvil in a certain spot) was shown to be very stable, whereas the path of the hammer during the countermovement showed exceptional variation between movements. Impaired motor systems, e.g. in the case of patients with Parkinson's disease, often show greater regularity in their kinematic trajectories when replicating the same movement pattern (albeit atypically), in comparison to healthy controls (Powell, Muthumani, & Xia, 2014). Nevertheless, the stability of the outcome (as in the case of gait for example, measured in parameters such as step length) seem to be more inconsistent (Hausdorff, Cudkowicz, Firtion, Wei, & Goldberger, 1998). Movement variability is thus assumed to be (up to a certain extent) a contributor to obtaining a stable outcome.

2.2.5 **Uncontrolled Manifold**

Controlled and uncontrolled DOF are an essential part of Bernstein's postulations on motor control. This problem has been conceptualised by Scholz and Schöner (1999) within the Uncontrolled Manifold Theory. The general assumption is that all the different DOF that are involved in a certain movement can be described as an n-dimensional space (with each degree of freedom forming one dimension).

Fig. 2.2 A dart throwing task in which only the velocity of the dart and the release point can be modified (A). The two-dimensional space is constituted by the two degrees of freedom, angular velocity (y-axis) and the release angle of the dart (x-axis) (B). The grey shaded region within the two-dimensional space displays the combinations of angular velocity and release point with successful outcomes. With increasing skill level, participants find a region that allows for stable outcome, while the degrees of freedom can be greatly varied (C) (reprinted from "Motor learning: changes in the structure of variability in a redundant task" by Müller & Sternad, 2009)

The uncontrolled manifold is a region within that space that allows for stable output while at the same time tolerates an increased variability of performance. Since it is difficult to imagine an n-dimensional space (and even more difficult to measure all DOF), experimental tasks designed in order to support that theory often require very limited DOF. An experiment where all the DOF are fixated except for two (leaving a two-dimensional space) was introduced by Müller and Sternad (2009). Participants performed a virtual dart throwing task in which the trajectories of the dart were only controlled by the speed of rotation of the forearm around the elbow and the release point of the dart. Experimental data shows that participants, with practice, implicitly discover an area within the uncontrolled manifold that allows them to maintain a stable performance even when the execution itself is very variable (a broader part of the grey shaded area, Fig. 2.2). The coordination of complex movements, with multiple DOF, is challenged to a greater extent in tasks which require the use of two hands.

2.3 Motor Learning: Principles and Theoretical Concepts

Most of the movements we can perform are not mastered by new born infants. In animals, we can sometimes observe relatively skilled movements being performed shortly after birth, e.g. the ability to walk on fours. But even for those animals and especially for humans, skilled movements have to be developed. Motor learning is thus an essential aspect of motor control and an important part of our lives. According to Schmidt and Lee (2011, p. 327), motor learning is:

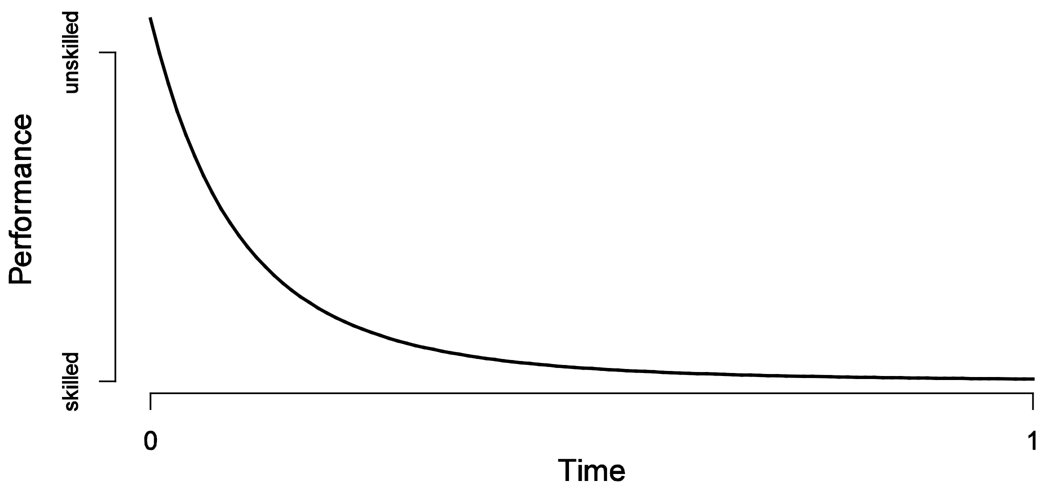
> *"…a set of processes associated with practice or experience leading to relatively permanent changes in the capability for skilled movement."*

The authors however do not further define the processes that lead to skill changes, but refer to them as the main research topic of learning theorists. Furthermore, motor learning is not directly observable due to the complexity of these processes that occur across different levels of the motor network. On small scales (i.e. single or small numbers of cells) the learning processes can be observed and described, such as by the Hebbian learning rule (Hebb, 1949). Some attempts have also been made in relating specific processes (of neural adaption) to certain aspects of motor learning (Hikosaka, Nakamura, Sakai, & Nakahara, 2002; Luft & Buitrago, 2005). It however remainsimpossible to directly observe all the processes (i.e. neurophysiologic adaptions) involved in the learning process. Observations can be made on the other hand on a behavioural level by monitoring performance. In the following section, distinct theoretical models of motor learning are shown on the basis of (observed) behavioural principles and theoretical conclusions are formulated about the organisation and the underlying processes.

This chapter provides a theoretical framework for the concept of motor learning, and demonstrates the behavioural principles and practical consequences constituting the result of extensive research within this filed. The concepts of upper limb therapy rehabilitation integrating the principles of motor learning are presented in the final part of this chapter.

2.3.1 **Performance Curves**

The performance[3] in motor tasks, similarly to cognitive tasks, often seems to follow a curve (Newell, Liu, & Mayer-Kress, 2001) that reflects decreasing gains between consecutive trials, with an increasing number of trials (e.g. that of an exponential function or power function – see Fig. 2.3). That is to say, performance gains are particularly pronounced during the initial stages of learning and decrease with experience. The flattening (or plateau) encountered towards the later stages of learning can be seen as a ceiling or floor effect given by the task (i.e. an error score can never fall below 0) or the abilities of the learner.



[3] Performance curves are sometimes referred to as learning curves. Since learning however relates to processes in the brain, i.e. changes in the neural network, the term performance curve seems to be more appropriate (Schmidt & Lee, 2011, p. 329).

Fig. 2.3 Changes in performance over time modelled by an exponential function. The performance variable (e.g. number of errors) improves at a higher rate during the early learning process and approximates towards an asymptotic value upon reaching a highly skilled level

Initial evidence of learning processes following a curve with rapid improvement in the early stages followed by later periods with little or no gain has been generated by Ebbinghaus (1885) for cognitive and Thorndike (1911) for motor learning processes in animals. Focusing on motor skills, the exponential improvement of performance as a function of time can be found on multiple different time scales, such as warming up or between sessions on different days (Adams, 1952) as well as over the course of several years (Newell et al., 2001). Even though this classic mode of skill acquisition may be observed, performance does not always improve in this particular manner. Liu and Newell (2015) found that some individuals' learning of a novel roller-ball task followed an s-shaped learning function, rather than an exponential or power law. The various stages and theoretical perspectives explaining performance changes will be described in the next sections.

2.3.2 **Closed- and Open-Loop Schemes of Learning**

The first fully developed theory of motor learning based on empirical observations was the closed-loop theory of motor learning (Adams, 1971). For Adams, the key in motor learning was represented by the development of two different traces, a memory trace and a perceptual trace. The memory trace was considered as the stored motor command for a movement, whereas the perceptual trace represented the stored expected sensory consequences. During the movement, a constant comparison of the feedback to the perceptual trace takes place and errors are corrected online. After each successful movement, the perceptual trace is updated subject to knowledge of results of the movement outcome. With an increasing number of practice trials, the perceptual trace grows and the movement can be performed in a more flexible manner under different task demands.

With reference to the logical problems and empirical contradictions, Schmidt (1975) developed a theory of motor skill learning based on the assumptions of open-loop, rather than closed-loop processes. Similarly to Adam's theory, the 'Schema Theory' of motor learning hypothesises that the movement parameters are stored in two distinct types of memory. Information is supposedly stored in the form of abstract rules or concepts, i.e. schemata (or generalised motor programs, see section 2.1.2) in a recall and recognition schema. One of the main differences for Schmidt is that movement is initiated and motor commands are already specified within the recall schema and therefore do not rely on sensory online corrections. In contrast, the recognition schema holds a prediction of the sensory consequences of a movement, which are evaluated to the actual sensory input after the movement and form the basis for learning. Schmidt acknowledged the importance of his theory particularly in view of fast ballistic movements where there is simply not enough time for online corrections to occur. At the same time, he also admits that a combination of recall and recognition schema could be used to control slow movements (Schmidt, 2003).

2.3.3 **Stages in Learning**

Several researchers have identified different learning stages. For Fitts and Posner (1967), the learning process consists of an early cognitive, an intermediate associative and a final autonomous phase. During the cognitive phase, the learner has to be very attentive and to process information on a cognitive level. In the subsequent associative phase, the learner has already learned the general pattern of movement(s) and is now able to repeat it without major errors. During the final stage, the skill becomes highly automatic and can be performed without paying particular attention to it or even simultaneously to other activities. It is however difficult to clearly discriminate between those phases or to measure at what stage the learner is located at a certain time.

Bernstein (1967) likewise identified three characteristic stages in motor learning. In the beginning, the learner does not have the optimal solution to control all the DOF for a certain task. Thus ‘freezing’ as many DOF (e.g. stiffen joints) may render the task easy to control. The learner then enters the second stage, in which he is able to release and reorganise the DOF. Movements then incorporate more joints, typically in distal locations (Newell & Vaillancourt, 2001). Novice writers seem to generate movement in their elbows and shoulders, whereas more experienced subjects move their wrist in order to accomplish the task (Newell & van Emmerik, 1989). For Bernstein the learning process concludes in a third and final stage in which the learner gains the capability to exploit and utilise the passive (spring-like) properties of the muscle-tendon system in order to accomplish maximum effectiveness and efficiency.

2.3.4 **Freezing and Releasing Degrees of Freedom in the Learning Process**

For Bernstein (1967), the essential problem in skill acquisition is how the motor system learns to control all the redundant DOF (see sections 2.2.3 & 2.3.3). Vereijken, van Emmerik, Whiting & Newell (1992) have investigated the ‘freezing’ and ‘releasing’ of the DOF during initial stages of learning on a ski simulator. Fixations of the joints of the lower limbs lead to relatively little movement in the beginning of the learning process. After practice, there was an increase in lower limb joint movement with an increased independency between joints (lower cross correlations of joint kinematics). In a comparison between skilled and unskilled (i.e. non-dominant hand) handwriting kinematics, Newell and van Emmerik (1989) showed that unskilled handwriting is characterised by a fixation of the more distal joints of the arm (i.e. wrist) and movement produced in the more proximal joint (i.e. shoulder). This pattern was reversed on the dominant side. Research reflecting the ‘fixation’ of joints in more immature stages of skill acquisition is evidenced from Utley, Steenbergen & Astill (2007) who showed that children with impaired motor coordination (i.e. Developmental Soordination Disorder) show less elbow movement with less success when trying to catch a ball than their non-impaired peers. In summary these results suggest that the ‘freezing’ of DOF is characterised by a fixation of the (more proximal) joints in the beginning of a learning process. This reduction of DOF seems necessary in the beginning of the learning process in order to reduce the complexity of the movement. With progressing skill levels, new coordinative structures are formed (B. Vereijken, Van Emmerik, Bongaardt, Beek, & Newell, 1997) that allow for the release of the DOF.

2.3.5 **Dynamic Principles of Motor Learning**

For the past thirty years, the theory of dynamical systems has expanded from the domains of motor control (see section 2.3.5) into motor learning (Newell et al., 2001) and development (Corbetta & Thelen, 1996; Thelen, Kelso, & Fogel, 1987). The general idea is that learning leads to changes in the attractor layout (see Fig. 2.4) (e.g. formation of new attractors or strengthening of existing ones).

Fig. 2.4 Dynamical systems model for the exemplification of coordinated movement and motor learning on different time scales with emphasis on behavioural changes and their theoretical explanation (reprinted from “Time scales in motor learning and development” by Newell KM, Liu YT and Mayer-Kress G, 2001)

A Dynamical Systems Model of Motor Learning

Newell et al., (2001) developed a theoretical model for the organisation of motor skills which applies the principles of the dynamical systems theory (see Fig. 2.4). The learning of new coordination patterns at the highest level of this model is achieved as a result of the evolution of the attractor landscape. Even though in their model, Newell, Liu and Mayer-Kress (2001) indicate that months or even years are required for the evolution of the attractor landscape, this does not depend on the amount of practice or the task to be learned and might actually occur sooner (i.e. within days or weeks).

Bifurcations in Motor Learning

Kostrubiec, Tallet and Zanone (2006) demonstrated that the formation of new attractor phase modes (e.g. at phase modes of 90°, 135° or 158°) resulted from learning in the classic bimanual Haken-Kelso-Bunz model (section 2.4.1). Interestingly, the 90° and 135° phase modes were learned more quickly and became more stable than the 158° mode. The authors found that modes that were further away from stable points showed reduced competition and thus new attractors could be formed more easily. The researchers could furthermore demonstrate that performance changes could take two distinct routes: i) a shift or ii) a bifurcation (Kostrubiec, Zanone, Fuchs, & Kelso, 2012). Performance shifts constitute gradual changes in the performance, for example fitted by a sigmoid function, whereas in the case of bifurcations sudden jumps in performance occur at a more specific point during the learning process and follow an s-shaped function (Kostrubiec et al., 2012). The specific route a learner takes depends on the interaction between the initial state of the learner and the task to be learned. Liu et al. (2003) made similar observations in relation to a more gradual progress during a simple discrete timing task (i.e. a gradual improvement of the error). Upon learning a qualitatively new movement pattern, they observed sudden performance jumps in some of the participants, which were considered as an indication of a bifurcation in the learning process (Liu & Newell, 2015).

2.3.6 **Practical Considerations for Motor Learning**

The theoretical concepts of motor learning are a crucial basis for the purpose of modelling and predicting motor learning and making practical suggestions[4]. They do not account however for the multiple modalities of practice that accompany and possibly influence the

[4] Practice itself is of course the most important aspect of motor learning and motor skills always increase with practice. Changing the modalities can however facilitate the learning process or the rate of motor skill acquisition.

learning processes, such as experience and or motivation. Thus, the following subsection gives an overview of possible confounders of learning and summarises the empirical results demonstrating their impact.

Distribution of Practice

There is an evident correlation between the amount of practice and performance. The intensity and duration of practice are other crucial temporal aspects of training. Distribution of practice is often compared in paradigms including massed and distributed practice, i.e. blocks of practice with little or no space and practice that is interrupted by breaks of different lengths. Empirical studies suggest that the performance associated to the distributed practice is higher compared to massed practice, provided that time and the other modalities of practice are the same (Donovan & Radosevich, 1999).

Shea et al. (2000) for example compared the performance improvements on a balance task between two groups who practiced a task for a total of 2 sessions comprising 7 trials, each of them with a duration of 90 seconds. One of the groups attended both sessions in one day (with a break of 20 minutes) and the other group had one session on the first day and the other one on the second day. Visual feedback was given during practice. Both groups completed a retention session 24 hours after completing their final practice session in which they did not receive visual feedback about their performance. The 2-day learning group showed better performance during the second session, as well as during the retention session (see Fig. 2.5).

Fig. 2.5 Performance expressed by the root-mean-square error (RMSE) of angular deviations from 0° during a balance task. Circles indicate group means for the 1-day and squares for the 2-day acquisition group for the practice and retention trials (reprinted from “Spacing practice sessions across days benefits the learning of motor skills by Shea CH, Lai Q, Black C and Park J-H, 2000)

The sum of the study results that compare massed versus spaced practice shows that longer intervals between sessions are almost always beneficial over shorter intervals. There is however one important caveat: the total time. The more time a learner spends off practice, the less time can be spent practicing. That means that more time spent on (or massed) practice is favourable if the limiting factor is the total time. On the other hand, if other resources are the limiting factors for example money in rehabilitation programs (and thus the total number of sessions) sufficient breaks between sessions can be an important factor to optimise outcomes.

Structuring Practice

Practice structuring is an important aspect that has received limited consideration in the learning process with respect to time. The effect of practice on skill acquisition is determined by a combination of the learner's skill level and the task difficulty. If practice tasks are too difficult (e.g. for beginners with a low skill level), they might not be able to successfully master it. If tasks are too easy (e.g. for experts with a high skill level) they might not constitute a strong enough stimulus to generate neurophysiologic adaptations (Guadagnoli & Lee, 2004).

Partial or Whole Practice

Very complex movements or sequences of movements can sometimes be broken down into several subparts. Whether or not splitting movements (part practice/whole practice) favours motor learning cannot be addressed generally since it is highly dependent on the modalities of the task to be learned. If a task is very complex and consists of several subtasks that need increased information processing capacity, it might be too overwhelming for a novice learner to remember and execute all of the task's details, particularly when a task consists of several sequences, e.g. dancing.

Park, Wilde and Shea (2004) investigated the differences between partial and whole practice in an experiment in which participants had to adjust a lever arm in a sequence of 16 angles. Participants received visual feedback of their current angular position and of the next position to be reached in the sequence. Performance was measured as the average duration required for reaching the position of the next element in the sequence. Two groups learned the sequence either as a whole (all 16 elements of the sequence at once, i.e. practice group AB) or partially (the first 8 elements of the sequence on the first and the whole sequence of 16 elements on the second day, i.e. practice group A). The results of this study are depicted in Fig. 2.6. The practice group with the partial approach showed quicker performance improvements on day one. This seems reasonable since they had to learn a shorter and thus easier sequence. On the other hand, the group adopting the whole approach showed a better performance on day two. Interestingly, during the retention test on day three, there was no difference in performance between the two groups. During the transfer test (following the retention test) each part of the sequence had to be executed independently, i.e. the first eight elements and the second eight elements in counter-balanced order. The partial practice group showed a much better performance in the retention test, particularly for the second part of the sequence.

Fig. 2.6 Performance on a sequence learning task for the partial (Group A) and whole (Group AB) practice group (reprinted from Park, Wilde and Shea, 2004)

Variability of Practice

In order to answer the question whether very specific or rather the general practice of a skill results in improved motor learning, it is important to consider if the learned skills are closed (i.e. very predictable, repetitive, less variation) or open (i.e. very unpredictable, context dependent, variable). The "…specificity of the learning hypothesis" (Schmidt & Lee, 2011, p. 388), which states that the conditions of practice should be as similar as possible to the conditions that will be met during retention is still widely accepted. Closed movement skills, such as for example brushing teeth, are practiced discreetly and can thus only be applied specifically (this becomes apparent when trying to perform those skills differently, e.g. using the non-dominant hand for brushing the teeth). On the other hand, many skills in daily life have to be considered as more open and adaptable to many different situations, namely they have to be transferred. It has been shown that certain aspects of a learned movement skill can be generalised and transferred onto different movements (Goodbody & Wolpert, 1998; Seidler, 2004) as hypothesised in the theory of generalised motor programmes (Newell & Shapiro, 1976; Schmidt, 1975). Hence, if the outcome of a motor learning process is the development of a generalised and transferable skill (e.g. bimanual skills in general) than that of a specific closed skill, practice exercises should be varied and should cover the range of the general trait to be learned.

2.4 Bimanual Coordination

The ability to coordinate both hands is an essential part of many activities of daily life. The problem of interlimb coordination constitutes a specialist area within the field of movement science. Within this section, the behavioural and neurophysiological characteristics of bimanual movements are presented.

2.4.1 Behavioural Characteristics

Bimanual movements can be executed for various different reasons and have various different forms. A completely symmetrical movement of both limbs can be essential for the performance of some tasks, such as rowing or pushing a shopping trolley (with both hands), whereas others might require an asymmetric (e.g. drum roll) or completely disparate use of each hand, e.g. to hold or grasp an object with one hand and manipulate it with the other hand.

Symmetric In- and Anti-Phase Bimanual Movements - The Dynamical Nature of a Bimanual Movement Paradigm

A bimanual movement paradigm was used as a model in order to explain the emergence of movement on the assumption of underlying evolving attractors, described within the theory of dynamical systems. Since its development in the 1980s, the Haken-Kelso-Bunz model was used extensively in order to research the self-organising properties of motor systems (Haken et al., 1985; Kelso, 1984; Kelso & Schöner, 1988; Schöner, Jiang, & Kelso, 1990; Swinnen, 2002). The order parameter of the movement is the relative phase between the fingers of the left and right hand swinging in an alternating manner from left to right. The frequency of the finger movement can be considered as the control parameter. The Haken-Kelso-Bunz model allows for a convenient way of modelling attractive coordination modes on a theoretical level (see Fig. 2.7).

Fig. 2.7 Mathematical modelling of the Haken-Kelso-Bunz Model. The curves are combinations of cosine waves with the form: $V = -a * \cos(\varphi) - b * \cos(2\varphi)$. The troughs of the curves illustrate stable attractor potentials. The ratio a/b (top right numbers) acts as a control parameter that changes the systems attractor potentials. The black illustrates the state of the system. Until the control parameter reaches 0.375, the system is at the stable attractor +π (anti-phase). With smaller numbers stability is lost and the system strives towards the more stable attractor at 0 (in-phase) (reprinted from "A Theoretical Model for Phase Transitions in Human Hand Movement" by Haken et al., 1985)

The two main modes studied by these scholars are the in-phase, in which homologous muscle groups are activated in both limbs at the same time and the anti-phase movements, in which they are activated reciprocally. Both in- and anti-phase movements constitute attractive modes (i.e. very stable and easy to perform); at higher frequencies (i.e. movement speed) however, a loss of stability of the anti-phase mode can be observed and participants tend to shift to the more attractive in-phase mode. As a result of motor learning, new stable patterns (or phase modes) can evolve that do not fall under any of the aforementioned categories, but are rather asymmetric (Kostrubiec & Zanone, 2002; Kostrubiec et al., 2012; Schöner, Zanone, & Kelso, 1992; Zanone & Kelso, 1992).Role-Differentiated Bimanual Movements

On a models level, the investigation of the phase modes provides interesting information about the nature of the interlimb coordination. Those phase modes are however studied within the framework of rhythmic continuous movement tasks, which is why the transfer of those principles onto bimanual movement in daily life is difficult. When performing typical two-handed tasks, the movement patterns of both hands are disparate, with each hand being assigned a different role (i.e. role-differentiated bimanual movements). Such role-differentiated actions can be usually observed after 7 months of age (Kimmerle, Ferre, Kotwica, & Michel, 2010; Kimmerle, Mick, & Michel, 1995) and seem to be related to the development of hand preference (Babik & Michel, 2015). An interesting hypothesis has been proposed by Guiard (1987). He argues that in role-differentiated bimanual actions, the dominant hand articulates with the movement of the non-dominant hand. The movement of the non-dominant hand thus forms the spatial frame of reference, to which the dominant hand adjusts[5]. Therefore, the non-dominant hand usually assumes the more stabilising or supporting role, whereas the dominant hand assumes the more manipulating role in a bimanual task.

2.4.2 **Neurophysiological Aspects of Bimanual Coordination**

On the lowest hierarchical level, reflex arcs and central pattern generators (CPG) in the spinal cord can modulate the motor output of one limb following the afferent input from the opposing limb. In quadrupeds for example, CPGs have been shown to maintain a very basic walking pattern without the influence of any higher centres of the CNS (Forssberg, Grillner, & Halbertsma, 1980; Forssberg, Grillner, Halbertsma, et al., 1980). In humans, spinal reflexes have also been shown to mediate between intermanual rhythmic arm movements (Zehr & Kido, 2001), playing a more substantial role in cyclic, walking-related (e.g. swinging the arms next to the body) movement patterns (Dietz, Fouad, & Bastiaanse, 2001) than in a disparate control of each arm.

Networks involved in the control of highly skilled bimanual movement patterns thus have to be sought in the higher regions of the brain. Various electrophysiological, lesion and imaging studies have shown that the execution of bimanual movements involves a complicated interaction between a variety of motor areas within the cortex, including the supplementary motor area, the primary and premotor cortex, the sensory cortices, the cingulate motor area and the cerebellum (Swinnen, 2002). In a functional magnetic resonance imaging (fMRI) study, Ullen et al. (2012) investigated brain activation during the in- and anti-phase movements, as well as the polyrhythmic tapping patterns of the index fingers. They showed that different phase modes are accompanied by different patterns of brain activation. The right anterior cerebellum and the CMA seem to be more active during the in-phase, whereas the SMA is active during the anti-phase movements. This is just a

[5] Guiard uses the model of the kinematic chain, in which the proximal segment forms the frame of reference for the more distal segment in order to illustrate his hypothesis.

very cursory description of the cortical and cerebellar regions involved. To describe the exact (known) interactions goes beyond the scope of this report, as it reflects more complicated brain functions, which are highly task dependent (Swinnen, 2002; Swinnen & Wenderoth, 2004).

With the development of more sophisticated methods for analysing the white matter tracts of the brain, such as diffusion tensor imaging (DTI), the interhemispheric connectivity via the corpus callosum (CC) constitutes the centre of focus of the bimanual control. As each side of the body is usually controlled by the contralaterally located brain hemisphere, an exchange of information appears to be essential in order to sustain that high quality of cooperative behaviour observed during the performance of the bimanual tasks. The CC, and in particular its anterior part seems to constitute the main structure which mediates this exchange of information (Gooijers et al., 2013). There is evidence for both an inhibitory function of the CC in order to suppress for example mirror movements (MMs), as well as an excitatory function in order to facilitate cooperative movements (Takeuchi, Oouchida, & Izumi, 2012). There is increasing evidence suggesting that an impaired bimanual control is accompanied by disturbances of the integrity of the CC (Gooijers et al., 2013; Johansen-Berg, Della-Maggiore, Behrens, Smith, & Paus, 2007; Weinstein et al., 2014). The role of the CC in the mediation of the interlimb movement control is not fully understood and researchers have only just begun to formulate a more precise definition (see Gooijers & Swinnen, 2014 for Review).

When considering highly skilled bimanual tasks, an enormous degree of cooperativity (on a kinematic and kinetic level) between the hands can be observed. As each limb is however controlled separately in opposing hemispheres of the CNS, the exchange of information between the hemispheres is necessary in order to warrant this cooperative behaviour (Gooijers & Swinnen, 2014). An interruption of the interhemispheric connectivity, as in the case of callosotomy patients, has been shown to have a major impact on the ability to perform symmetrical or in-phase movement patterns (Kennerley, Diedrichsen, Hazeltine, Semjen, & Ivry, 2002). Crosstalk between hemispheres can however also lead to an interference effect when both hands perform a disparate movement task, particularly during the early stages of learning (Wenderoth, Puttemans, Vangheluwe, & Swinnen, 2003). Sectioning parts of the CC can thus result in a better performance of the asymmetrical movement patterns, e.g. drawing different shapes at the same time (Eliassen, Baynes, & Gazzaniga, 1999). The performance of interlimb coordination thus requires a high degree of cooperation with little or no interference in order for it to be successful.

2.5 Summary and Reconciliation

The human motor system is highly complex and it is not yet fully understood how all the subsystems located on different levels interact in order to produce such stable yet adaptable movement, which can be observed both in humans and in animals. Nonetheless, this chapter sought to provide an overview of the most important physiological aspects, as well as of the theoretical models of motor control and learning. In addition, the special case of bimanual coordination is highlighted with focus on involved systems and behavioural characteristics. This is important in order to understand the impact of the specific impairments of these systems and the implications thereof for motor control which will be discussed in the subsequent chapter.

3 Early Childhood Motor Impairments and Impact on Bimanual Function

Congenital motor impairments associated with cerebral disturbances were originally described in Little's seminal work *"On the Nature and Treatment of the Deformities of the Human Frame"* (1853). Subsequently, CP became known as 'Little's Disease' for several years (Morris, 2007). Osler (1889) then categorised the clinical representations of CP into hemiplegia, bilateral hemiplegia or paraplegia based on an investigation of 151 cases of cerebral paralysis. Throughout the 20th century, different classification schemes have been developed that involved topologic or neurologic characteristics or a mix of both (Morris, 2007). The most recent definition for CP proposed and agreed upon by a panel of experts (Bax et al., 2005, p. 572; Rosenbaum et al., 2007, p. 9) describes a complex motor disorder:

> *"Cerebral Palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour, by epilepsy, and by secondary musculoskeletal problems."*

A recently suggested scheme classifies the subtypes into unilateral or bilateral types of motor disorder, namely spastic, dyskinetic or ataxic, with the spastic subtypes accounting for the largest proportion amongst all diagnoses (Cans, 2000; Krägeloh-Mann & Cans, 2009). The different types of impairments are based on the characteristics of abnormal movement with i) hyperexcitability of the stretch reflex in the spastic subtype; ii) involuntary, uncontrolled movements, occasionally stereotypical with variable muscle tone, in the dyskinetic subtype (includes dystonia and choreoathetosis) or iii) generally reduced coordination in individuals with ataxia. This research project focuses on the group of children with predominantly unilateral and spastic CP , which is identified in about 1/3 of all children with CP (Arnfield et al., 2013). The following chapter shall provide an overview of the neurological aetiology and behavioural aspects of CP with a focus on the predominantly unilateral manifestation of motor impairments.

3.1 Neurophysiological Characteristics

With an incidence of 2-3 per 1000 live births, CP is considered to be the most common cause of motor impairments among children born in Western countries (Cans, 2000). As the definition of CP (Rosenbaum et al., 2007) is intentionally rather vague, a broad range of different subtypes may be identified. This subsection focuses on the neurophysiological characteristics of CP, including the neuropathology and aetiology on the one hand, and the structural changes in the developing brain as a consequence of the different types of impairment on the other hand.

3.1.1 Neuropathology & Aetiology

Pathological brain development that causes CP can be roughly classified into three different categories: i) Brain maldevelopments, ii) Periventricular white matter lesions and iii) Grey matter lesions. The different neuropathological manifestations may be a consequence of genetics, whereas the different timings of insult related to different ages of gestation (Staudt et al., 2004) result in different forms of reorganisation of the CNS. In a systematic review of a range of magnetic resonance imaging (MRI) studies investigating the pathogenesis of CP, Krägeloh-Mann & Horber (2007) identified the extent to which each of the categories was assumed to be the causal factor of the motor impairment. They found that brain maldevelopments only made up about 9% of the cases, periventricular white matter lesions had the highest share with 56%, and grey matter lesions accounted for 18% (see Fig. 3.1). The remaining 17% in that study were made up by miscellaneous factors (e.g. porencephalic cysts) or cases in which no abnormality could be found from within the imaging data.

Maldevelopments

Maldevelopments which account for the smallest subgroup usually occur between the 1st and 2nd trimester of gestation. The causal factors (and manifestations) can be fairly variable and include genetic abnormalities; pathological mechanisms can include defects in the proliferation, migration and organisation of neurons (Barkovich, Guerrini, Kuzniecky, Jackson, & Dobyns, 2012; Krägeloh-Mann, 2004). Disturbances in the proliferation thereof result in abnormal numbers of neurons and glial cells[6] being produced. This can have a dual

[6] Glial cells are cells within the central and peripheral nervous system that provide non-neuronal functions, such as the production of myelin (so-called oligodentrocytes within the central or Schwann cells within the peripheral nervous system) or supply of nutrients

effect, i.e. a decreased (microcephalus) or increased number of cells (megalocephalus). Unilateral (or hemi-) megalencephaly (Barkovich & Chuang, 1990; Flores-Sarnat, 2002) for example, is a disorder which leads to an enlargement of the cerebrum in only one hemisphere, and which can affect a hemisphere either partially or wholly (even including the brain stem or cerebellum) with variable severities. Seizures, mental retardation and hemiparesis are often symptomatic. Callosotomy (surgical sectioning of the CC) or hemispherectomy (surgical removal or disconnection of one hemisphere) is occasionally necessary for the treatment of seizures.

Fig. 3.1 MRI images of a variety of lesions of the CNS causing CP. Lesions are bilateral in the upper row and predominantly unilateral in the lower row. In this study, 83% of the MRI images could be classified into one of the following three groups: I. Brain maldevelopments, II. Periventricular lesions and III. Grey matter lesions. Additional unclassifiable images (normal and miscellaneous) were adding up to 100% (reprinted from "The role of magnetic resonance imaging in elucidating the pathogenesis of cerebral palsy: a systematic review" by Krägeloh-Mann & Horber, 2007)

The second category of maldevelopments includes disorders related to neuronal migration. Neuronal migration describes the mechanism of the differentiated neurons' travel from the ventricular and subventricular zones to their designated area in the cortical surface. Lissencephalies are among the most common manifestations of neuronal migration disorders (Guerrini & Filippi, 2005; Spalice et al., 2009). The brain surface of patients with a lissencephaly has a distinctive smooth pattern resulting from a reduced depth or number of gyri and sulci. Severities vary from very broad and flat gyri (pachygyiria) to an almost flat surface with no visible gyri (agyria). The causal factors are mainly genetic (Moon & Wynshaw-Boris, 2013). Clinically, lissencephalies almost always result in seizures and children show developmental delay, mental retardation, spastic quadriparesis and reduced longevity (Spalice et al., 2009).

Some malformations result from an abnormal cortical organisation in the postmigration phase e.g. polymicrogyria or schizencephalies which can both lead to spastic motor impairments (Guerrini & Filippi, 2005). As opposed to lissencephalies associated with a reduced number of gyri, polymicrogyria is characterised by an increased number of small gyri and low sulci, as well as an abnormal structure of the layers of the cortex. Various parts of the cerebrum can be affected sporadically. Polymicrogyria can occur with unilateral or bilateral symmetric or asymmetric presentation. Generally, the areas around the Sylvian fissure (i.e. the lateral sulcus that separates the frontal and parietal lobes) and thus the primary motor and sensorimotor areas are affected (Guerrini & Filippi, 2005). Clinically, polymicrogyria can lead to hemi- or quadriparesis, epilepsy and developmental delay (Barkovich, 2010). Extreme forms of perisylvian polymicrogyria can lead to a literal cleft in the perisylvian area i.e. a schizencephaly (Guerrini & Filippi, 2005). Schizencephalies often completely separate the frontal and parietal lobes (uni- or bilaterally) and clefts are lined with grey matter. Kułak et al. (2011) identified schizencephalies as being the causal factor among 6.6% of the participants in an MRI study which included 180 children with spastic CP.

Periventricular White Matter Lesions

Lesions acquired in the early/mid stages of the third trimester result in damage of the periventricular white matter. Damage can either result from a restricted flow of blood or oxygen, i.e. periventricular leukomalacia, or from a haemorrhage in the ventricular area, i.e. intraventricular or periventricular haemorrhage (Krägeloh-Mann, 2004). The causes for periventricular leukomalacia as well as infarcts can be various but are often related to complications occurring during preterm birth (Back & Rivkees, 2004; Rezaie & Dean, 2002). Approximately 10% of the children who survive extreme preterm birth (21 – 25 weeks of gestation) develop severe neuromotor disabilities (Wood, Marlow, Costeloe, Gibson, & Wilkinson, 2000). Periventricular leukomalacia consists of a focal infarct region due to the restricted oxygen supply, which results in the necrosis of all cellular elements in this area and the formation of a cyst. A diffusely affected region with injured glial cells usually surrounds the focal area (Volpe, 2001). Among the risk factors for developing periventricular leukomalacia are fetal infections or impaired autoregulation of the cerebral blood flow (Back & Rivkees, 2004). Intraventricular haemorrhages on the other hand are often subject to fragility in the germinal matrix (Ballabh, 2014), the densely vascularised region in which neurons and glial cells are produced.

Grey Matter Lesions

Lesions that occur towards the end of gestation (i.e. late 3rd trimester) mainly affect the grey matter of the cortex or deeper regions (Krägeloh-Mann, 2004). Perfusion failure due to asphyxia at or close to birth in term born babies mainly leads to lesions in the basal ganglia and thalamus which are of importance for the execution of volitional movements. Impairments thus often lead to dystonic motor impairments. The central regions and the hippocampus can however also be affected (Krägeloh-Mann et al., 2002). Another causal factor for grey matter lesions in term born children might be an infarct at the level of the middle cerebral artery.

Involvement of the Cerebellum

Apart from lesions in the cerebral areas, there are incidences with additional involvement of the cerebellum, which plays a role in the coordination and sequencing of movements. Impairments of the cerebellum can lead to signs of ataxia. Cerebellar lesions are found especially in preterm children with white matter lesions (Bodensteiner & Johnsen, 2005).

3.1.2 **Developmental Neuroplasticity**

Even though a high specialisation of the areas in the brain seems to be a necessary feature for its functionality, there is some room for variation within the CNS to maintain functionality. Structures and connective pathways can take over brain functions from other areas in some cases in addition to their original function. Children with uCP show for example an increased thickness of the non-affected areas of the motor cortex (Artzi et al., 2016). According to the Kennard principle (Kennard, 1936; Kirton, 2013), the age of occurrence of a brain lesion plays a crucial role in its reorganisation capacity and pre- or perinatal lesions should lead to a better motor recovery than those occurring later in life.

Intra- or Interhemispheric Shift of Motor Control Areas

In children with focal lesions, one can sometimes observe a transition of the areas involved in motor control into perilesional areas (Kirton, 2013). Corticomotor projection patterns (CMPP) show similar to normal contralateral development, or in other words the limbs on the right side of the body are controlled by the left hemisphere and vice versa[7]. The functional outcomes resulting from such intrahemispheric shifts of the motor areas can be very good.

Fig. 3.2 Schematic Illustration of contralateral, mixed and ipsilateral corticomotor projection patterns. Typical contralateral projections are present in individuals with small lesions (SL, Patient 1), bilateral projections in individuals with intermediate lesions (Patient 5) and ipsilateral projections in individuals with large lesions (LL) (reprinted from "Two types of ipsilateral reorganization in congenital hemiparesis: a TMS and fMRI study" by Staudt et al., 2002)

In individuals with predominantly unilateral CP, the motor control of the affected limbs can sometimes be taken over by the non-lesioned hemisphere ipsilateral to the affected side of the body (Staudt, 2010). Ipsilateral downstream projections do not emerge as a product of axonal sprouting, but are present during normal early development and disappear as a

[7] The axons of the upper motoneurons cross over in the pyramidal decussation which is located in the medulla. The majority of muscles in the body are thus typically controlled by the hemisphere that is contralateral to the side of the muscles

result of non-use during development (Eyre et al., 2001). Early childhood unilateral brain lesions can thus lead to the utilisation of these ipsilateral projections. Whether the affected side of the body is being controlled by ipsi- or contralateral projections patterns is likely to be a result of the lesion size (see Fig. 3.2). Mixed patterns can be observable as well in which both hemispheres are involved in the control of the affected limbs (Staudt et al., 2002). Interestingly, such interhemispheric shifts are usually only found in motor, and rarely in sensory pathways (Guzzetta et al., 2007).

3.2 Motor Impairments

After discussing the neurophysiological basis of early childhood motor disorders, the following section focuses on the actual motor impairments.

3.2.1 Gross Motor Function Classification

The Gross Motor Function Classification (GMFCS) is a system that evaluates the ability to self-initiate movements with a special focus on functional mobility across five different levels. Guidelines are available for different age bands (Palisano et al., 1997). Achieving a categorisation in the early years of life is however rather difficult due to the developmental differences in the quantity and quality of motor development between children, and potentially complicated by any additional sensory or cognitive impairments (Rosenbaum, 2014).

3.2.2 Classifying Motor Types

The GMFCS is a useful tool for example in clinical decision-making and stratification in larger studies (Rosenbaum, 2014). Nevertheless, it does not look at the type, or the topography of the motor impairments. Topographical categorisation systems look at the number of impaired limbs, differentiating between categories of hemiplegic (one side of the body), diplegic (both sides of the body predominantly affecting the legs) and quadri- or tetraplegic (all four limbs equally) involvement. Classifications by motor function look at the specific type of muscular dysfunction which is usually constituted of: i) spasticity, ii) dyskinesia or iii) ataxia.

A recent categorisation system that includes both topographic and motor function categories has been proposed by Cans (2000) in order to establish a common classification system for comprehensive research across Europe, referred to as the Surveillance of CP in

Europe. The authors also developed a decision tree that allows for the categorisation of individuals in an iterative manner (see Fig. 3.3).

Fig. 3.3 Decision tree for the classification of cerebral palsy (reprinted from “Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Surveillance of Cerebral Palsy in Europe (SCPE)” by Cans, 2000)

Spasticity, Dyskinesia and Ataxia

Spasticity is the most frequent motor impairment in CP. It is usually observed in over 70% of the patients with slightly higher incidences of bilateral impairments such as di- and quadriplegia, as opposed to unilateral impairments or hemiplegia (G. L. Andersen et al., 2008; Arnfield et al., 2013). In the Surveillance of CP in Europe, spasticity should be diagnosed in the presence of an increased muscle tone and pathological reflexes (Cans, 2000). Physiologically however, the key feature of spasticity has been identified as a velocity-dependent increase in muscle tone, i.e. a pathological stretch reflex (Forssberg, 2014; Lance, 1990) which provides a clearer differentiation from dystonic dyskinesia characterised by an involuntary increase in muscle stiffness. There are multiple possibilities that contribute to an increased stretch reflex and hence a spastic movement behaviour. Spasticity stems from a hyperexcitability of both the α- and the γ-motoneurons and this can be attributed to a variety of reasons (Nielsen, Crone, & Hultborn, 2007). Despite their hyperexcitability however, the strength of the muscles is often reduced in the case of CP. In the long term, the combination of spasticity and muscle weakness leads to musculoskeletal deformities, such as a shortening of the muscle tendon unit or scoliosis (Graham & Selber, 2003).

The non-spastic subtypes of CP, i.e. dyskinesia and ataxia are observed in considerably smaller proportions of the entire population, as opposed to the spastic ones. In Denmark for example, the incidence of dyskinesia has been reported in approximately 6% of the studied cases and is only marginally higher than that of ataxia (5%) in CP (G. L. Andersen et al., 2008).

Dyskinesia by definition is characterised by involuntary recurring and sometimes stereotyped movement patterns that can either lead to i) dystonia and decreased movement activity or ii) choreoathetotic movement behaviour with decreased muscle tone but increased movement activity (Cans, 2000). Dyskinetic (or mixed spastic-dyskinetic) subtypes are mainly observed in individuals with lesions that affect the basal ganglia and thalamus regions (Krägeloh-Mann et al., 2002).

Ataxia is characterised by a loss of muscular coordination that results in abnormal force, rhythm and accuracy in movements (Cans, 2000). Force, rhythm and accuracy are particularly dependent on the correct integration of the afferent sensory information into the efferent motor commands, a process in which the cerebellum is largely involved. Disorders of the cerebellum can thus result in so-called cerebellar ataxia (Manto et al., 2012). Hence, children with CP that also present cerebellar injuries often display clinical signs of ataxia (Bodensteiner & Johnsen, 2005).

3.2.3 **Relation between Brain Lesions and Motor Impairment**

The non-spastic subtypes in particular seemed to be clearly related to damage in certain areas of the CNS, i.e. dyskinesia to lesions in the basal ganglia and ataxia to lesions in the cerebellum. In order to establish the correlation between the different types of pathogeneses and the specific motor impairment, Arnfield, Guzzetta & Boyd (2013) performed a meta-analysis of studies that reported pathological findings on MRI and motor impairments. Interestingly, they did not find a clear connection between the specific pathway of the neurodisability (i.e. malformations, white or grey matter lesions) and the type of motor impairment. The subtype distribution was found to be similar in all categories, except for white matter lesions which included a higher number of non-spastic subtypes. The authors did however not differentiate between dyskinetic or ataxic manifestations. It is likely that this group is mainly constituted by dyskinetic subtypes since the basal ganglia are prone to be affected in white matter lesions. Similarly to the ambiguities in type, the relation between the neuropathological pathways and the severity of motor impairments on the GMFCS was not well defined. There was however a higher incidence of more severely affected individuals associated with malformations and grey matter lesions, as opposed to white matter lesions.

3.2.4 **Sensory Functional Impairments**

Sensory and motor areas are closely connected in the CNS, both regionally and functionally. In addition to their motor impairments, children with CP often present impairments of the sensory function, which in itself has negative effects on the motor function.

Somatic Sensory System

The somatic sensory system processes information derived from the peripheral nervous receptors, such as tactile (i.e. subcutaneous receptors of touch, pain, temperature and pressure) or proprioceptive information (i.e. receptors of muscle mechanics such as muscle spindles or Golgi tendon organs). Impairments within this system can lead to kinaesthetic disturbances. Compared to their healthy peers, children with CP may experience impairments processing proprioceptive information (e.g. detecting joint angles or movement) particularly in the absence of visual feedback (Klingels et al., 2012; Wingert, Burton, Sinclair, Brunstrom, & Damiano, 2009), which is why visual feedback is often more necessary for adequate movements. Furthermore, tactile sensing can be reduced, or for example expressed by reduced two-point discrimination or stereognosis (e.g. object recognition). This seems to have implications, particularly for isometric movements in which the force needs to be adjusted, i.e. gripping and lifting of an object (Smits-Engelsman, Klingels, & Feys, 2011).

Visual System

Lesions of the visual pathways are an additional cause of sensory dysfunction commonly encountered in CP. The disorders that are synthesised under the term visual-perceptual impairments are various and involve for example oculomotor coordination or visual acuity. According to Ego et al. (2015), a reduced visual function can be observed in 40% to 50% of children with CP. The authors did not find a relation between the subtypes of CP and visual impairments; they did however find higher incidences with an increasing severity of the lesions. This is a worrying fact since visual feedback is often essential for motor control due to the decreased somatic sensory capacity as outlined above.

3.2.5 **Accompanying Impairments**

Motor and sensory impairments are the main challenges in CP. However a variety of accompanying impairments may also occur, which can constitute additional challenges for the affected children. Problems with speech and language, such as aphasia or disturbances of the oromotor function and also hearing loss may lead to problems in communication or nutritional intake. Children with CP also often present lower cognitive abilities, such as IQ, or executive functions compared to their peers, which are often exacerbating with the increasing level of impairments on the GMFCS (Sigurdardottir et al., 2008). About one third of all individuals with CP (slightly higher in the case of tetraplegic CP) develop epilepsy over the course of their childhood (Carlsson, Hagberg, & Olsson, 2007). Attention deficit hyperactivity disorders or autism (higher incidence in non-spastic CP) are not uncommon diagnoses (Christensen et al., 2014).[8]

3.3 Upper Limb Functionality

3.3.1 Manual Ability Classification

The capability to appropriately use the upper limbs is a crucial factor facilitating the participation in daily activities. The upper limb function is often severely impaired in children with uCP and thus requires special focus. The extent of the impairment can however vary greatly between individuals and also between the limbs of a single individual. Following the publication of the GMFCS, Eliasson et al. (2006) developed the manual ability classification system (MACS), an evaluation scale from I (i.e. child is able to handle objects easily and successfully) to V (i.e. child does not handle objects and has a severely limited ability to perform even simple tasks) that defines the child's ability to use his hands in tasks of daily life. Children with uCP tend to have impairments of a maximum level of III in the MACS (i.e. child handles objects with difficulty and needs help to prepare and or modify activities).

The scale does not directly reflect the capacity of a single limb, but rather the functionality of both limbs in manual tasks. Consequently, children with unilateral involvement often score higher (i.e. spastic hemiplegic individuals are categorised mainly between levels I-III) than children with bilateral involvement (i.e. tetra/quadriplegia or dyskinetic CP commonly present at levels IV and V). Even though the focus of the two classification systems, gross motor function and manual ability is different, the two scores show a relatively high agreement in the same individuals (Eliasson et al., 2006).

3.3.2 Unilateral Lesions and Consequences for Bimanual Movements

The predominantly unilateral nature of impairments in children with hemiplegia implies that one side of the body is not affected (or is significantly less affected) than the other. Due to the early occurrence, children develop handedness on the less-affected side. Activity limitations are thus usually not related to unimanual tasks, as they can be executed with the better functioning hand (as in typical developing peers). Severe activity limitations can be observed however when tasks require the coordinated use of both hands at the

[8] Cerebral Palsy: Science and Clinical Practice (Dan, Mayston, Paneth, & Rosenbloom, 2014) provides a thorough overview of accompanying impairments and their management in the last section of the book

same time, i.e. bimanual activities, which form the basis of many if not most daily activities (Hermansson, Sköld, & Eliasson, 2013; Sköld et al., 2004).

Frequency of Hand Use & Developmental Disregard

Children with uCP often avoid the use of their AH due to its poor functionality. As a consequence, bimanual activities are often not executed at all or strategies are sought to perform those tasks by only using the LAH, or sometimes with the assistance of teeth or legs or environmental surfaces (Sköld et al., 2004). Even though the AH may involve some capacity which makes it usable in an assisting fashion (Krumlinde-Sundholm & Eliasson, 2003; Krumlinde-Sundholm, Holmefur, Kottorp, & Eliasson, 2007), the use of both hands at the same time seems to entail additional difficulties.

Similarly to the learned non-use seen in stroke patients (Taub, Uswatte, Mark, & Morris, 2006) children with uCP often show an habituated non-use of the AH. In the case of CP this is referred to as developmental disregard (DD) (Houwink et al., 2011). Children that present DD show a substantial difference between their actual performance (use of the AH during bimanual tasks in which the use of two hands is **not** essential) and capacity (use of the AH during bimanual tasks in which the use of two hands is essential) (Aarts et al., 2007; Houwink, Geerdink, Steenbergen, Geurts, & Aarts, 2013).

Impaired Bimanual Cooperation

Kinematic and kinetic measurements of movement have been used in order to look at the actual parameters of bimanual coordination. Considering the spatiotemporal aspects of the hands during a bimanual task for example, children with uCP show a more segmented pattern (i.e. one hand finishes its subtask before the other hand starts) when performing a bimanual task than in the case of TDC, who are able to perform overlapping movement patterns (Hung, Charles, & Gordon, 2004, 2010). Appropriate bimanual training has been shown to improve movement overlaps in many children with uCP (Hung, Casertano, Hillman, & Gordon, 2011).

Bimanual Interference/Mirror Movements

Apart from the lack of cooperation, children with uCP may also show an increase in interference between limbs. During the repetitive force production in one hand for example, MMs i.e. involuntary simultaneous activation of the contralateral hand, can be observed in individuals with uCP (Kuhtz-Buschbeck, Sundholm, Eliasson, & Forssberg, 2000), particularly in the LAH. Similarly, when executed at the same time, the kinematics of movement patterns (reaching and grasping) show a high similarity, which is not the case for a separate execution (Utley & Sugden, 1998). Interestingly, it is usually the LAH that seems to correlate its movement pattern with the AH. Children that display MMs seem to experience greater problems when performing bimanual movement tasks than children without MMs with similar levels of impairment of the AH (Adler, Berweck, Lidzba, Becher, & Staudt, 2015; Rudisch et al., 2016).

3.4 Therapeutic Treatment to Improve the (Bimanual) Hand Function

The therapeutic treatment of CP can be applied on many levels. Novak et al. (2013) performed a systematic review in order to identify the most appropriate therapeutic interventions for each level of the International Classification of Functioning, Disability and Health (ICF) Framework (World Health Organization, 2001). The ICF differentiates between the levels of i) Body Structures and Function; ii) Activity; iii) Participation; iv) Environmental Factors and v) Personal Factors. It was found that most interventions to date have been related to the levels of “Body Structures and Function” as well as “Activity”, with fewer being related to “Participation”. Interventions that showed solid evidence of their effectiveness are the injections with the botulinum toxin (for spasticity management) with additional therapy, casting (for the management of contractures), as well as constraint-induced movement therapy (CIMT) and bimanual training (both for the improvement of motor activities).

3.4.1 Treatment of the Body Function

Spasticity, caused by a hyperexcitability of the lower α-, and/or γ-motoneurons (Nielsen et al., 2007) is the most common motor impairment in CP. The botulinum toxin describes a group of neurotoxins that can inhibit the release of acetylcholine at the synapses. If injected in a muscle it can thus focally decrease the excitability thereof. Important for the success of botulinum toxin injections are especially the treatments that are being administered with it. The constantly increased tone of some muscles in spastic CP often leads to a limitation or failure of muscle growth during development. Simple stretching of the affected muscles would not be effected since the pathological stretch reflex would only result in an increased muscle tension. The botulinum toxin can disrupt this mechanism and facilitate the stretching of the relaxed muscles leading to their elongation (for Review, see Pavone et al., 2016).

The long term consequences of constant spasticity and the associated flexed position can lead to contractures and deformities of the joints. Serial casting is a technique that fixates the affected limbs in a slightly extended position. A gradual increase of the extension over time should increase the joint range of motion. In addition, it has been hypothesised that serial casting decreases spasticity due to an increased muscle length. Despite the sound rationale of this method there is relatively little evidence suggesting that the casting of the upper limbs leads to (long term) improvements in the hand function (Lannin, Novak, & Cusick, 2007).

3.4.2 **Treatment at Activity Levels**

Originally developed for patients with stroke or traumatic brain injury, CIMT has been adapted for the recovery of the function of the AH in children with uCP (Taub, Ramey, DeLuca, & Echols, 2004). The basic idea of the CIMT programmes is the forced use of the AH during therapy by constraining the use of the LAH by means of slings, splints or casts. Additionally, patients have to perform functional therapeutic movement tasks with their AH. For Taub et al. (2006) the idea of forced use should impose a sufficient amount of practice on the patients in order for them to overcome their learned non-use and to start using their AH in activities even after removing the constraining device at the end of the therapy.

Charles and Gordon (2006) however saw several conceptual problems in the application of the CIMT in children with uCP. Since this specific group (other than adults with hemiplegia following stroke or traumatic brain injuries) never actually learned to use their AH in bimanual activities, the focus of the therapy should not be to overcome the learned non-use but to actually train the children to use their AH in bimanual tasks. They developed the Hand-Arm Bimanual Intensive Therapy (HABIT) approach in order to facilitate the forced use of the AH during two-handed tasks. Interestingly however, in randomised controlled comparisons both the CIMT and the HABIT showed similar outcomes on standardised assessments, i.e. the Jebsen Taylor Test of Hand Function (JTTHF) and the Assisting Hand Assessment (AHA) (Gordon et al., 2011). Looking at the actual spatiotemporal bimanual cooperation however, the HABIT (in contrast to the CIMT) has been shown to improve the movement overlap between hands (Hung et al., 2011).

Following the initial ideas, several modified forms of the HABIT and CIMT therapies have been developed, such as mixed forms to combine the advantageous effects of both programmes (Aarts et al., 2012; Boyd et al., 2013) or themed approaches that increase motivation and thus adherence (Green et al., 2013). Essential questions about intensity and dosage however have not yet been answered and should be addressed in future research (Eliasson et al., 2013). In addition, it is not known whether these types of therapy are recommended for all individuals with uCP or if there are specific subtypes in which adverse effects can be triggered.

3.5 Summary and Reconciliation

The aetiological and pathogenetical diversity in congenital and early childhood motor impairments is vast. Different genetic, physiological or idiopathic factors can be causal for a variety of brain lesions that can be categorised as malformations, white and grey matter lesions. Different categories of motor impairments have been identified, such as the spastic, dystonic and ataxic subtypes. Their relation with the various types of brain impairments is however less than well-established.

About one third of the individuals diagnosed with CP present predominantly unilateral motor impairments. Regarding the upper limb function, movements that require the coordinated use of both hands seem to be the biggest challenge for children with uCP. Movement patterns often display a lack of spatiotemporal cooperation or excessive interference. The treatment of activities using motor learning-based approaches such as CIMT or HABIT has been shown to be promising. Research so far has however not been addressing essential questions such as the appropriate dosage and intensities of therapies or individual differences in response. The following chapter will focus on ways to measure the quality of bimanual coordination as an essential prerequisite for monitoring changes in performance. In addition, the development of an experimental paradigm to measure hand kinematics during the disparate bimanual box-opening task will be described.

4 Measuring (Bi-) Manual Function

Many therapeutic programs are designed explicitly to improve bimanual coordination skills in children with CP (Charles & Gordon, 2006; Gordon et al., 2011; Green et al., 2013), thus the measurement of therapy outcomes is of utmost importance in order to evaluate the success of these programs. In the following section measurements of upper limb functionality from different scientific areas are reviewed and the necessity of a method for the assessment of the spatiotemporal coordination of bimanual movement is highlighted. In this chapter, the development of a measurement system to quantitatively investigate bimanual coordination by means of a functional box-opening task and a 3-dimensional motion analysis is outlined. The established measurements of upper limb functionality and coordination are being presented in the first part, followed by some theoretical considerations, as well as mathematical and technical descriptions of the development of the new system. In the last part of this chapter, the experimental evaluation of the new system is discussed.

4.1 Standardised Measures of Upper Limb Functionality

An examination of the scientific literature in the field of upper limb rehabilitation among children with uCP presents a large variety of different behavioural assessments for the measurement of upper limb function that are used extensively in research and clinical settings. However, only few of them have undergone psychometric evaluation (Gilmore, Sakzewski, & Boyd, 2010). In the following part, a brief overview of the most common measures is presented.

4.1.1 Unimanual Measures

A number of different measures can be found in order to assess the upper limb function, but which predominantly do so in a unimanual manner, i.e. by administering tasks that evaluate each limb separately. The focus of measurements varies from the observation of basic physiological patterns, such as reflexes or dissociated movements, up to fairly targeted and functional tasks, such as turning cards or handwriting.

The Quality of Upper Extremity Skills Test (Dematteo & Pollock, 1992) measures hand function on 4 different domains: i) dissociated movement/range of motion, ii) grasp, iii) weight bearing and iv) protective extension. Due to the differences between domains, the test has also been shown to measure more than one dimension (Thorley, Lannin, Cusick, Novak, & Boyd, 2012) hence the scores associated to each domain should be regarded separately.

The Melbourne Assessment of Upper Limb Function (Randall, Carlin, Chondros, & Reddihough, 2001), another measure of unimanual hand function consists of 16 items that reflect very general functional tasks such as reaching, grasping of different objects, pointing etc. The instrument shows high internal consistency supporting the assumption of one measured dimension (Randall et al., 2001). A more recent inspection using the Rasch model refutes the assumption of uni-dimensionality and suggests modifications for better test results (Randall, Imms, Carey, & Pallant, 2014).

The Box and Block test was initially designed to assess individuals with physical disabilites, but not explicitly children with CP, despite occasionally being used for this purpose (e.g. Holmström et al., 2010). The test consists of transferring as many small wooden cubes (2.5 cm) as possible from one box into another in 60 seconds. Setup and administration is therefore very easy and takes less than 5 minutes. Normative scores for the Box and Block test are available from 3 to 75+ years of age (Jongbloed-Pereboom, Nijhuis-Van Der Sanden, & Steenbergen, 2013; V. Mathiowetz, Volland, Kashman, & Weber, 1985; Virgil Mathiowetz, Federman, & Wiemer, 1985).

A commonly used tool to assess hand function in children with CP is the JTTHF (Jebsen, Taylor, Trieschmann, Trotter, & Howard, 1969; Taylor, Sand, & Jebsen, 1973). The JTTHF is an assessment that measures the time required to perform movement tasks that necessitate a certain amount of dexterity. The items include for example, turning over cards and scooping up beans. Even though the JTTHF is frequently used in clinical trials in children with uCP[9] (Gordon et al., 2011; Islam et al., 2014), evidence regarding its psychometric properties within this group is sparse (Gilmore et al., 2010).

[9] The JTTHF is one of the most frequently used outcome measure in studies (as well as in clinical settings) used to assess the (uni-) manual function in children with uCP (Dong, Tung, Siu, & Fong, 2013; Sakzewski, Ziviani, & Boyd, 2014) and it is used for the same purpose within the context of this study.

4.1.2 Bimanual Measures

In addition to the measures pertaining to the manual function in unimanual tasks, several instruments designed to assess the functionality of the AH during bimanual tasks have been developed.

The ABILHAND-Kids is a 21-item parent-rated questionnaire that evaluates the child's ability to perform daily activities, such as buttoning up trousers or opening a bread box (Arnould, Penta, Renders, & Thonnard, 2004). The items are answered on a 3-point Likert scale ranging from 0 (impossible to perform) to 2 (easy to perform). Some of the items can be achieved unimanually but most require the involvement of both hands. A Rasch Analysis of the questionnaire revealed an increase in item difficulty with the increasing importance of the involvement of both hands (Arnould et al., 2004).

The Children's Hand-Use Experience Questionnaire (CHEQ) is a self- or proxy- (parent or carer) rated questionnaire including 29 items that assess the use of the AH during bimanual tasks (Sköld, Hermansson, Krumlinde-Sundholm, & Eliasson, 2011). The items are Rasch scaled and range from easy such as "pulling up track suit trousers" to difficult such as "fastening a necklace whilst around the neck" (Sköld et al., 2011, p. 439). Upon providing the answers for each item it is evaluated: 1) whether the item can be performed independently; 2) whether the item is performed a) with one hand, b) with two hands and the AH has a holding/stabilising role or c) with two hands and the AH has a supporting role (only if question 1 is answered with "yes"); 3-5) how effective the grasp/support of the second hand is compared to their peers, how much extra time it takes and how bothering it is (only if question 2 is answered with b) or c)). Further psychometric properties of the CHEQ are yet to be established. In fact only one study has been identified that investigates the test-retest reliability of the CHEQ in children with uCP with ICC's ranging from 0.88 to 0.91 for the outcomes efficacy of grasp, time taken and feeling bothered (Amer, Eliasson, Peny-Dahlstrand, & Hermansson, 2016).

The pattern of hand use in childhood hemiplegia makes it particularly difficult to study the bimanual coordination in daily tasks, as children frequently avoid using their AH and try to accomplish tasks by using their better hand exclusively. The AHA (Krumlinde-Sundholm & Eliasson, 2003; Krumlinde-Sundholm et al., 2007) was conceptualised in order to gain information about the usage quality of the AH in hemiplegic children (8 months to 12 years). The Rasch-built measure consists of 22 items which are rated upon observing the child's usage of its impaired hand while playing with specific toys, but does not measure the bimanual functionality. The items range from very easy (touching or holding of objects) to difficult (adjustment or manipulation of objects). As shown by the Rasch Analysis, the AHA measures a uni-dimensional latent trait (Holmefur, Krumlinde-Sundholm, & Eliasson, 2007; Krumlinde-Sundholm & Eliasson, 2003; Krumlinde-Sundholm et al., 2007). Both the interrater reliability (ICC=0.98) (Holmefur, Aarts, Hoare, & Krumlinde-Sundholm, 2009) and the test-retest reliability (ICC=0.99) are considered to be excellent.

A recently published comparison of the AHA and the CHEQ indicated rather low levels of agreement between the two (R^2=0.25 between the AHA and CHEQ grasp efficiency; R^2=0.18 between the AHA and CHEQ time taken) suggesting that they measure somewhat different domains (Ryll, Bastiaenen, & Eliasson, 2016).

4.1.3 **Summary**

The overview of the measurement tools reflects the variety of different measures and their qualitative differences that are commonly used in the assessment of the upper limb function in children with CP. Although the different measures often test similar dimensions (hence the outcome variables of these tests are mostly correlated to a certain extent) their objective is different, with a focus on either body structure/impairment or activity performance. The former is more common in unimanual measures whereas the latter is commonly associated to bimanual measures. The type of test should be selected in conformity with the research question. With regard to current investigations, none of these measures seem to be appropriate for the investigation of bimanual coordination (collaborative interaction of the two hands) and motor learning-related changes in performance from a dynamical systems theory point of view (Liu et al., 2003; Schöner et al., 1992).

4.2 Measuring Kinematics of Discrete Bimanual Movement in Children with Unilateral Cerebral Palsy

Standardised measures of uni- or bimanual function can provide valuable information about the level of functional impairment or frequency of use of the AH. They do however offer very little insight into the quality of the movement itself (although the frequency of use and functional impairment are certainly heavily influenced by the capacity and quality of the movement). In order to investigate bimanual coordination on the basis of motor control and learning theories (such as the dynamical systems theory), it appears to be more appropriate to describe the quality of the movement by observing temporal and spatial aspects of simple experimental tasks (Schöner et al., 1992). A few experiments have been designed to establish such quantitative parameters of upper limb coordination in children with uCP using measures of movement kinematics and kinetics.

4.2.1 **Coupling during Synchronous Bimanual Movements**

The problem of bimanual coupling during synchronous reaching movements has been studied in the case of spastic hemiparesis among children, for example by Utley and Sugden (1998) or Steenbergen et al. (1996). Velocity profiles during several tasks, involving reaching, touching and grasping were explored under uni- and bimanual conditions. The data showed significant differences in the velocity profiles between hands under unimanual conditions, with slower more jerky movements on the affected side (see Fig. 4.1A). In contrast, the movement patterns identified under bimanual conditions showed increased similarity, with both hands resembling the movement pattern of the AH under the unimanual condition (see Fig. 4.1B).

Fig. 4.1 Velocity profiles of the affected (hemiparetic) and less affected hand during unimanual (A) and bimanual (B) reaching in children with unilateral cerebral palsy (reprinted from "Interlimb coupling in children with hemiplegic cerebral palsy during reaching and grasping at speed" by Utley & Sugden, 1998)

Hung et al. (2004) developed a goal-directed task in which the participants had to open a drawer with one hand and press a switch inside the drawer with the other hand (see Fig. 4.2). The spatial position of a marker on each wrist was traced by means of a 3-dimensional motion analysis. In order to determine the temporal landmarks characteristic of the movement, the tangential velocity of each hand was calculated, and prominent time points (start of movement, highest velocity and end of movement) were extracted.

Fig. 4.2 The drawer task. a) Experimental setup of the drawer task. Subjects are instructed to open the drawer by pulling the handle with one hand and pressing the switch inside the drawer with the other hand. The tangential velocity of each hand is determined by a tracking of the trace of two reflective markers in the 3-dimensional space. b) Graphical representation of the velocity of both hands against time. The events are i) start of movement of the 'drawer hand'; ii) start of movement of the 'switch hand; iii) highest velocity of the 'drawer hand'; iv) highest velocity of the 'switch hand'; v) end of movement of the 'drawer hand'; vi) end of movement of the 'switch hand' (reprinted from "Bimanual coordination during a goal-directed task in children with hemiplegic cerebral palsy" by Hung et al., 2004)

A comparison of the movement patterns among children with uCP and a control group of TDC showed intriguing differences in these sequential patterns. A significant decrease in the movement overlap[10] and an increase in goal synchronisation[11] were found in the group of children with uCP. Within this group, the movement overlap was reduced when the drawer had to be opened with the AH. Interestingly, with the imposition of velocity constraints, i.e. to complete the task as fast as possible instead of in a self-paced manner, the movement overlap increased and the differences to the typical group disappeared. Nevertheless, accuracy constraints, i.e. smaller handle or a smaller switch, seemed to exert little influence on the movement pattern (Hung et al., 2010).

Research has also been undertaken by the same research group in order to compare the effect of the different HABIT and CIMT treatments on the movement pattern (Hung et al., 2011). The results show an exceptionally high increase in the amount of movement overlap from an average of 25% pre-intervention to 64% post-intervention for the HABIT and a very low increase from 26% pre-intervention to 34% post-intervention for the CIMT group, when the LAH is used to open the drawer. Yet no significant changes were found when the AH was the draw-opening hand.

The results indicate that the observed temporal aspects of the bimanual drawer task are highly coherent with the quality of bimanual coordination when comparing children with hemiplegia with age-matched TDC. The measure also has the potential to show changes in bimanual skills due to therapeutic approaches.

4.3 The Bimanual Box-opening Task

A bimanual box-opening task in which participants are required to perform a role differentiated bimanual activity has been used to study hand preference and bimanual development in infants and children (Birtles et al., 2011; Ramsay & Weber, 1986). Instead of a drawer, the task used a Perspex box with a lid which contained a little toy that had to be retrieved from the box. The research team was interested in the developmental aspects of bimanual coordination and explored how infants, children and adults would solve this task. The bimanual box-opening task was chosen and further developed as the main paradigm within the framework of this dissertation in order to study the discrete disparate bimanual coordination in children with uCP. Compared to the drawer task (Hung et al.,

[10] Movement overlap is defined as the amount of time required when both hands move in synchrony, i.e. the timeframe between the time points ii) and v) (expressed as a percentage of the total cycle).

[11] Goal synchronisation refers to the temporal difference of each hand's closure of the movement, i.e. the difference between points v) and vi) (in seconds).

2004) the latter provides the advantage of the developmental norms from infants to adults having already been reported on (Birtles et al., 2011). In addition, the nature of the drawer task (direct chain of extension-flexion movement of the drawer hand) might trigger spasticity in the AH which can confound subsequent trials.

4.3.1 **Technical Aspects**

The Box

The dimensions of the box are depicted in Fig. 4.3. The box is made of transparent Perspex. The hinges, likewise made of plastics, are attached to the box using strong adhesive to prevent the volume increase of metals, which could affect the measurement of the electromagnetic motion tracking system. Differently from the box used in Birtles et al. (2011), the toy inside has been replaced with a big red button, acting as a synchronisation switch which indicates the conclusion of the movement.

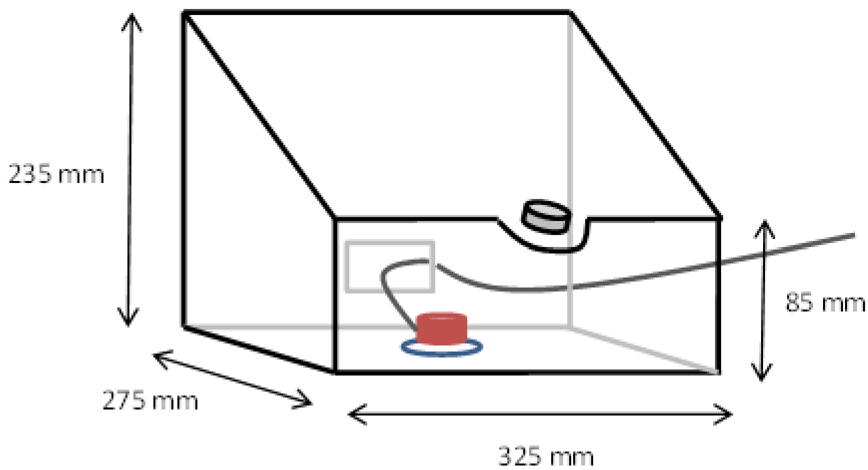


Fig. 4.3 The box and its dimensions. Participants can keep hold of the lip, jutting out, to open the lid. A digital input from the red button inside the box is sampled at a frequency of 120Hz

3D Motion Analysis

The motion tracking device used to determine the spatial position and orientation of the segments of the upper limbs (hand, forearm and upper arm), was the Polhemus G4™ (Polhemus, Colchester, Vermont, USA). The system uses a source in order to produce a 3-dimensional electromagnetic field which constitutes the capture volume. According to the producer's information, the capture volume of a single source measures about 4.9 m in general and 1.8 m for best results. Electromagnetic sensors can detect their position and orientation (within the capture volume produced by the source). The sensors have a size of 2.82*2.29*1.52*cm* and weigh 9.1 grams.

In the field of kinematic motion analyses, electromagnetic tracking devices are rarely used instead of optical systems or inertial sensors. Two particular reasons seem to limit the utility of these devices:

i) Due to the limitations in the size of the capture volume, electromagnetic systems are more suitable to be used for stationary experiments, e.g. focusing on the upper limbs (Biryukova, Roby-Brami, Frolov, & Mokhtari, 2000; Bottlang, Madey, Steyers, Marsh, & Brown, 2000; Meskers, Vermeulen, de Groot, van Der Helm, & Rozing, 1998)

ii) A second major disadvantage of the electromagnetic systems is the magnetic distortion, caused by large metal objects. Depending on the size and shape of the metal objects in the capture volume, magnetic distortion can lead to significant data deviations and should be handled very carefully.

The experimental setup fulfils both requirements for the use of electromagnetic tracking. The capture volume of 1.8m around the source provides more than enough space to perform the measurements. In order to reduce any electromagnetic interference, the measurement space was maintained metal-free [12] and possible sources of eddy currents were avoided. For this reason, the electromagnetic tracking device is an appropriate instrument for the collection of spatiotemporal motion data and for the calculation of the angular rotation (Biryukova et al., 2000) of the wrist and elbow joints. Compared to other available motion tracking systems, such as optical or ultrasonic systems, the electromagnetic allows for the position and orientation of the markers to still be recorded even if these are blocked for example by other parts of the body, confounded by limb distortion (e.g. due to spasticity) or objects. Another advantage of the system is its small size and weight, making it extremely portable for use in field work.

4.3.2 **Experimental Setup & Procedures**

Participants were seated on a height adjustable wooden Tripp Trapp® chair (Stokke AS, Norway). The box and the electromagnetic source were placed on a height adjustable plastic table in front of the participant. The position of the box was 25cm from the edge of the table, secured via a strong adhesive.Height of the table and chair and footplates were adjusted so that participants sat in a comfortable position of 90^0 hip and knee flexion with a right angle (90^0) in their elbows when placing their hands on the starting position on the

[12] The chair and table are made of wood or plastic, resp. All box components are made of Perspex (casing, lid and hinges).

table. After the seating position was adjusted, participants were instructed to place their hands at the starting position. A strip of tape that was attached parallel to and 10cm away from the edge of the table marked the starting position (see Fig. 4.4).

Fig. 4.4 Illustration of the experimental setup showing a participant using his left hand to open the lid and his right hand to press the button. The black line in front of the participant marks the starting point for both hands at the beginning of the trial. Sensors are attached to the back of each hand using Velcro strips. The black cube in the bottom right corner of the picture is the electromagnetic source (reprinted from 'Developmental Characteristics of Disparate Bimanual Movement Skills in Typically Developing Children', by Rudisch, Butler, Izadi, Birtles, & Green, 2017)

Participants were then told to then open the box with one hand and press the button located inside with the opposite hand. The hand that should be used to open the lid was announced prior to the commencement of each trial. Furthermore, the participants were told to perform the task at a self-selected speed that was natural to them.

4.3.3 **Data Recording**

Raw data was recorded using a customised program, written in LabVIEW 2014 (National Instruments, Austin, Texas) (see Fig. 4.5). Position and orientation of each sensor, timing information and the digital input signal of the button was sampled at a frequency of 120Hz. Data recording was started before issuing the start command and was stopped immediately upon completion of the task (i.e. after pressing the button). Files were named with the trial number and stored automatically after each trial. Upon the occurrence of an error (e.g. participant being inattentive and uses hands in the wrong order), the trial was recommenced instantly and the stored trial was overwritten.

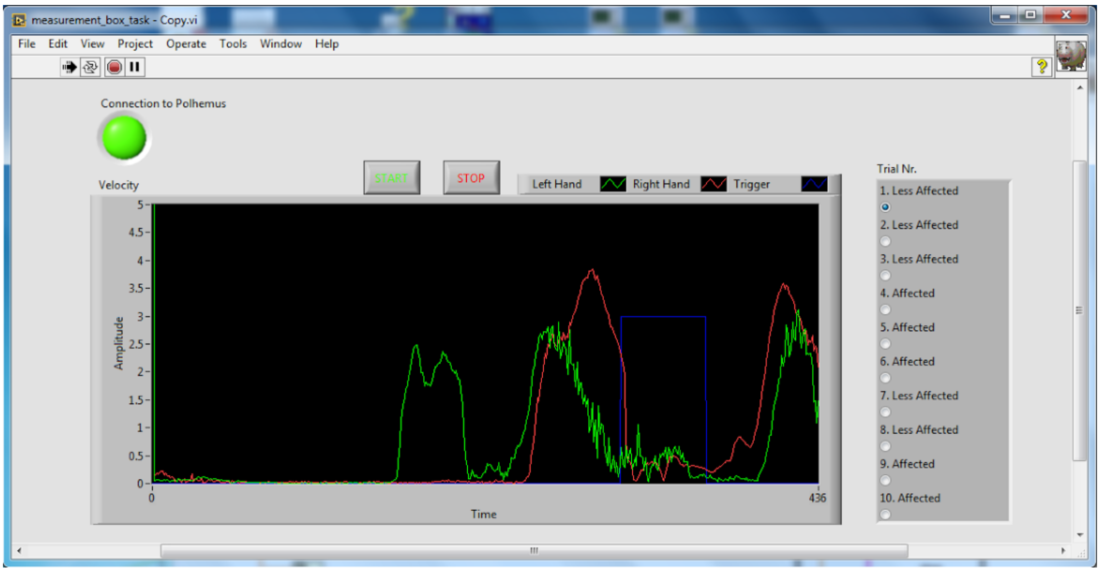


Fig. 4.5 Screenshot of the custom measurement programme, written in LabVIEW. The graphical user interface contains a start and stop button (to begin and end a trial), radio buttons with consecutive trial numbers (1-10) and it

plots the (unfiltered) velocity profiles of the left (green line) and right (red line) sensor as well as the digital signal derived from the button switch (blue line)

4.3.4 **Data Processing and Outcome Variables**

Filtering and Pre-Processing

Primary data processing was performed using a customised script written in MATLAB R2014b (The MathWorks, Natick, MA). Raw data was filtered using a low-pass 2nd order Butterworth filter with a cut-off frequency of 1/15. In order to calculate the velocity of each sensor in m/s, the Euclidean distance between the sensors position at two consecutive measurement points was calculated and multiplied by the measurement frequency of 120Hz

$$v_i = \sqrt{(x_{i+1} - x_i)^2 + (y_{i+1} - y_i)^2 + (z_{i+1} - z_i)^2} * 120$$

Identifying Events

A semi-automated algorithm was used to identify and localise the following events: i) Start of First (Lid-opening) Hand; ii) Start of Lid-opening; iii) End of Lid-opening; iv) Start of Second (Button Press Hand); v) Button Press (see Fig. 4.6).

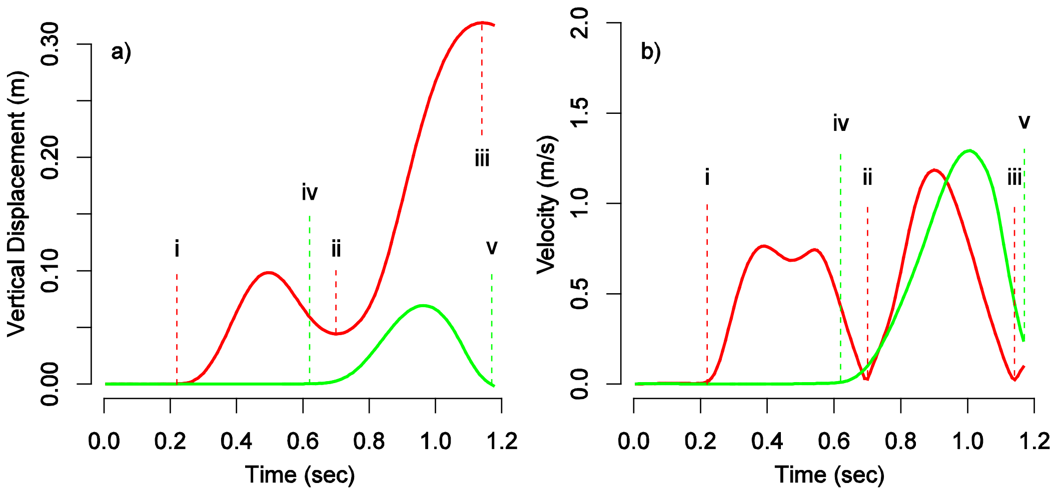


Fig. 4.6 Vertical displacement (a) and velocity profiles (b) of the lid-opening (red line) and button press (green line) of a single trial (individual without motor impairment) plotted against time. See text for description of the events i) – v)

In order to identify the start of movement of each hand (events i and iv) the first data point in which the velocity was greater than 0.1 m/s was searched and then looped back to find the first data point with positive acceleration. The onset of lid-opening (event ii) was identified as the local minimum between the two velocity peaks, the first of which arises from the hand's movement towards the lid and the second from the opening of the lid. The end point of the box-opening was identified when the vertical displacement of the lid-opening hand reached its maximum. A signal from the button indicating the pushed and released state was used in order to identify the button press (event v) directly.

4.3.5 **Outcome Variables**

Three outcome variables were extracted from the data:

a) Total Task Duration (TTD); i.e. the temporal difference between the onset of the first hand movement (event i) and the trigger press (event v) as a measure of movement speed

b) Temporal Coupling (TC); i.e. the temporal difference between the box-opening event (ii) and the onset of the second hand's movement (iv) as a measure of spatiotemporal cooperation (with negative numbers resulting from an initiation of the second hand movement after beginning of the lid opening – late start)

c) Total Path (TP); i.e. the total length of the movement trajectories of the trigger press movement as a measure of movement accuracy

Birtles et al. (2011) as well as Hung et al. (2004) have demonstrated that a faster task execution of the bimanual box-opening task (or the drawer task respectively) is a consequence of increased bimanual coordination (i.e. typical children compared to adults, or children with uCP compared to TDC). In addition, they showed an increase in movement overlap as a consequence of an earlier start of the second hand (i.e. TC). TC is a particularly interesting factor. Guiard (1987) hypothesised that bimanual actions are characterised (similarly to kinematic chains) by one limb providing the (spatial) frame of reference and the other hand adjusting to the movement. The theory can also be expanded on the temporal sequencing during the bimanual box-opening task. The lid-opening action would thus constitute the frame of reference. The timing of the second hand has to be adjusted to the box-opening. Inadequate timing would lead to i) an increase in the movement time as a consequence of a late start or ii) jerky movement behaviour as a consequence of an early start and the necessity to slow down the second hand so as to wait for the box to be sufficiently opened. According to Guiard's (1987) theory the movement of the first hand (the lid-opening subtask) should be similar regardless of whether the task was executed in uni- or bimanual fashion. For the movement of the second hand (subtask button press) bimanual task execution should be differentiated from the unimanual case since (in the bimanual case) adjustments to the frame of reference need to be made.

4.4 Summary and Reconciliation

Children with uCP display limited functionality at the level of one of the upper limbs. This has a particular impact on everyday activities that require the coordinated use of both hands at the same time, i.e. bimanual tasks. A variety of standardised measures have been developed in order to assess the functionality of the AH during uni- or bimanual tasks. Furthermore, measuring movement kinematics has helped unravel specific behavioural characteristics of movement impairments. Based on previous research studies using disparate bimanual movement paradigms, a bimanual box-opening task has been further developed in order to research bimanual skills and motor learning in children with uCP.

The next chapter provides the result of a study in which the performance on the bimanual box-opening task is measured on TDC of different age ranges. Understanding the typical development of bimanual coordination is an important step in evaluating the atypical characteristics of the bimanual skills investigated in the subsequent chapter.

5 The Development of Disparate Bimanual Movement Skills in Typically Developing Children

Relevant Publication for this Chapter

Rudisch J, Butler J, Izadi H, Birtles D and Green D (accepted for publication on 04.12.2016 in Journal of Motor Behaviour). Developmental Characteristics of Disparate Bimanual Movement Skills in Typically Developing Children (see Appendix A-1)

5.1 Introduction

Few studies have been conducted in order to investigate the development of role-differentiated bimanual skills. Generally, very young infants (i.e. neonates) present very symmetric interlimb movement behaviour (e.g. two-handed reaching) (Corbetta & Thelen, 1996), whereas the actual role-differentiated behaviour usually develops after 7 months of age (Kimmerle et al., 2010, 1995). In accordance with Guiard's (1987) theory of the asymmetric division of labour, the non-dominant hand often takes over the holding/stabilising role, whereas the manipulating role is assumed by the dominant hand. In the case of sequenced bimanual movements, adults preferentially use their non-dominant hand for the leading role (initial part of the sequence) and their dominant for the subsequent movement (Birtles et al., 2011; Kazennikov, Perrig, & Wiesendanger, 2002), a pattern that was shown to be negligible in young infants (4-6 years) (Birtles et al., 2011).

The development of structures and connections of the CNS is not finished immediately after birth but continues during childhood. Different structures develop at different rates and peak at different times. After the age of around 6 years the CC, which is involved in the exchange of information between the two hemispheres shows a distinct reduction in growth and myelination (Tanaka-Arakawa et al., 2015; Uda et al., 2015). The frontal lobe, containing the supplementary motor area and premotor cortex (which are important for motor planning, sequencing and cognitive motor control) have been shown to reach peak development at 10 years of age (Gogtay & Thompson, 2010).

The aim of the present study was to investigate age-related performance of role-differentiated bimanual movement skills in TDC in order to identify salient periods of skill development. Age groups were selected to reflect distinct stages in the development of structures related to the execution of bimanual movements. Participants were thus grouped into young children (YC) of 5-6 years and older children (OC) of 7-9 years pre and post the changes in growth and myelination of the CC (Tanaka-Arakawa et al., 2015; Uda et al., 2015), as well as adolescents (AD) of 10-16 years representing a group post the peak development of the prefrontal cortex (Gogtay & Thompson, 2010).

5.2 Methods

5.2.1 Participants

Recruitment and testing was completed during a University open-day event. Children and adolescents who visited the event received an information sheet about the study and signed an informed consent form prior to participation. The research was approved by the Oxford Brookes Research Ethics Committee (Reference 130713, see Appendix B-1).. A total of 37 children participated in this study (see Table 5.1 for group characteristics).

Table 5.1 TDC participants' gender and handedness by age band

Group (n)	Age Band (years)	Gender (m/f)	Handedness (r/l)
YC (15)	5 - 6	7/8	11/4
OC (13)	7 - 9	3/10	11/2
AD (9)	10 - 16	4/5	7/2

TDC=Typically Developing Children, m=male, f=female, r=right (handed), l=left (handed), YC = Young Children, OC = Older Children, AD = Adolescents

5.2.2 Apparatus/ Materials

Bimanual Coordinatino

Hand Kinematics were measured using an electromagnetic 3D motion tracking device Polhemus G4™ (Polhemus, Colchester, Vermont, USA). Bimanual coordination was investigated using the bimanual box-opening task (chapter 4.3.1).

Handedness

Handedness of the children was determined, using the Edinburgh Handedness Inventory (Oldfield, 1971). The ten item scale asks participants for their preferred hand in daily life unimanual tasks, such as holding a toothbrush or knife. For each item, one or two points are given to either the left or right hand depending on how strongly participants feel they were using the respective hand during the task. A laterality quotient: $\frac{R-L}{R+L} * 100$ was calculated with negative scores indicating left- and positive scores indicating right handedness.

5.2.3 Procedures

Handedness was determined prior to the bimanual experiment in order to determine the starting condition of the sequence for the bimanual experiment. Participants then performed the bimanual box-opening task (as shown in 4.3.2) a total of 10 times, 5 times under the dominant hand (DC) and 5 times under the non-dominant hand (NC) leading condition, in the sequence: 3*DC, 3*NC, 2*DC, 2*NC. The variables TTD, TC and TP were extracted as described in section 4.3.

5.2.4 Analysis

Kinematics of hand movement during the bimanual box-opening task were recorded and processed as demonstrated in Chapter 4.3. Statistical analysis of the outcomes was performed using R 3.1.2. Two-way mixed measures Analyses of Variance (ANOVA) were calculated in order to establish whether the participants' age (between factor) or the condition of execution (within factor) had an effect on the box-opening performance variables. Bonferroni corrected post-hoc testing was performed in case of significant results of the ANOVA.

5.3 Results

Exemplary vertical displacement and velocity profiles from participants of the three different age groups are displayed in Fig. 5.1, Fig. 5.2 and Fig. 5.3. Participants for each group were selected by the age being closest to the midpoint of the age range of their respective group.

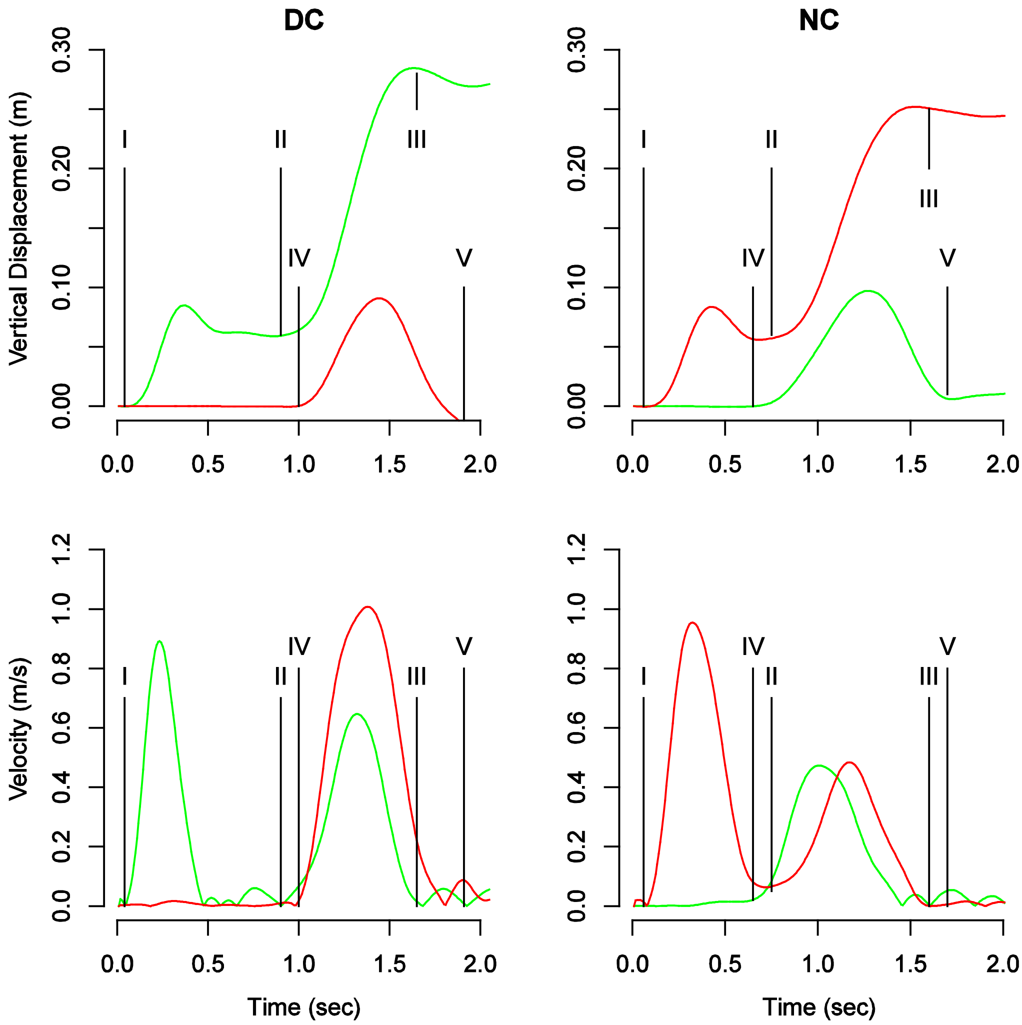


Fig. 5.1 Exemplary vertical displacement and velocity profiles of the hand movement during the bimanual box-opening task of a 69 months old participant (i.e. YC-group). One trial is shown from the dominant hand leading condition (DC) and non-dominant hand leading condition (NC) respectively. Green lines indicate movement of the dominant, red lines of the non-dominant hand. Roman numerals indicate events: I) start of first hand; II) Start of lid opening; III) End of lid opening; IV) Start of second hand and V) Button press

In Fig. 5.1, kinematics profiles of two single trials (in DC and NC) of 69 months old (i.e. YC) right-handed participant are displayed. TTD is greater than 1.5 sec both in DC and NC with hands reaching a maximum velocity of around 1.0 m/s. In both cases, lid-opening and start of the second hand are temporally close together, TC is however negative in DC and positive in NC. Despite the relatively long time it takes the participant to open the lid in DC (i.e. the flat sequence before event II), movement of the second hand is not initiated prior to the opening of the lid.

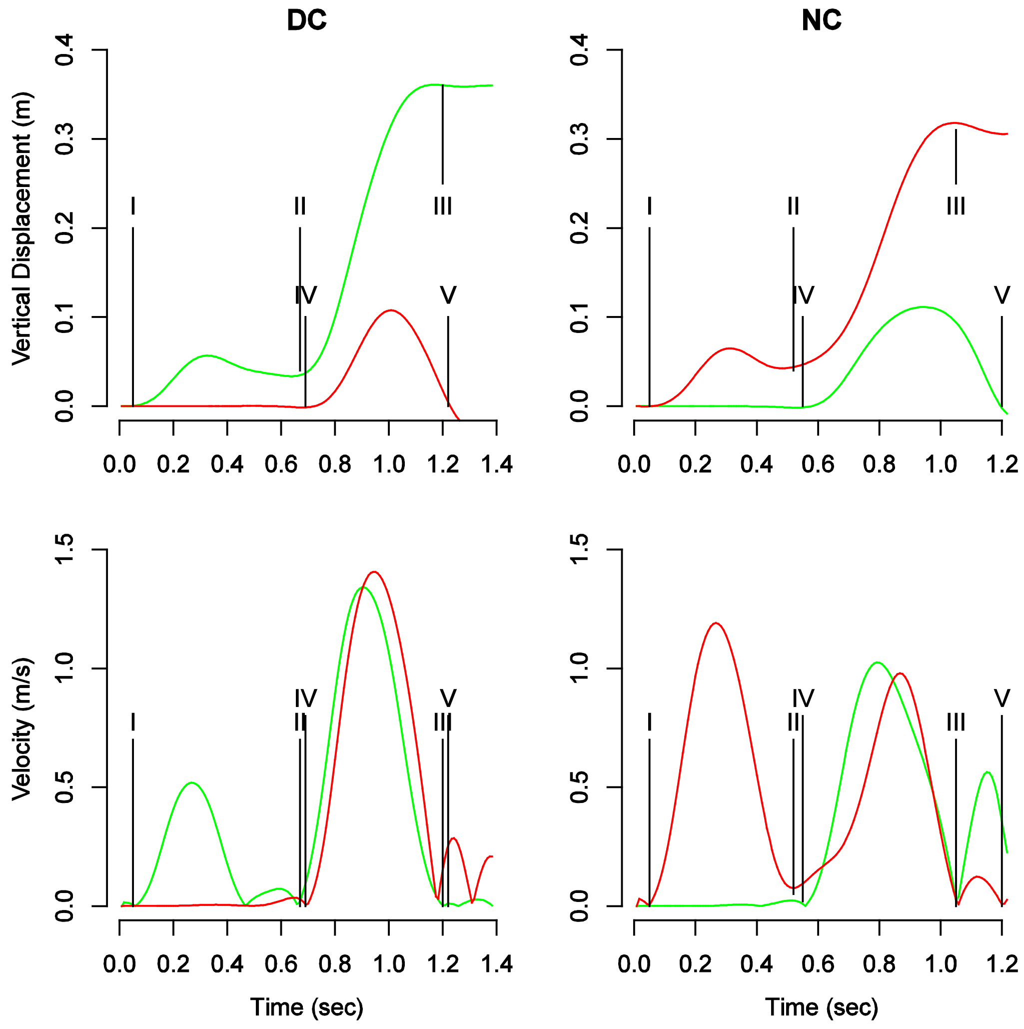


Fig. 5.2 Exemplary vertical displacement and velocity profiles of the hand movement during the bimanual box-opening task of a 102 months old participant (i.e. OC-group). One trial is shown from the dominant hand leading condition (DC) and non-dominant hand leading condition (NC) respectively. Green lines indicate movement of the dominant, red lines of the non-dominant hand. Roman numerals indicate events: I) start of first hand; II) Start of lid opening; III) End of lid opening; IV) Start of second hand and V) Button press

In Fig. 5.2, kinematic profiles of two single trials (in DC and NC) of 102 months old (i.e. OC) right-handed participant are displayed. TTD is around 1.2s in both conditions, maximum velocity is higher (1.5m/s) in DC as compared to NC. Similarly to the 69 months year old participant in Fig. 5.1, the start of the second hand is temporally closely connected to the start of lid opening yet slightly later in both conditions.

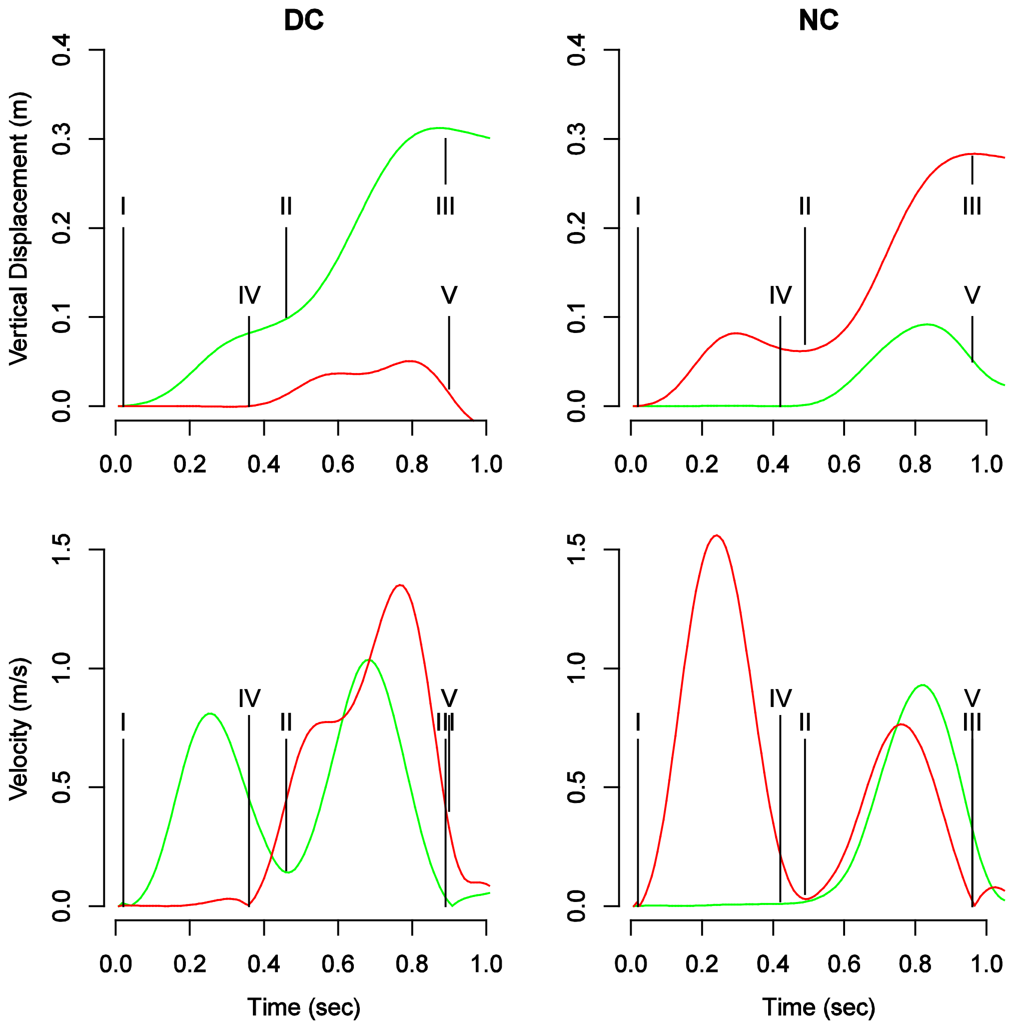


Fig. 5.3 Exemplary vertical displacement and velocity profiles of the hand movement during the bimanual box-opening task of a 147 months old participant (i.e. OC-group). One trial is shown from the dominant hand leading condition (DC) and non-dominant hand leading condition (NC) respectively. Green lines indicate movement of the dominant, red lines of the non-dominant hand. Roman numerals indicate events: I) start of first hand; II) Start of lid opening; III) End of lid opening; IV) Start of second hand and V) Button press

In Fig. 5.3, kinematic profiles of two single trials (in DC and NC) of 147 months old (i.e. AD) right-handed participant are displayed. TTD is faster than 1s in both conditions. The start of the second hand is earlier than the lid opening in both conditions too. The characteristic profiles of the non-dominant hand in DC suggest a short interruption of the acceleration phase due to an early (too early) start of the second hand.

5.3.1 Total Task Duration

On a group level, absolute values of the TTD were significantly affected by the participants' age ($F(2,34)=6.260$, $p=.005$) but not by the condition of execution ($F(1,34)=1.005$, $p=.323$). Post-hoc comparison revealed that TTD was significantly increased in YC as compared to OC (p=.002) and AD (p<.001) (see Fig. 5.4a). Coefficient of variation (CV) of TTD was not shown to be affected by age (F(2,34)=1.865, p=.170). It was however affected by the condition of execution (F(1,34)=10.115, p=.003) with reduced variability in NC (see Fig. 5.4b).

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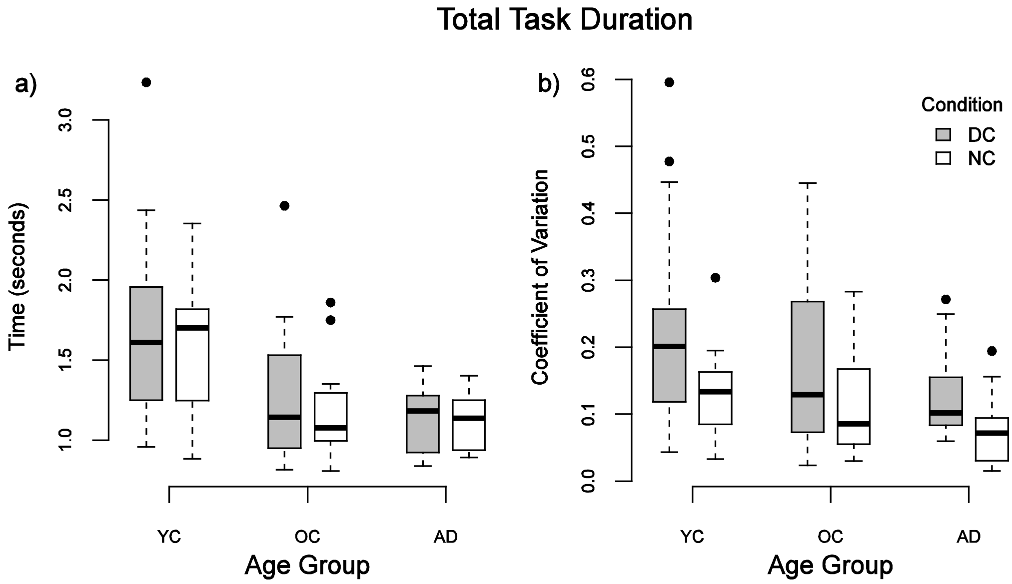

Fig. 5.4 Boxplots showing median, upper and lower quartiles, range and outliers of the absolute values (a) and the coefficient of variation (b) of total task duration for different age groups: young children (YC), old children (OC) and adolescents (AD) and the conditions dominant hand leading (DC) and non-dominant hand leading (NC)

5.3.2 **Temporal Coupling**

Absolute values of TC were neither affected by age (F(2,34)=1.240, p=.302) nor by the condition of execution (F(1,34)=0.603, p=.443) (see Fig. 5.5a).CV of TC was not affected by age either (F(2,34)=0.659, p=.524). Condition of execution did however have an effect on the CV of TC (F(1,34)=6.044, p=.019) with reduced variability in NC (see Fig. 5.5b).

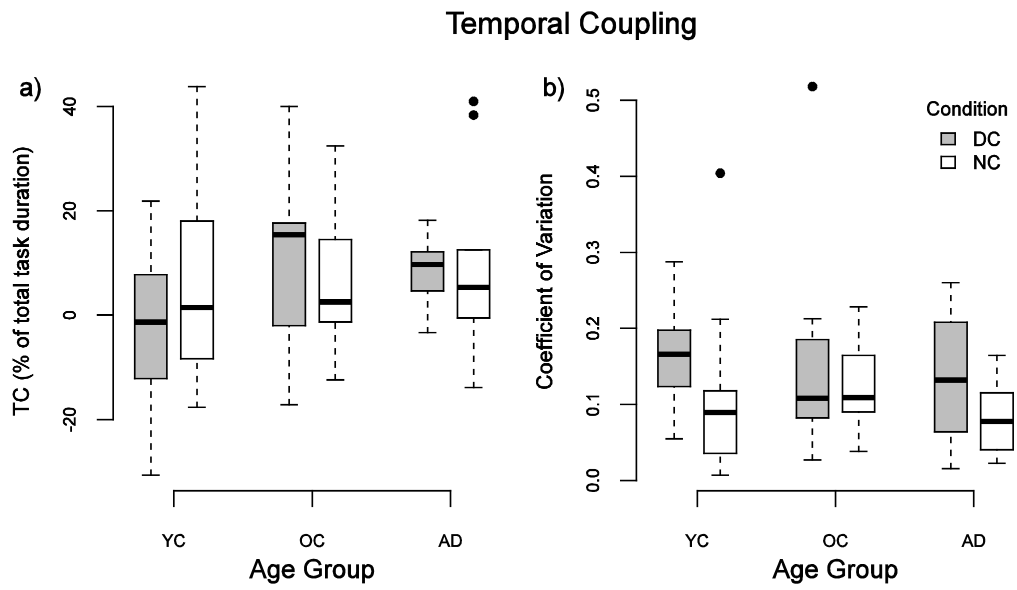

Fig. 5.5 Boxplots showing median, upper and lower quartiles, range and outliers of the absolute values (a) and the coefficient of variation (b) of temporal coupling for different age groups: young children (YC), old children (OC) and adolescents (AD) and the conditions dominant hand leading (DC) and non-dominant hand leading (NC)

5.3.3 **Total Path**

TP of the trigger press task was significantly affected by the participants' age ($F(2,34)=4.282$, $p=.022$). Post-hoc comparison showed a significant reduction of TC between YC and AD ($p=.002$). Values also decreased between YC and OC ($p=.488$) and between OC and AD ($p=.071$), yet both failed to reach significance. Results of the ANOVA did not indicate a significant effect on the condition of execution of the TP ($F(1,34)=1.451$, $p=.905$) (see Fig. 5.6a). In the case of the TP CV, minor effects could be identified on the participants' age ($F(2,34)=2.243$, $p=0.123$) and condition of execution ($F(1,34)=3.503$, $p=.070$) which however both failed to reach significance (see Fig. 5.6b).

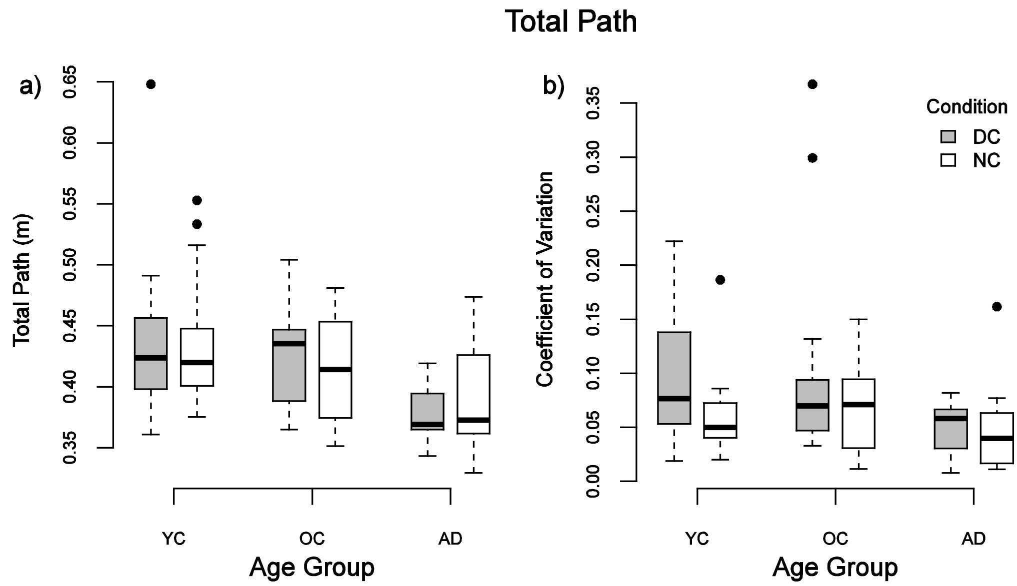

Fig. 5.6 Boxplots showing median, upper and lower quartiles, range and outliers of the absolute values (a) and the coefficient of variation (b) of total path for different age groups: young children (YC), old children (OC) and adolescents (AD) and the conditions dominant hand leading (DC) and non-dominant hand leading (NC)

5.4 Discussion

The study was set out to investigate the developmental characteristics in the ability to perform a disparate bimanual box-opening task that requires the sequencing of both hands. Participants across three different age groups were selected for the purpose of this study. Age groups reflect different development stages at the level of the central nervous structures that are attributed to the execution of bimanual movements.

The task was executed under the two NC and DC conditions. According to Guiard's (1987) theory of the asymmetric division of labour in bimanual tasks, the movement of one hand serves as the frame of reference for the movement of the other hand. For tasks that involve holding and manipulating an object, the frame of reference is usually the movement of the holding hand. For tasks that involve sequenced movements, a temporally earlier movement would naturally serve as the frame of reference.

Developmental studies have shown that the non-dominant hand is preferably used for holding, whereas the dominant hand is used for manipulating within the framework of the role-differentiated bimanual movement task (Kimmerle et al., 2010, 1995). For a sequenced bimanual drawer task, adults have been shown to preferentially use their non-dominant hand for the first part of the sequence (Wiesendanger, Kazennikov, Perrig, & Kaluzny, 1996). Birtles et al. (2011) have shown similar results in adults and reversed or mixed preferences in young children (up to 6 years of age). Interestingly, even though the NC condition is supposed to be preferred (or become preferred with increasing age) no difference in any of the absolute values of the outcome variables could be shown across the age groups. The results do however show significant differences in terms of intra-individual variability. Participants showed more stability in their execution in NC as compared to DC. A decrease in variability can be the result of a higher level of automatisation of the movement pattern due to an increase in practice. Similar sequential movement tasks in daily life are hence likely to be executed with the non-dominant hand leading. Müller and Sternad (2009) have shown that variability of movement in repetitive tasks decreases with practice. In accordance with the uncontrolled manifold concept (Scholz & Schöner, 1999) as well as Bernstein's postulations (Bernstein, 1967), a certain degree of variability is however required even for highly skilled movements.

Significant changes occurring with increasing age could be observed for the TTD and TP variables, but not for TC. Improvements in TTD were mainly made between YC and OC, however not between OC and AD. Furthermore, marginal (yet non-significant) changes occurred in TC between YC and OC. Considering the timing of maturation of the CC (Tanaka-Arakawa et al., 2015; Uda et al., 2015), this would be indicative of the fact that developmental changes in the CC are related to a faster and better sequenced execution of bimanual movements. Robertson (2001) has shown that the stability of interlimb coupling in a continuous cyclical task (similar to the HKB model) strongly decreases after 5 years of age. The crosstalk through the CC seems to be an important factor in the sequencing of movements (Kennerley et al., 2002) which is why developmental changes might become apparent in sequencing variables. Despite the visible trend towards higher values of TC in older and adolescent children (Fig. 5.5), there seems to be an optimum solution which seems to be located at around 5-10% of TTD. A start of the second hand that is too early would be detrimental for the movement fluency (see condition DC in Fig. 5.3 for example). The narrowing of the variance of TC in children of the AD group (Fig. 5.5) suggests a convergence towards this optimum in this group.

The TP of the button press movement on the other hand showed only marginal changes between YC and OC, and a significant improvement between OC and AD. In view of the development of CNS structures, this would rather be related to the maturation of the prefrontal areas (Gogtay & Thompson, 2010). Since the prefrontal cortex plays a major role in movement inhibition, the reduced TP might be attributed to the inhibition of the bimanual interference. De Boer, Peper and Beek (2012) have however shown that the spatial interference between hands decreases from children to adolescents, and even shows further decrease from adolescents to young adults.

5.4.1 **Limitations**

The order of execution of DC and NC was not counterbalanced, which might have influenced the difference detected between the two conditions. The study design was cross-sectional (and not longitudinal) and as a result the intraindividual development variability might have distorted the results. Including measures of brain activity or neuroimaging might have helped explain some of this intraindividual variability.

5.5 Summary and Reconciliation

This first study was set out to investigate changes in the performance of the bimanual box-opening task that may be attributed to age. Three different age groups were contrasted in order to reflect the developmental changes of the CC and the prefrontal cortex, i.e. YC (5-6 years), OC (7-9 years) and AD (10-16 years). It was found that temporal sequencing and movement speed mainly seemed to improve between the YC and OC, indicating a correlation with the development of the CC. TP however rather improved between OC and AD which might be attributed to the inhibition of bimanual interference, resulting in a straighter movement path.

These results are important to i) obtain the numeric results of typical bimanual development in order to compare the results associated with children with impairments and ii) to consider the assumptions about the relation between the different parts of the CNS (i.e. CC and prefrontal cortex) in relation to the bimanual coordination (i.e. temporal sequencing and inhibition of interference). The following chapter of the dissertation investigates the performance of children with uCP when executing the bimanual box-opening task. Chapter 8 then focuses on the case studies involving children with unilateral motor impairments in which the bimanual coordination skills are related to the neuroimaging findings of brain impairments.

6 Disparate Bimanual Movement Skills in Children with Unilateral Cerebral Palsy

Relevant Publication for this Chapter

Rudisch J, Butler J, Izadi H, Zielinski IM, Aarts P, Birtles D and Green D (2016) Kinematic parameters of hand movement during a disparate bimanual movement task in children with unilateral Cerebral Palsy. *Human Movement Science* 46: 239–250. (see Appendix A-2)

6.1 Introduction

As a consequence of their unilateral impairment, children with uCP experience problems in the execution of bimanual movement tasks. Bimanual skills naturally also depend on the unimanual capacity, meaning that people with little capacity in one hand will consequently perform worse in the execution of bimanual tasks, particularly if the task demands for the AH are high. RDBM movement tasks in daily life however often involve disparate actions in which one hand holds or supports and the other hand manipulates an object. Children with uCP usually (if any) use their AH mainly in an assisting fashion in order to hold or stabilise objects (Krumlinde-Sundholm & Eliasson, 2003). The behaviour is thus similar to typical developing individuals where the non-dominant hand usually assumes the assisting roles in bimanual task execution (Kimmerle et al., 2010, 1995). Linking this behaviour to the theory of asymmetric division of labour in bimanual movement tasks (Guiard, 1987), the movement of the less well-controlled AH constitutes the frame of reference. The LAH which exerts better control can adjust its manipulating movement to the AH.

On the basis of the bimanual sequencing in the drawer task, Hung, Charles and Gordon (2004) have interestingly demonstrated that the movement overlap is increased and thus more similar to the pattern identified among typical children when the children with uCP use their LAH as a leading hand. Interestingly, a two-week HABIT program has been shown to increase the movement overlap only when the LAH is leading, as opposed to when the AH is leading (Hung et al., 2011). An increase in the movement overlap is indicative of better temporal sequencing; hence these results would contradict the idea that using the AH as a frame of reference would benefit bimanual sequencing.

Although Hung, Charles and Gordon (2004), as well as Hung et al. (2011), explored performance of children with uCP with reference to the completion of a bimanual task (drawer opening), the relationship, the performance and the functional skills or levels of manual impairment have not been investigated. The present study was thus set out to investigate the impact of different levels of impairment, as well as the results of the standardised measure of uni- and bimanual performance in relation to the performance on the bimanual box-opening task in children with uCP.

6.2 Methods

6.2.1 Participants

As part of this study, data from 37 children with uCP, performing the bimanual box-opening task was collected. The children were participating in different intensive therapy interventions with duration of either two weeks in London or Cardiff in the United Kingdom (UK), or one week in Nijmegen or Enschede in the Netherlands (NL). Ethical approval for this and the subsequent studies including the same group was granted by the National Research Ethics Committee in the UK (Reference 10/H0804/40 – see Appendix B-2) and Research Ethics Coimmitte of Sint Maartenskliniek in the NL (Reference 2014/12/011B/MV/eb – see Appendix B-3). Participant characteristics are presented in Table 6.1.

Table 6.1 Children with uCP participant group characteristics

	N	Gender (m/f)	Age (years)	MACS (I/II/III)
Nijmegen	13	7/6	10.9 +/- 1.7	7/5/1
Enschede	11	4/7	13.1 +/- 2.6	1/9/1
London	8	6/2	8.2 +/- 1.6	3/3/2
Cardiff	5	3/2	9.6 +/- 1.5	2/2/1
Total	37	20/17	10.9 +/- 2.6	13/19/5

uCP = Unilateral Cerebral Palsy, m=male, f=female, MACS= Manual Ability Classification System

6.2.2 Apparatus/ Materials

Bimanual Coordination

Hand Kinematics were measured using an electromagnetic 3D motion tracking device Polhemus G4™ (Polhemus, Colchester, Vermont, USA). Bimanual coordination was investigated using the bimanual box-opening task (chapter 4.3.1).

Standardized Assessments

In order to compare the bimanual performance to the functional capacity, the participants' function was measured on the following clinical assessments:

i) The JTTHF (Jebsen et al., 1969; Taylor et al., 1973) as a measure of unimanual function of the AH and LAH separately. Participants had to perform 6 different tasks requiring manual skills such as scooping beans or stacking checkers (a hand-writing task was excluded due to difficulty in scoring). Tasks were timed and a maximum of 180s was given per task (yielding a total possible score of 1080s). Faster execution of the items is considered higher skills (see also chapter 4.1.1).

ii) The CHEQ (Sköld et al., 2011) as a measure of the quality of use of the AH in the bimanual tasks of daily life (see also chapter 4.1.2). Participants answer (self or parent rated) a 29 item questionnaire asking how children involve their affected hand in bimanual tasks of daily life (e.g. buttoning up a shirt). Answering procedure involves stating if the task can be performed independently. If this was answered with yes, if it is solved with a) 1 hand, b) 2 hands with stabilizing support of the AH or c), 2 hands with grasping support of the AH. In case 2 hands are used, it is furthermore asked on a 4-point Likert scale how effective, quick and bothersome the use of the AH was compared to their peers. Four different outcomes were extracted from the measure: CHEQ R1 as a ratio score of all tasks performed with two hands in relation to all independent tasks; CHEQ R2 as a ration of all tasks in which the AH is used to actively grasp in relation to all tasks in which the AH is involved; CHEQ E. as the average score effectiveness of the AH (higher scores mean more effective) and CHEQ T. as the average score of how quick the movement was (higher scores mean quicker movements).

iii) The AHA (Krumlinde-Sundholm & Eliasson, 2003) as the current clinical gold standard of functionality of the AH in bimanual tasks in children with uCP (section 4.1.2).The AHA, tests the frequency of spontaneous use of the AH in a playful setting. Due to the number of assessments the participants underwent over the course of this study and risk of assessment fatigue, only a small subgroup of 5 children was assessed on this measure and this data was not included in the original publication. Due to its importance as being the gold standard, the results will be integrated within this dissertation.

6.2.3 **Procedures**

The standardized assessments were measured either prior to or on the first day of the therapy intervention. The JTTHF was administered by trained occupational therapists. CHEQ questionnaires were completed individually by the children or (in case they had problems understanding the questions) with the help of the parent. The AHA was administered by trained occupational therapists.

Performance on the bimanual box-opening task was likewise measured either prior to or on the first day of the therapy intervention. The task was performed in the two conditions, affected hand leading (AHC) and less-affected hand leading (LAHC) which refers to the hand that is used to open the lid. Participants performed a total of 10 trials in the sequence 3*LAHC, 3*AHC, 2*LAHC, 2*AHC.

6.2.4 **Analysis**

Kinematics of hand movement during the bimanual box-opening task were recorded and processed as demonstrated in Chapter 4.3.

Statistical analysis of the outcomes was performed using R 3.1.2. Assumptions of normality of the outcome variables were tested using Shapiro-Wilk test for normality with Lilliefors correction. Homogeneity of variances was tested using Levene's test. Associations between the outcome variables of the box-opening task and clinical measures of uni- and bimanual function were calculated using Spearman's rho (since normality was rejected for all outcome variables). Two-way mixed measures ANOVAs were calculated in order to explore the effect of the level of impairment on the MACS (between subjects) and the condition of execution (within subjects) performance in the case of the box task. In case that level of impairment had a significant effect on one of the outcome variables, post hoc testing was performed separately for each condition, using pairwise t-tests with Bonferroni corrections.

Upon inspection of the distribution of TC in AHC a somewhat abnormal bimodal distribution pattern was revealed, which was tested using Silverman's Test for Multimodality (Hall & York, 2001). Since these subgroups showed specific differences in their characteristics of movement execution, differences in the clinical measures and outcome variables between the subgroups were tested using the Wilcoxon rank-sum test.

6.3 Results

Exemplary vertical displacement and velocity profiles from a representative participant from each MACS level are displayed in Fig. 6.1, Fig. 6.2 and Fig. 6.3. Participants whose JTTHF-AH scores were closest to the average in each group were selected to being displayed.

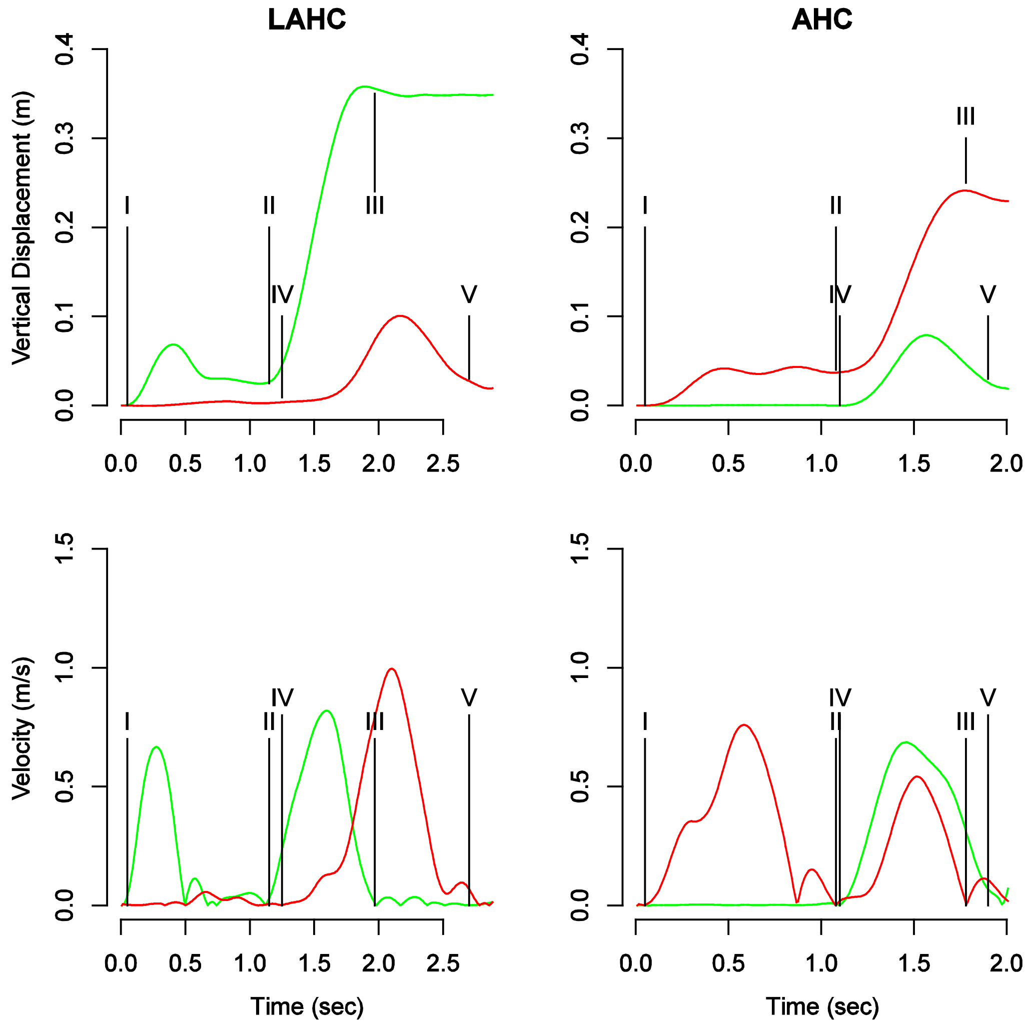

Fig. 6.1 Exemplary vertical displacement and velocity profiles of the hand movement during the bimanual box-opening task of a 10 year old participant with a left hemiplegia and a MACS level I. One trial is shown from the less-affected hand leading condition (LAHC) and affected hand leading condition (AHC) respectively. Green lines indicate movement of the less-affected, red lines of the affected hand. Roman numerals indicate events: I) start of first hand; II) Start of lid opening; III) End of lid opening; IV) Start of second hand and V) Button press

In Fig. 6.1, kinematic profiles of two single trials (in LAHC and AHC) of a participant aged 10 years with a left hemiplegia and MACS-level I are displayed. Scores on the JTTHF are 98s and 36s for the AH and LAH respectively. All items on the CHEQ the participant performs independently are also performed with the use of the AH.

TTD is longer in LAHC (2.7s) as compared to AHC (1.9s). In both trials, the participant initiates the second hand movement after beginning of the lid opening. Acceleration of the second hand is however somewhat slower in LAHC, leading to a delayed button press. In AHC, start- and endpoint of the button press movement are almost simultaneous with the beginning and end point of box opening.

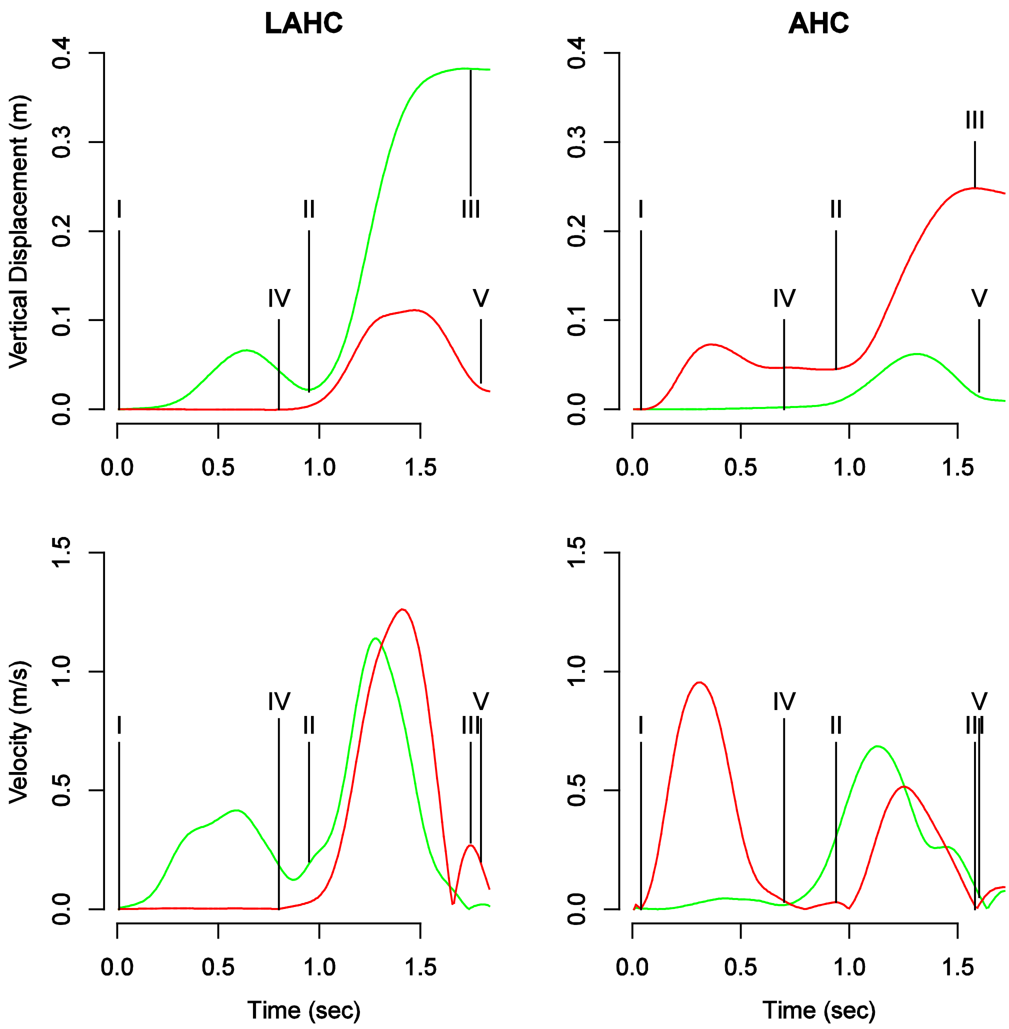

Fig. 6.2 Exemplary vertical displacement and velocity profiles of the hand movement during the bimanual box-opening task of a 14 year old participant with a left hemiplegia and a MACS level II. One trial is shown from the less-affected hand leading condition (LAHC) and affected hand leading condition (AHC) respectively. Green lines indicate movement of the less-affected, red lines of the affected hand. Roman numerals indicate events: I) start of first hand; II) Start of lid opening; III) End of lid opening; IV) Start of second hand and V) Button press

In Fig. 6.2, kinematic profiles of two single trials (in LAHC and AHC) of a participant aged 14 years with a left hemiplegia and MACS-level II are displayed. JTTHF scores are 187s for the AH and 57s for the LAH. The participant manages 25 items on the CHEQ independently and all with the use of his AH.

TTD is between 1.5 and 2s in both trials (however slightly shorter in AHC). The participant initiates the second hand movement before beginning of the lid opening in both conditions too.

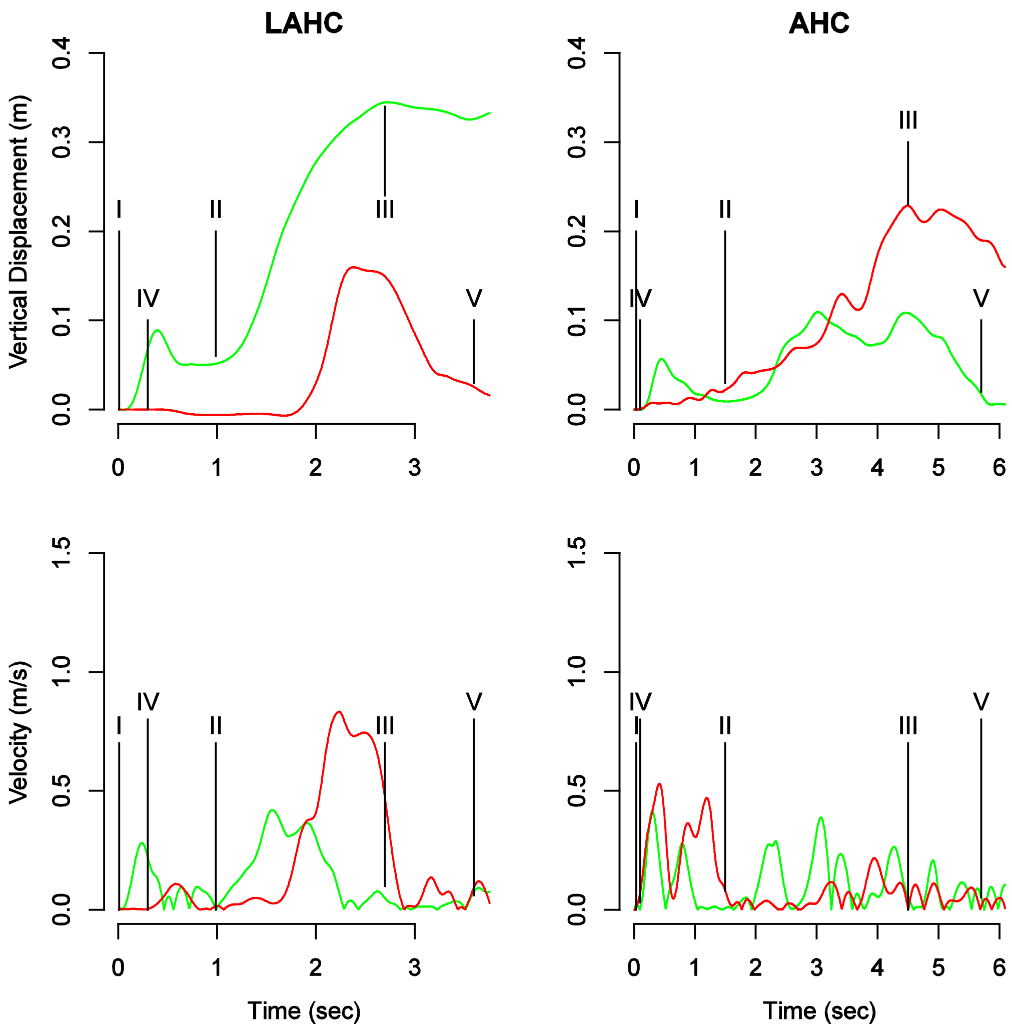

Fig. 6.3 Exemplary vertical displacement and velocity profiles of the hand movement during the bimanual box-opening task of an 8 year old participant with a left hemiplegia and a MACS level III. One trial is shown from the less-affected hand leading condition (LAHC) and affected hand leading condition (AHC) respectively. Green lines indicate movement of the less-affected, red lines of the affected hand. Roman numerals indicate events: I) start of first hand; II) Start of lid opening; III) End of lid opening; IV) Start of second hand and V) Button press

Fig. 6.3 shows kinematic profiles of two single trials (in AHC and LAHC) of a participant aged 8 years with a left hemiplegia and MACS level III. The participant has a maximum JTTHF score of 1080s for the AH and 50s for the LAH. Items on the CHEQ that are solved independently are 18, only 13 of which are with the AH supporting function.

Task duration in LAHC is 3.6s and 5.7s in AHC. In both cases, movement initiation of the second hand is considerably earlier than the beginning of the lid opening. In AHC, the movement of both, the AH and LAH seem to be characterised by redundant or jerky movement.

6.3.1 Total Task Duration

On a group level, TTD was significantly affected by the level of impairment (F(2,34)=8.368, p=.001) with post hoc comparison showing a significant difference between children with MACS level III and those with level I (p<.001) and II (p=.002). In addition, the ANOVA showed a significant effect for condition of execution (F(1,34)=27.483, p<.001) with a faster task execution in the case of the LAHC. A significant interaction effect between the two factors (F(2,34)=11.272, p<.001) showed that the differences between AHC and LAHC were significantly greater for children with MACS level III as opposed to level I (p<.001) and level II (p<.001) (see Fig. 6.4a). The CV of TTD was neither affected by the level of impairment (F(2,33)=0.141, p=.868) nor by the condition of execution (F(1,33)=1.347, p=.254) (see Fig. 6.4b).

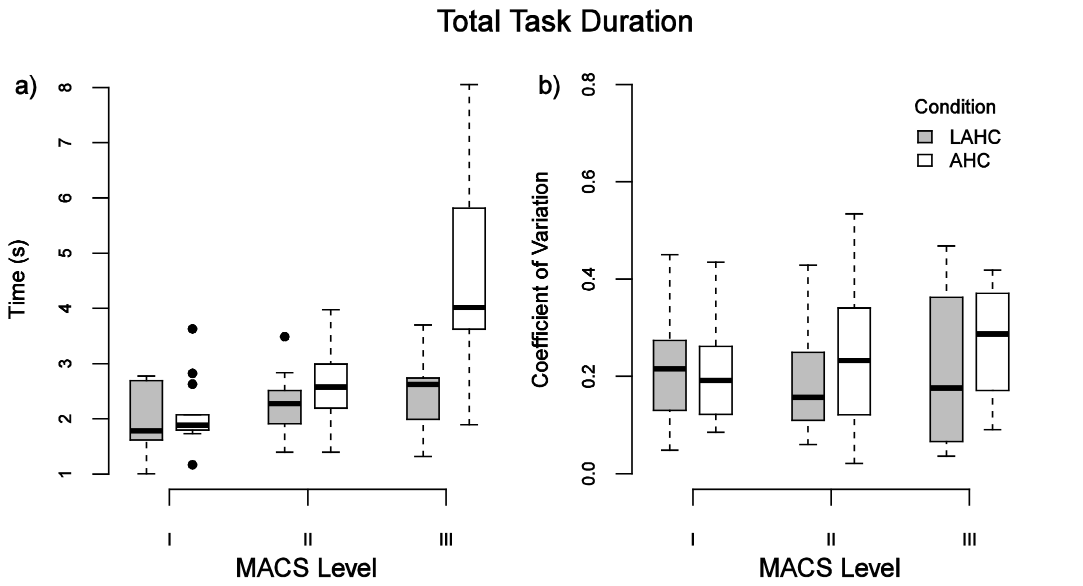

Fig. 6.4 Boxplots showing median, upper and lower quartiles, range and outliers of the absolute values (a) and the coefficient of variation (b) of the total task duration for different levels of impairment on the MACS and the conditions less affected hand (LAHC) and affected hand leading (AHC)

The JTTHF scores for the AH show significant positive correlations with task duration in AHC. Scores for the LAH show significant positive correlations with the task duration in LAHC. The CHEQ efficiency scores show moderate correlations and the CHEQ time scores show weak negative correlations with TTD only in AHC. High negative correlations between the logit scores on the AHA were found in the case of both AHC and LAHC (see Table 6.2).

6.3.2 **Temporal Coupling**

Participants' level of impairment did not have a significant effect on TC ($F(2,34)=0.362$, $p=.699$). Results of the ANOVA did however show a significant effect for condition of execution ($F(1,34)=8.079$, $p=.008$) with greater values of TC in AHC (see Fig. 6.5a). The CV of TC did not show any significant effects for level of impairment ($F(2,33)=2.398$, $p=0.107$) nor for condition of execution ($F(1,33)=3.305$, $p=.078$) (see Fig. 6.5b).

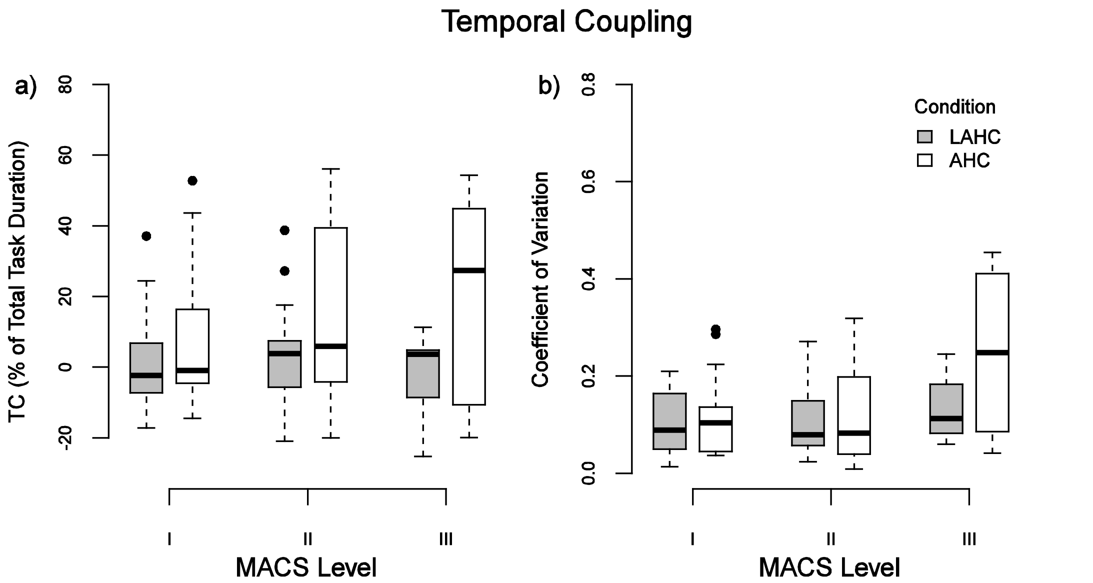

Fig. 6.5 Boxplots showing median, upper and lower quartiles, range and outliers of the absolute values (a) and the coefficient of variation (b) of temporal coupling for different levels of impairment on the MACS and the conditions less affected hand (LAHC) and affected hand leading (AHC)

A moderate significant correlation was found between TC under the condition AHC and the CHEQ R2. In addition, a high positive correlation was found between TC under the condition LAHC and the outcomes of the AHA (see Table 6.2).

Fig. 6.6 Distribution of the outcome variable temporal coupling (in % of the total task duration) in AHC (a) and LAHC (b). Histograms are superimposed by a kernel density plot (black line), as well as by a vertical line (blue) in order to emphasise the 0 intercept (Reprinted from **"**Kinematic parameters of hand movement during a disparate bimanual movement task in children with unilateral Cerebral Palsy" by Rudisch et al., 2016)

A closer examination of the variable TC under each condition shows that the distribution follows a bimodal pattern under the AHC (see Fig. 6.6a) with one mode being slightly negative and the other mode being highly positive. The results of Silverman's test for multimodality show that the unimodal distribution has to be rejected (p=.018) in favour of a bimodal distribution (p=.894). In contrast, the distribution of the LAHC seems to be symmetrical and normally distributed (see Fig. 6.6b) and Silverman's Test did not reject unimodal distribution (p=.494).

6.3.3 **Total Path**

The TP was significantly affected by the level of impairment (F(2,34)=7.620, p=.002) with post-hoc comparison revealing significant differences in children with MACS level III as opposed to levels I (p<.001) and II (p=.001). No significant effect of the condition of execution was found on the TP (F(1,34)=1.043, p=0.314). There was however an interaction effect between the two factors (F(2,34)=7.464, p=.002). Post-hoc comparison revealed that the differences between AHC and LAHC were significantly greater in children with MACS level III as opposed to levels I (p=.015) and II (p=.001) (see Fig. 6.7a).

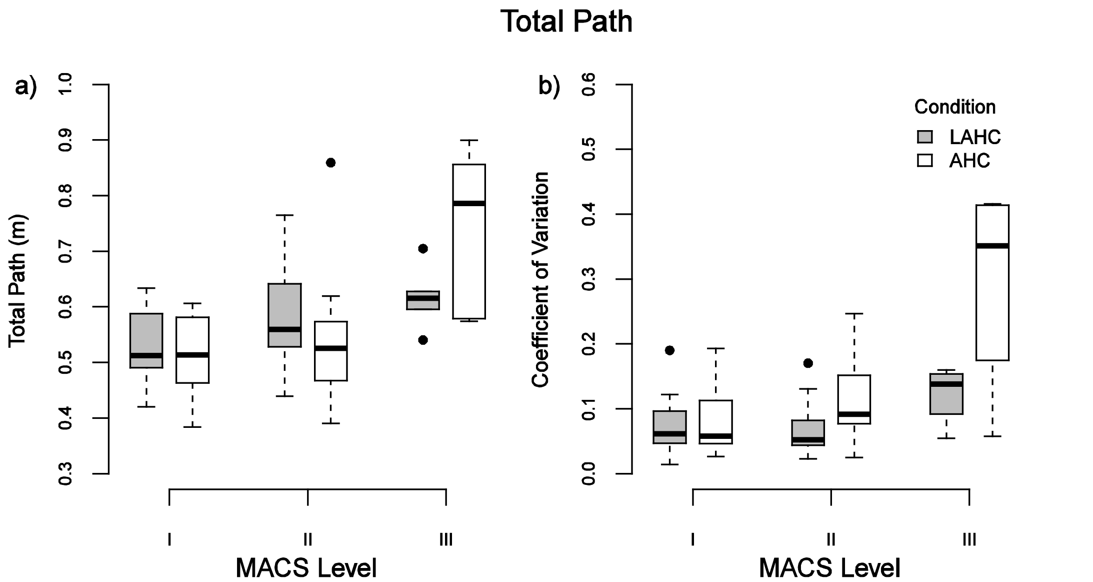

Fig. 6.7 Boxplots showing median, upper and lower quartiles, range and outliers of the absolute values (a) and the coefficient of variation (b) of the total path for different levels of impairment on the MACS and the conditions less affected hand (LAHC) and affected hand leading (AHC)

The CV of TP was significantly affected by the level of impairment (F(2,33)=13.485, p<.001). Differences were found in children with MACS level III as opposed to both levels I and II (p<.001). In addition, a significant effect of condition of execution was found

(F(1,33)=22.938, p<.001) with reduced variability in LAHC. An additional interaction effect was found (F(2,33)=7.333, p=.002), with post-hoc comparison showing significantly greater differences in those with MACS level III as opposed to levels I and II (p<.001) (see Fig. 6.7b).

There were significant moderate negative correlations between spatial accuracy in the AHC and all outcome variables for the CHEQ, as well as a significantly high negative correlation for the AHA. In addition, spatial accuracy during the LAHC was highly correlated with the outcomes on the AHA (see Table 6.2).

Table 6.2 Spearman's (Pearson's in case of AHA) correlation coefficients between the outcome variables on the box-opening task and the clinical measures of the uni- and bimanual hand function

	n	TTD (s)		TC (%)		TP (m)	
		AHC	LAHC	AHC	LAHC	AHC	LAHC
JTTHF AH (s)	32	0.39*	0.21	-0.10	0.06	0.27	0.32
JTTHF LAH (s)	32	0.15	0.37*	0.11	0.26	0.10	-0.13
CHEQ R1	37	-0.32	-0.10	-0.29	-0.04	-0.46**	-0.19
CHEQ R2	37	-0.22	-0.05	-0.36*	-0.22	-0.41*	-0.04
CHEQ E.	37	-0.51**	-0.27	0.01	-0.18	-0.59***	-0.31
CHEQ T.	37	-0.41*	-0.02	0.01	-0.12	-0.45**	-0.13
AHA (Log)	5	-0.94_p*	-0.93_p*	-0.60_p	0.81_p	-0.95_p*	-0.88_p*

TTD=Total Task Duration, s=Seconds, TC=Temporal Coupling, %=Data as a percentage of the Total Task Duration, TP=Total Path, m=Meters, AHC=Affected Hand Leading Condition, LAHC=Less Affected Hand Leading Condition, JTTHF=Jebsen Taylor Test of Hand Function, AH=Affected Hand, LAH=Less Affected Hand, CHEQ=Children's Hand-Use Experience Questionnaire, R1=Ratio Score 1, R2=Ratio Score 2, E=Efficiency, T=Time, AHA=Assisting Hand Assessment, *p<0.05, **p<0.01, $_p$=Pearson's Correlation Coefficient

6.3.4 **Subgroup Analysis**

The vertical displacement and velocity profiles associated to the exemplary movements of a single participant under the two conditions are shown in Fig. 6.8. The participant displays a slightly positive TC (i.e. second hand starts before the onset of the lid-opening) under the LAHC, as opposed to strongly positive TC under the AHC (i.e. the second hand starts almost at the same time as the first hand).

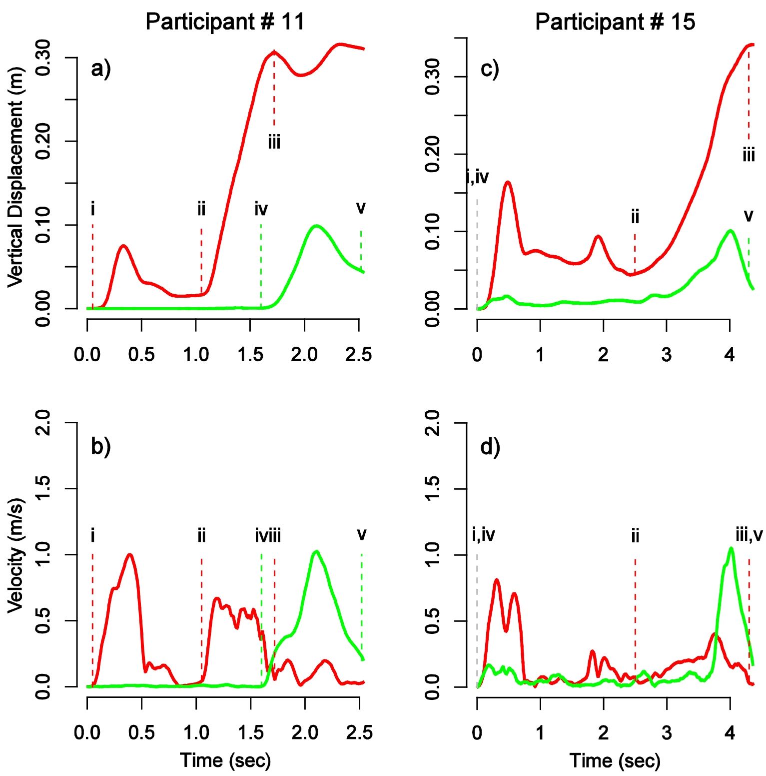

Fig. 6.8 Vertical displacement and velocity profiles of a single trial of two different subjects that show segmented movement behaviour (Participant # 11) and bimanual interference (Participant # 15) in the AHC. The affected hand opens the lid (red lines) and the less affected hand presses the button (green lines)

The bimodal distribution of TC under the AHC (Fig. 6.6a) indicates that participants use two different strategies for the movement task. In order to further investigate whether the two strategies imply qualitative differences in terms of functional impairments, participants are divided into two subgroups based on the gap in values between 30% and 35%. Participants with values below 30% subsequently form group strategy 1 (S1) and participants with values above 35% form group strategy 2 (S2).

Table 6.3 Frequencies of MACS levels and male or female participants in each subgroup. Differences were tested using chi-square statistics

	S1	S2	χ^2 (p-value)
MACS (I,II,III)	11,12,3	2,7,2	1.99 (.369)
Gender (m/f)	15,11	5,6	0.47 (.495)

MACS = Manual Ability Classification System; S1 = Strategy 1; S2 = Strategy 2; m = male; f = female

Table 6.3 shows the frequencies of the different MACS levels, as well as male or female participants in each subgroup. Relative frequencies among children with MACS level II or III are greater in S2, yet these differences are not significant. Relative frequencies among female participants are slightly higher in S2, yet not significant either.

Functional skills differences between the two groups are depicted in Fig. 6.9. No significant differences between the groups were found in the case of unimanual skills, i.e. the JTTHF, for either hand. Children in group S1 however were shown to use their AH more often (CHEQ R1) and qualitatively better (CHEQ R2) when performing bimanual tasks in daily life.

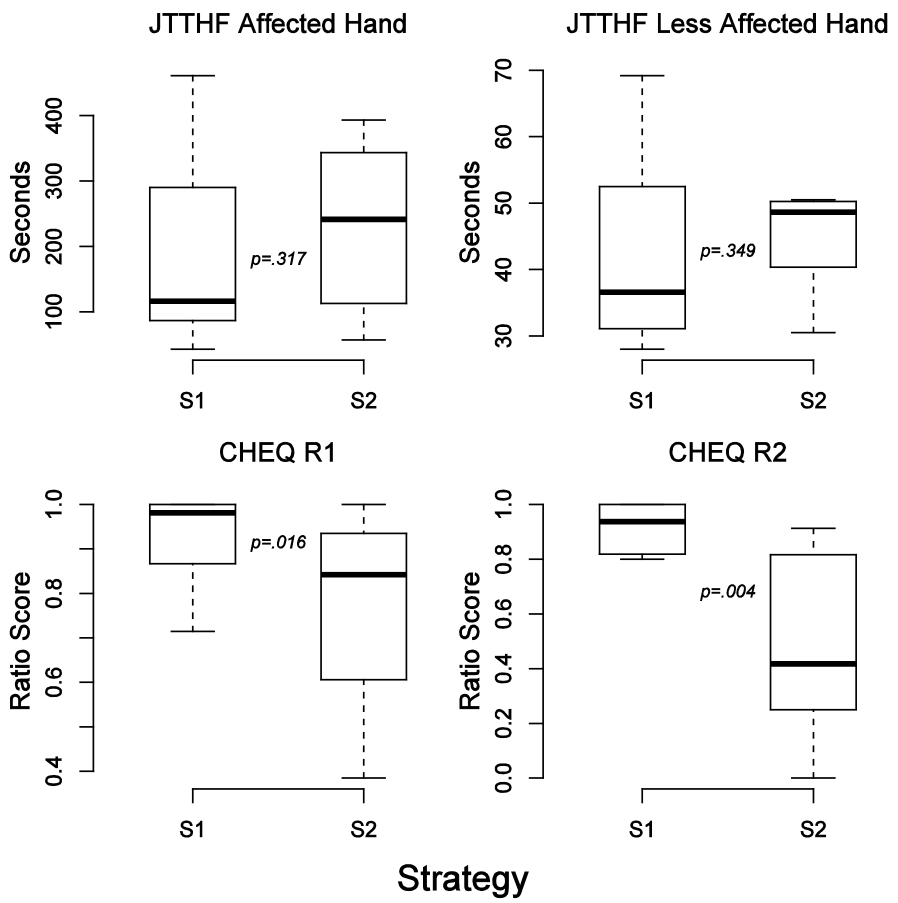

Fig. 6.9 Boxplots indicating the median, upper and lower quartiles as well as ranges associated to the scores on the Jebsen-Taylor Test of Hand Function (JTTHF) of the affected or less affected hand and the two CHEQ (Children's Hand-Use Experience Questionnaire) ratio scores. P-values for the differences were obtained from the nonparametric Wilcoxon Rank-Sum Test

6.4 Discussion

This study was set out to explore the kinematics of hand movements during a bimanual box-opening task in children with uCP across different levels of functional impairment. The results suggest that the task performance outcome variables were strongly affected by the functional level on the MACS, particularly when participants had to open the box with their AH.

As opposed to the TDC, who did not show any difference between the execution of the task in NC or DC, children with uCP seemed to be strongly affected by the condition of execution. Specifically, differences exacerbated with increasing levels of impairment. Especially in the case of children with MACS level III, TTD and TP were shown to be worse under the condition AHC. For the TP this means that the movement trajectories constitute less of a straight line in the LAH than in the AH and are characterised by a higher jerkiness as shown in the velocity profiles in LAHC in Fig. 6.3. Considering the significant differences in movement execution, the LAHC seems to be exceptionally worse and thus less preferred in children classified under MACS level III (e.g. Fig. 6.3). Hence, this group greatly deviates from the preferred patterns that could be found in typical children and adults (Birtles et al., 2011; Wiesendanger et al., 1996). In contrast, especially children with good functionality of their AH seem to perform bimanual movement tasks in a pattern that is more similar to TDC with optimised coupling of the two hands (e.g. Fig. 6.1 & Fig. 6.2).

In view of the intra-individual variability of TTD and TC, no differences could be found between the two conditions or between the different levels of impairment. The CV was however found to be higher for both TTD and TC in children with uCP, as compared to TDC. According to Müller and Sternad (2009), this would indicate that the movement pattern is less automatic in children with uCP.

The lid-opening movement is qualitatively more complex (i.e. reach and grasp, extension and elevation) than the button press movement (i.e. simple reaching task). Thus, a successful task execution very much depends on how the first part of the sequence is performed. That means that if due to very poor capacity in the AH, the first part of the sequence cannot be performed successfully or quickly enough, using the LAH becomes more attractive since it allows for more successful or quicker completion. Correlations with the JTTHF support the assumption that the functional ability of the leading hand (i.e. the hand that opens the box) has some impact on the movement speed during the box-opening task. Scores for the AH correlated moderately with TTD in AHC. In addition, scores for the LAH showed moderate positive correlations with TTD in LAHC, which were also significant. The CHEQ efficiency and time scores also showed (negative) correlations with TTD, however only in AHC. It appears that the task imposes bimanual challenges, particularly when the non-dominant hand is used as a leading hand. Interestingly, task duration under both conditions showed high negative correlations with the outcomes of the AHA (i.e. a higher score on the AHA is associated with a faster task execution). Owing to the small sample, those results need however to be interpreted with caution.

The values of TC have been shown to be reduced in LAHC as compared to those of TDC. Interestingly however, TC was on a group level increased and more similar to TDC when looking at AHC, thus indicating a better sequencing under this condition. These results contradict the findings of Hung, Charles and Gordon (2004), who detected an increased movement overlap when the LAH was leading. The improved sequencing would however support the frame of reference hypothesis (Guiard, 1987) in that the LAH, due to its better control, improves the temporal sequencing of the movement task. A closer examination of the distribution of TC in AHC however revealed a bimodal distribution, indicating two qualitatively different strategies used in order to solve the task. In fact it seems that a subgroup (S1) of children shows a particularly sequenced movement behaviour in which the second hand starts at a substantially later instance after the lid opening. Conversely, a second subgroup (S2) presents a very early start (often at the same starting point as the first hand). The second subgroup could be a result of bimanual interference, due to similar mechanisms being employed as in the MMs. Two possible mechanisms could be: i) ipsilateral CMPP in which the AH is being controlled by the undamaged hemisphere with close proximity between the areas of control for both hands (Guzzetta et al., 2007; Staudt et al., 2004) or ii) a decreased ability to inhibit neural crosstalk between hemispheres within the prefrontal cortex (Grefkes, Eickhoff, Nowak, Dafotakis, & Fink, 2008). Whether S2 constitutes a strategy that is functionally used (i.e. using the movement of the LAH to drive or initiate the movement of the AH) remains to be explored. A comparison of the functional abilities between the two groups nevertheless shows that the use of the AH in daily bimanual activities is avoided to a greater extent in S2, as compared to S1. Conversely, the JTTHF scores for either hand were only shown to be slightly worse in S2, without however bearing significance.

Participants with higher levels of impairment also showed an increase in TP under the condition LAHC. More interestingly, the TP of children with MACS level III was especially affected in AHC. This is another indicator of decreased control in the case of the LAH when the AH is used to open the lid. In addition, correlations with the outcomes on the CHEQ show that increasing values of TP in AHC have been shown to range from moderate to high.

It appears that the control over the LAH is affected among children who use their AH in a bimanual task. Hence, the use of the AH is more likely to be avoided on bimanual tasks or its efficiency is reduced as compared to their peers.

The influence of the AH over the LAH during a synchronous bimanual task has been previously described in children with uCP (Utley & Sugden, 1998), whereas their interfering effect for disparate bimanual movement tasks is yet to be explored (Hung et al., 2011, 2004, 2010). Children who display that type of movement behaviour may have been present in these studies, yet they remained undiscovered since the onset of the movement was regarded only in the case of movement in forward direction. In this case however, children often moved their hand asymmetrically to the opposing hand in an upward or downward direction.

6.5 Summary and Reconciliation

This chapter reports the results of a study investigating the performance of children with uCP on the bimanual box-opening task. The performance was assessed using the two conditions of execution, AHC and LAHC, as well as across the different levels of impairment. It was shown that the task duration and path length increase with higher levels of impairment. Likewise, with higher levels of impairment, performance seems to be strongly affected in AHC. In addition to these findings, two qualitatively different performances were evident: i) a late start and segmented movements, and ii) an early start and bimanual interference in this group, indicating that the performance of the second group might be affected by problems in terms of interhemispheric inhibition.

The following section reports on additional neuroimaging and electrophysiological data that has been acquired from a small sample of these participants. It will be attempted to unravel the neurophysiological basis of some of the problems in terms of bimanual coordination reported within this chapter. The acquired results also constitute the foundation for the motor learning study on which the second part of this thesis will be based.

7 Exploring Neuropathologies of Bimanual Impairments

Relevant Publication for this Chapter

Weinstein M, Green D, **Rudisch J**, Zielinski I, Benthem-Muniz M, Jongsma M, McLelland V, Steenbergen B, Shiran S, Ben Bashat D, Barker G (Under Review – European Journal of Paediatric Neurology). Understanding the relationship between brain and upper limb function in children with unilateral motor impairments: A multimodal approach

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Preamble

Data reported in this chapter has been collected and analysed as part of a collaborative project to investigate the relation of unilateral brain impairments and upper limb function. People that were involved in the project are included in the list of authors of the relevant publication (above). All neuroimaging was performed at the King's College London Centre for Neuroimaging Sciences. TMS was performed at King's College Hospital. Within the framework of this chapter, the data was analysed with special focus on bimanual impairments.

7.1 Introduction

Despite the common term being used for children with congenital and early childhood motor disorders, CP can be caused by a variety of different factors and can take a variety of different forms (see section 3.1.1). Malformations, white or grey matter lesions can affect different areas of the brain and the extent of damage can vary (Krägeloh-Mann & Horber, 2007). These factors, as along with the ability of the brain to reorganise some of its structures and restore functionality up to a certain extent (Kirton, 2013; Staudt, 2010), determine the quality of the motor skills in children with CP.

Specific features of the damage in the CNS, as well as the reorganisation patterns might have a particular impact on the limb coordination in children with uCP. As presented in section 3.1.2, individuals with uCP sometimes present ipsilateral CMPP, whereas others show mixed or (typical) contralateral patterns (Guzzetta et al., 2007; Staudt et al., 2002). Both, the AH as well as the LAH, are being controlled by the same hemisphere in the case of ipsilateral CMPP. The proximity between the areas that control each hand might cause involuntary cross-activation, an issue that might constitute a problem in the case of disparate bimanual movement tasks in which both hands have to perform different actions at the same time. MMs for example are stronger and usually retained into adulthood among individuals with ipsilateral CMPP (Holmström et al., 2010).

In the case of typical contralateral CMPP, an exchange of information between the hemispheres via the CC is crucial in order for both hands to work in a cooperative manner (Gooijers & Swinnen, 2014). Some children with uCP have previously been shown to display a decreased integrity of the fibres of the splenium and midbody of the CC (Weinstein et al., 2014). Especially when deprived of visual feedback, individuals with a split brain (i.e. following the sectioning of the CC) lose the ability to appropriately couple both hands in a temporal manner (Kennerley et al., 2002). In the case of an intact CC, efferent copies of the movement of one limb are constantly sent to the opposing hemisphere. In the case of unimanual or asynchronous movements, the supplementary motor area and the premotor cortex inhibit these copies so that they do not lead to an involuntary activation in the opposing hemisphere. In the case of bimanual synchronous movement execution, the efferent copies are positively modulated in the supplementary motor area and premotor cortex in order to align the movement of both hands spatiotemporally (Grefkes et al., 2008).

This study explores the impact of different types of neuropathologies on children's ability to perform bimanual movement tasks. Various neuroimaging methods were utilised in order to explore the structural and functional integrity of the CNS. Furthermore, the laterality of the CMPP was investigated using transcranial magnetic stimulation (TMS). Utilising a multiple single-case design, the CNS integrity and consequent behavioural impairments in the performance of uni- and bimanual movement tasks will be explored within the framework of subsequent study.

7.2 Methods

7.2.1 Participants

Children who were to participate in a two-week intervention to improve their bimanual skills using a themed HABIT approach (Green et al., 2013) were invited to participate in this study. The same children who were asked to participate in the study reported in section 6 and to take part in the London intervention were approached. Children diagnosed with uCP were also included in this study. Children with uncontrolled seizure activity were excluded from the TMS. Children with contraindications to MRI were excluded from the scanning procedures. Children who underwent an intervention to improve their motor functions six months before were excluded from the general study. Not all children who underwent the neuroimaging also agreed to participate in the bimanual box-opening task study (section 6).

7.2.2 **Apparatus/ Materials**

Participants performed different standardized assessments and behavioural measures in order to investigate functional impairment and quality of bimanual coordination. In addition, neuroimaging was performed in order to obtain details about the characteristic neural impairment of the individuals.

Standardized & Behavioural Measures

i) The MACS in order to classify upper limb impairments (section 3.3.1)

ii) The JTTHF in order to assess the (unimanual) functionality of both the AH and the LAH (chapter 4.1.1)

iii) The CHEQ independent score in order to assess the child's general ability to perform bimanual tasks in daily life (chapter 4.1.2)

iv) Hand Kinematics were measured using an electromagnetic 3D motion tracking device Polhemus G4™ (Polhemus, Colchester, Vermont, USA). Bimanual coordination was investigated using the bimanual box-opening task (chapter 4.3.1).

Structural and Functional Neuroimaging

3T GE MR750 Scanner (GESigna EXCITE, Milwaukee, WI, USA) was used for the imaging procedures. Structural MRI was acquired using a high-resolution anatomical 3D fast spoiled gradient echo sequence (FSPGR) with slice thickness/gap = 1/0 mm, field of view/matrix = 240mm/256x256, time to repeat/time to echo = 8.6/3.3ms. The injury coding was based on a radiological scoring system for children with hemiplegia (Shiran et al., 2014) allowing for the calculation of a total radiological score (RS). In patients with unilateral hemispheric involvement, scores can range from 0-18, with higher numbers indicating an increasing impairment. The injury coding was performed by a senior paediatric neurologist.

The fMRI procedures were performed using T2*-weighted gradient echo echo planar imaging sequence (GE- EPI) with slice thickness/gap = 3.5/0mm; field of view/matrix = 240mm/128x128, time to repeat/time to echo/flip angle = 2.250/29msec/79^0. DTI was acquired along 19 diffusion gradient directions (b = 1000sec/mm^2) and one direction with no applied diffusion gradient with slice thickness/gap = 2.5/0mm, field of view/matrix = 256/128x128, time to repeat/time to echo = 11.8/77ms.

Transcranial Magnetic Stimulation

TMS was used to identify characteristics of CMPP (i.e. ipsi- or contralateral or mixed) using a Magstim stimulator (Magstim Company Ltd, Whitland, UK) with a figure-of-eight magnetic coil.

7.2.3 **Procedures**

Standardized & Behavioural Measures

Standardized functional as well as behavioural measures of bimanual coordination (i.e. the bimanual box-opening task) were administered as shown in chapter 6.2.3.

Neuroimaging

Before the actual scanning, children were familiarised with the procedures using a 'mock scanner'. For the fMRI task, children performed a repetitive squeezing task on two sphygmoemeters they held in their hands. The squeezing task consisted of several blocks including rest, only left hand squeeze, only right hand squeeze and both hand squeeze with a block duration ranging between 9 and 12 seconds. The squeezing had to follow an auditory signal set at a frequency of 2Hz. Pressure of the sphygmometers was measured at a frequency of 20Hz. The maximum pressure, the sum of pressures and the sum of pressure changes were calculated for every block.

Transcranial Magnetic Stimulation

The CMPPs were tracked using TMS. Motor evoked potentials (MEP) were measured at the first dorsal interosseous muscle of each hand. During the trials, participants were asked to squeeze two sponge balls in order to activate the muscles. A figure-of-eight coil was used to apply TMS over the sensorimotor cortex with coil orientation based on Mills (1992). The optimal location to evoke MEPs was searched systematically over each hemisphere. Once the optimal location was found, electric field strength was increased continuously until the MEPs were detected in at least 50% of the trials, i.e. the active motor threshold. Subsequently, eight suprathreshold pulses (1.5 times active motor threshold) were applied and central motor conduction times (CMCT) were calculated bilaterally.

7.2.4 **Analysis**

Kinematic data from the bimanual box opening task was processed and analysed as described in chapter 4.3.4.

Data from the fMRI scanning procedures were analysed using BrainVoyager QX 2.4 (Brain Innovation, Maastricht, the Netherlands). Seed regions for the resting state fMRI were based on the active condition for the left and right hand. Analysis of the sphygometer data was performed using MATLAB R2014b (The MathWorks, Natick, MA). The sum of pressures and the sum of pressure changes were normalised to the block duration. In addition, signals were cross-correlated in order to see if the participant displays MMs (Zielinski et al., 2016). Signals of the left and right hand were therefore shifted for a maximum of 5 data points in each direction, corresponding to half of the duration of a squeezing cycle. If the highest correlation coefficient exceeded r=.30, the participant was considered to present MMs.

Tractography analysis was performed using DTIStudio software (John Hopkins University, Baltimore, MD, USA) using streamline fibre tracking method with Fibre Assignment by Continuous Tracking algorithm (Mori, Crain, Chacko, & van Zijl, 1999). Regions of interest were the CC and the left and right CST. The CC was segmented into three parts: genu, midbody and splenium. The mean eigenvalues of the axial and radial diffusion rates of water molecules were calculated. Diffusivity is generally less hindered in parallel to the direction of the axons (axial) and should thus have higher values than when the latter is perpendicular to it (radial). Less matured or injured axons can cause a decrease in axial diffusivity. A decrease in the diameter of an axon (e.g. due to reduced myelination) or the axon density can lead to an increase in radial diffusivity. The fractional anisotropy (FA) was calculated as a relative measure of axial diffusivity in relation to radial diffusivity, with higher values indicating an increased white matter integrity (for Review, see Alexander, Lee, Lazar, & Field, 2007).

7.3 Results

An overview of the different measures acquired per subject is given in Table 7.1. Participant #1 completed the neuroimaging procedures. Data processing was however impossible due to excessive head movements. Excessive head movements were also the reason for data loss in the other subjects, where some of the imaging data is missing. Child #5 was excluded from the TMS due to risk of epilepsy.

Table 7.1 Overview of the measures acquired for the individual subjects. White shaded boxes with checkmark = data present; grey shaded boxes with cross = data not present

Child	MRI	fMRI Rest	fMRI Act.	DTI	TMS	MACS	JTTHF	CHEQ	BBT
#1	✓	×	×	×	✓	✓	✓	✓	×
#2	✓	✓	✓	✓	✓	✓	✓	✓	✓
#3	✓	✓	✓	✓	✓	✓	✓	✓	✓
#4	✓	×	×	✓	✓	✓	✓	✓	×
#5	✓	✓	✓	✓	×	✓	✓	✓	✓
#6	✓	×	×	×	✓	✓	✓	✓	✓
#7	✓	×	×	✓	✓	✓	✓	✓	×
#8	✓	✓	✓	×	✓	✓	✓	✓	✓
#9	✓	×	×	×	✓	✓	✓	✓	×

MRI=Magnetic Resonance Imaging; fMRI Rest=resting state functional Magnetic Resonance Imaging; Act.=Active; DTI=Diffusion Tensor Imaging; TMS=Transcranial Magnetic Stimulation; MACS=Manual Ability Classification System; JTTHF=Jebsen-Taylor Test of Hand Function; CHEQ=Children's Hand-Use Experience Questionnaire; BBT=Bimanual Box-Opening Task

7.3.1 Behavioural Assessments

Individual behavioural outcomes are presented in Table 7.2. Participants cover all MACS levels from I to III, with level II being the most frequent. The JTTHF scores for the AH ranged from 50s to 1015s, which correlated largely with their MACS level. The scores for the LAH were generally smaller (faster) than for the AH. JTTHF scores for the LAH in the case of participants #2, #3, #4, #5, #6, and #8 were greater than two standard deviations of age-matched TDC.

The number of independent items that could be achieved on the CHEQ also spanned over a broad range from as little as 10 up to 25 (out of a maximum of 29). Some of the children performed all items independently using two hands (i.e. subject #5, #7 and #9), while others used their AH in less than 65% of the items (i.e. subjects #1, #6 and #8).

The outcomes of the bimanual box-opening task were consistent with those of other children having the same level of functional impairment. TC values were mostly negative (i.e. segmented movement) in AHC and slightly positive in LAHC. Subject 6 however showed large deviations in AHC with particularly high values for TTD, TP, as well as a strongly positive TC, indicating movement interference in AHC.

Table 7.2 Individual outcomes of the various behavioural uni- and bimanual assessments, as well as classification of manual ability

Child	MACS	JTTHF (s)		CHEQ		BBT					
						TTD (s)		TC (%)		TP (m)	
		AH	LAH	Ind.	R1	AHC	LAHC	AHC	LAHC	AHC	LAHC
#1	II	382	34	21	0.62	-	-	-	-	-	-
#2	I	108	52	15	0.93	1.73	1.78	-0.5	6.4	0.606	0.588
#3	II	394	53	17	0.76	3.97	2.05	-10.3	4.5	0.539	0.556
#4	II	363	45	16	0.86	-	-	-	-	-	-
#5	I	50	36	25	1	2.63	2.71	-3.6	11.2	0.604	0.594
#6	III	1015	59	10	0.6	9.27	3.1	69.5	-3.9	1.532	0.424
#7	II	795	33	18	1	-	-	-	-	-	-
#8	III	461	62	22	0.64	3.62	2.74	-10.6	11.3	0.579	0.596
#9	II	395	48	22	1	-	-	-	-	-	-

MACS=Manual Ability Classification System; JTTHF=Jebsen-Taylor Test of Hand Function; AH=Affected Hand; LAH=Less Affected Hand; CHEQ=Children's Hand-Use Experience Questionnaire; Ind.=Number of independent items on the CHEQ; R1=CHEQ Ratio Score 1; BBT=Bimanual Box-Opening Task; TTD=Total Task Duration; TC=Temporal Coupling; TP=Total Path; AHC=Affected Hand Condition; LAHC=Less Affected Hand Condition

7.3.2 **Structural and Functional Neuroimaging**

Pathology and Radiological Scoring

Participants presented different pathologies on the MRI (see Table 7.3). White matter impairments in the area of the lateral ventricles were found in subjects #2, #4, #7, #8 and #9, three of whom were born prematurely (i.e. before week 37). The RS of these individuals were generally in the middle range (i.e. 7-11). Despite their similar RS, the subjects covered all impairment levels from I to III on the MACS. The JTTHF scores (for both hands), as well as the CHEQ were also broadly spread for these subjects. No unusual performance was shown on the bimanual box-opening task. Data was however only acquired for 2 out of 5 participants with white matter impairments (see Table 7.2).

Two of the participants (child #1 and #6) presented hypoxic–ischaemic encephalopathy, one of which was in combination with a middle cerebral artery infarct. Both were term born. These participants also had the highest RS (12 and 15), indicating extensive impairments. Behavioural measures indicated medium to severe impairments of the AH. In addition, both participants were the ones who mostly refrained from using their AH during bimanual tasks, as indicated by their CHEQ R1 scores. The outcomes on the bimanual box-opening task also showed that subject 6 experienced extraordinary difficulties when his AH was the leading hand.

Table 7.3 Gestational age at birth. Brain impairment as identified on the structural MRI and radiological scores for each subject. Columns are shaded according to the pathological category as follows: white matter damage=white; grey matter damage=grey; malformation=purple

Child	Age (years)	AH	Gestational Age (weeks)	Pathologies (MRI)	RS
#1	7.1	L	38	Hypoxic-Ischaemic Encephalopathy	12
#2	7.0	R	40	Intraventricular Haemorrhage	7
#3	7.5	R	42	Cystic Encephalomalacia	9
#4	8.7	R	31	Intraventricular Haemorrhage	8
#5	11.0	R	42	Congenital Malformation	4
#6	7.3	L	41.5	Middle Cerebral Artery Infarct, mild Hypoxic-Ischaemic Encephalopathy	15
#7	10.6	R	38	Periventricular Leukomalacia	11
#8	7.8	R	35	Intraventricular Haemorrhage	11
#9	8.1	R	36	Periventricular Leukomalacia	11

AH=Affected Hand; MRI=Magnetic Resonance Imaging; RS=Radiological Score

Participant #3 presented cystic encephalomalacia and medium RS. Behaviourally, the participant had average (for this group) scores on the JTTHF, the CHEQ and the bimanual box-opening task. The participant was classified as level II on the MACS.

Participant 5 was the only participant that presented a congenital malformation, which resulted in a mild form of polymicrogyria. The term born participant also had the lowest RS within the group. Likewise, he exhibited MACS level I and showed a generally good performance on the JTTHF and CHEQ outcome measures.

fMRI

Results of the active and resting state fMRI are depicted in Fig. 7.1. Participants 2 and 3 show some bilateral activation in the active fMRI in condition AH. Both children showed some functional connectivity between the hemispheres in the resting state. Strong patterns of activation around the central sulcus were observed in subject 5, for both the affected hemisphere in the AH squeezing condition and the less affected hemisphere in the LAH squeezing condition. The participant did not show bilateral activation. A high level of functional connectivity between motor cortices but also between other areas in the frontal lobe could be observed during the resting state. Participant 8 likewise showed activations in the area of the central sulcus of the affected hemisphere when squeezing the AH and of the less affected hemisphere when squeezing the LAH. The resting state fMRI did not show functional connections between the motor areas of both hemispheres.

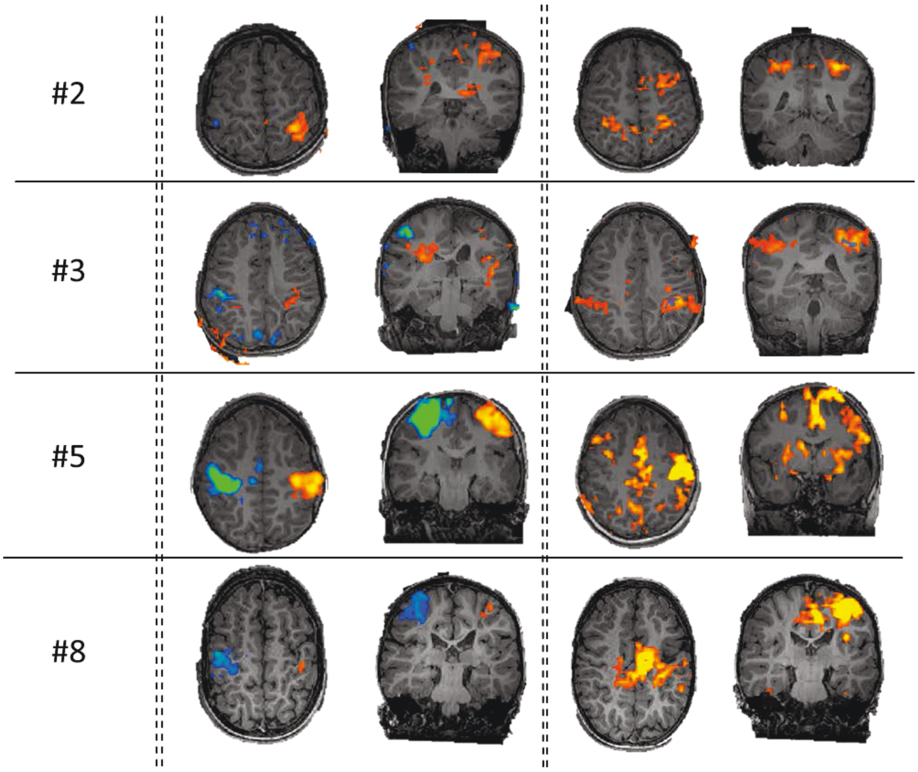

Fig. 7.1 Axial and Coronal images of the active (left column) and resting state fMRI (right column). Note that the axes are flipped and thus the right side of the image depicts the left hemisphere and vice versa. All subjects present a right hemiplegia, hence the affected hemisphere is to be observed on the right hand side of all images. In the active condition, orange and yellow indicate the active voxels in the right hand squeezing condition, blue and green are used when the left hand is squeezing

The actual squeezing movement during the fMRI was measured using the two sphygmometers the participants held in each hand. Exemplary data snippets for each participant are shown in Fig. 7.2. Squeezing was generally more pronounced in the LAH than in the AH, except for subject #2. Subjects #4 and #7 seemed to be more capable of squeezing with their AH in both conditions, as compared to the AH condition. Subjects #1 and #9 seemed to struggle to squeeze either hand in the 'both' condition despite displaying a capability to do so in the LAH condition. Only very few trials with actual squeezing patterns for the AH could be identified for subject #9. Subject #8 showed some peculiarities in the 'both' condition in that the squeezing patterns seemed to be temporally uncoupled.

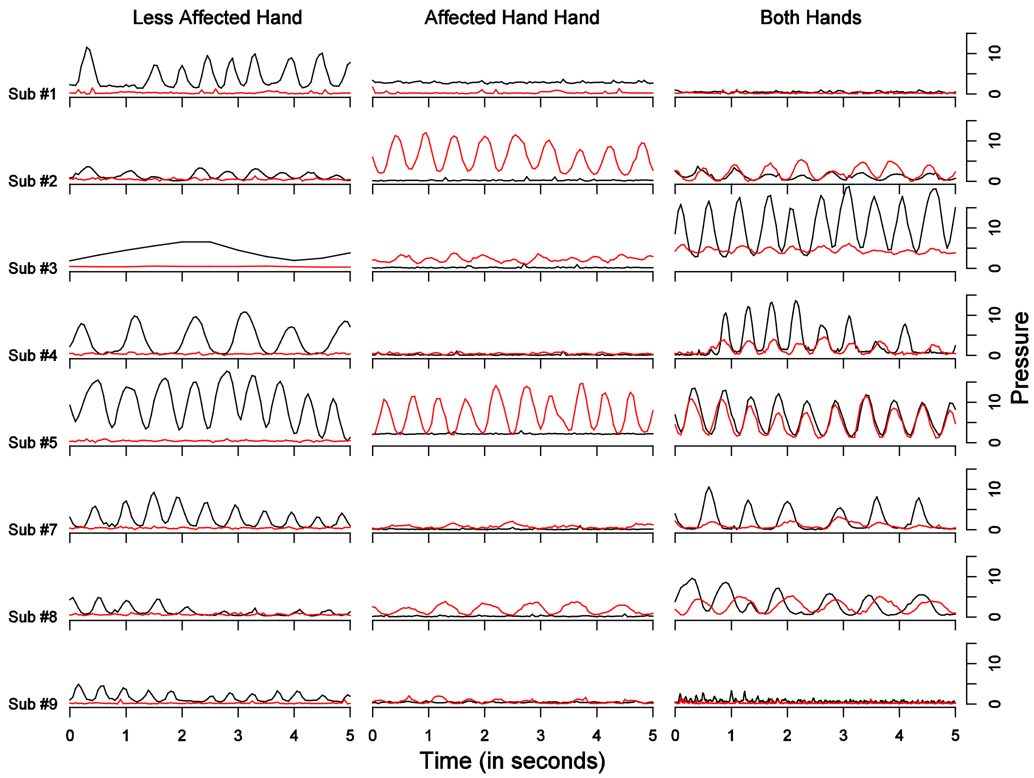

Fig. 7.2 Exemplary sphygmometry data for individual subjects. Data snippets of 5s length were extracted from the second block associated to each condition, LAH, AH and 'both hands squeezing'. Pressure data from the AH (red line) and the LAH (black line) is plotted against time

The results of the signal cross-correlation are presented in Fig. 7.3. A large portion of the subjects' upper quartile in both conditions was smaller than the *r*=0.3 threshold. Participant #4 was the only participant that showed a tendency towards higher correlation coefficients when squeezing with the AH, indicating slight mirrored movements. Medians for the both hands squeezing conditions were high (i.e. close to 1) in subjects #2, #3, #4, #5 and #7. The median of participant #1 was rather low, but the interquartile ranges were high (similarly to subject #4). This was attributed to the unimanual squeezing (only LAH) in trials where both hands were required. Almost no squeezing of the AH was detected in subject #9, hence the median of correlation between the signals was close to 0 even in the 'both' condition. The median of the correlation coefficients in the 'both' condition was also low in subject #8, who displayed temporal uncoupling in the 'both' condition (Fig. 7.2).

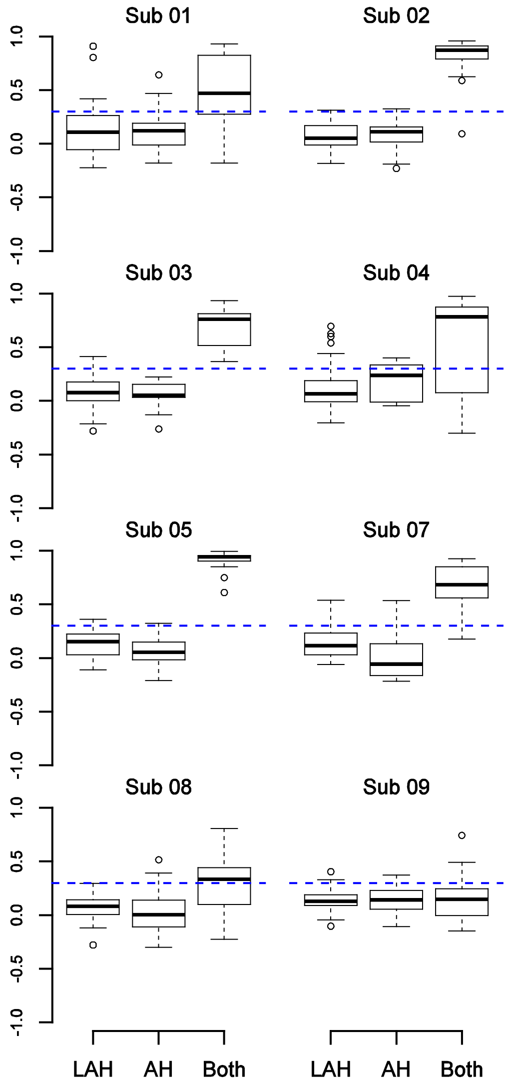

Fig. 7.3 Boxplots showing the median, upper and lower quartile, range and outliers of the highest correlation coefficient (Pearson's r) from cross-correlating the signals for the left and right hand for each trial (1TR, i.e. 2.25s) between participants and conditions

DTI

In the case of CC fibres, participants generally displayed higher FA in the genu and splenium, as compared to the midbody. Subject #5 however showed a different pattern with reduced FA in the genu and midbody, as compared to the splenium (see Fig. 7.4a).

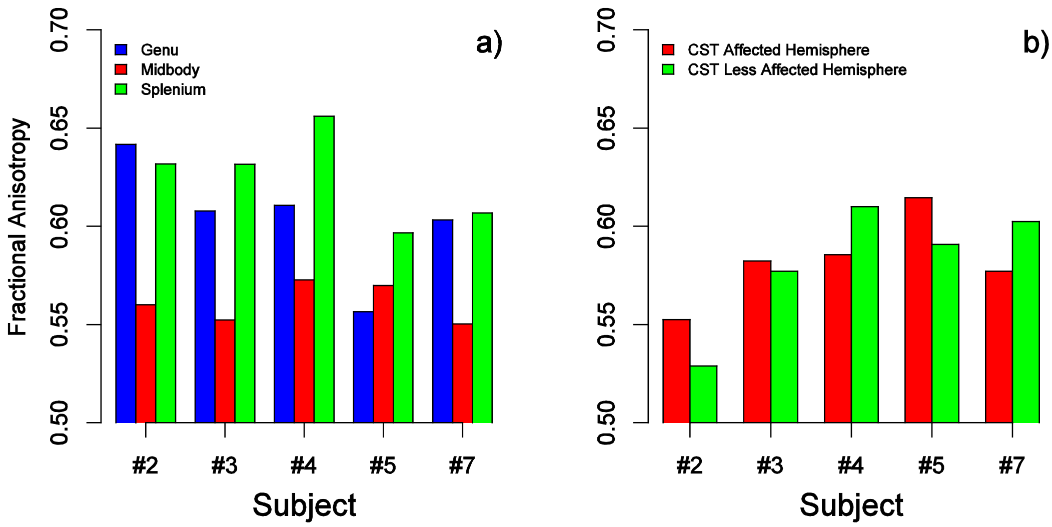

Fig. 7.4 Fractional anisotropy of the different parts of the corpus callosum (a), as well as the affected and less affected corticospinal tracts (b) in individual subjects

When comparing the left and right CST, only subjects #4 and #7 showed higher FA in their less affected hemispheres. Subjects #2, #3 and #5 showed reversed patterns, with subject #2 having the lowest values for both hemispheres across all subjects (see Fig. 7.4b).

7.3.3 **Transcranial Magnetic Stimulation**

The average ipsi- and contralateral CMCTs for the LAH and the AH are shown in Table 7.4. Subject 5 was excluded from the TMS due to risk of epilepsy. Contralateral CMPP from the less affected hemisphere to the LAH could be tracked in all subjects.

Table 7.4 Average central motor conduction time (i.e. time between a single-pulse TMS and the measurement of motor evoked potentials in ms) in the individual subjects for contra- and ipsilateral corticospinal tracts of the affected and less affected hemisphere

Child	C-CST Less Affected H.	I-CST Less Affected H.	C-CST Affected H.	I-CST Affected H.
#1	5.1	NR	6.8	NR
#2	5.5	NR	4.9	NR
#3	5.6	5.3	NR	NR
#4	5.4	NR	6.7	NR
#5	-	-	-	-
#6	5	NR	NR	NR
#7	5.6	5.3	5.6	NR
#8	5.5	NR	NR	NR
#9	3.7	NR	NR	NR

C-CST = Contralateral Corticospinal Tract; I-CST = Ipsilateral Corticospinal Tract; H. = Hemisphere

None showed ipsilateral CMPP from the affected hemisphere to the LAH. Contralateral CMPP from the affected hemisphere could be tracked in 4 subjects (#1, #2, #4 and #7). Subjects #1, #2 and #4 only showed contralateral CMPP to each hand. Subject 7 additionally showed ipsilateral CMPP from the less affected hemisphere to the AH, indicating mixed patterns. Subject 3 only showed ipsilateral CMPP from the less affected hemisphere to the AH. No MEPs in the AH could be triggered in subjects 6, 8 and 9.

7.4 Discussion

The purpose of this study was to explore neuropathologies and their relation to (bi-) manual abilities in children with uCP. Neuropathologies were explored using MRI, fMRI and DTI. The reorganisation of the CMPP was investigated using TMS. Children were classified according to their level of upper limb impairment (MACS level). Uni- and bimanual function was assessed using the JTTHF and the CHEQ. The outcomes of the bimanual box-opening task and the bimanual squeezing (fMRI) task were used to evaluate the characteristics of impaired bimanual coordination.

Despite a unifying diagnosis of uCP, children participating in this study presented a variety of different neuropathologies from all categories. Similar to the distribution in larger studies (Arnfield et al., 2013; Krägeloh-Mann & Horber, 2007), periventricular white matter lesions (5 subjects) were predominant, followed by grey matter lesions (3 subjects). Only 1 subject presented a brain maldevelopment.

Children with Periventricular White Matter Lesions

Children with white matter lesions often show motor impairments of lesser severity than those with white matter damage or brain malformations (Arnfield et al., 2013). Yet all levels of manual impairment (MACS I-III) were present in this group. In addition, there was a large range of JTTHF scores on the AH and the LAH, as well as on the CHEQ.

There was only one participant in this group presenting white matter damage in which ipsilateral or rather mixed CMPP could be tracked (subject 7). The fMRI squeezing task did however not show any signs of MMs, which is contrary to the hypothesis that ipsilateral CMPP promote MMs (Balbi, Trojano, Ragno, Perretti, & Santoro, 2000). In fact, only subject #4 showed a tendency towards MMs when squeezing with the AH, yet the TMS results indicate contralateral CMPP to each hand. Both subjects #4 and #7 present lower FA in the CST descending from the affected hemisphere (compared to their less affected) indicating a reduced maturation of this tract. The other two participants with white matter damage and relatively large lesions (as determined by their RS) did not present any trackable ipsilateral CMPP. Contralateral CMPP could not be tracked either, which might be due to i) a large shift in the motor cortex location or ii) the threshold to evoke an MEP was above the maximum electric field strength determined for safe use in this study. Since a systematic search for the optimal location did not provide any location to evoke an MEP, the latter reason is more probable. In fact, failure to evoke an MEP due to high MEP thresholds has been shown as a result of the immaturity of the corticospinal pathways in typical children that decreases with age (Nezu et al., 1997).

FA values of the CST were relatively low for subject 2 compared to the other participants. One explanation might be a lack of maturation in this area due to the young age of the participant (7 years). A levelling of the FA values has been shown for typical children above 7 years of age following a steep increase in younger years (Yeo, Jang, & Son, 2014). Interestingly however, subject #2 displayed higher FA in his affected hemisphere as opposed to his less affected hemisphere. Likewise, the CMCT was faster in the affected hemisphere. This child, while having a clinical history of hemiparesis, with relative hypotonicity and weakness of the right side, showed some signs of mild dyskinesis, presenting a more diffuse white matter injury on the left side.

The midbody of the CC is typically the region of information exchange between primary motor cortices (Wahl et al., 2007). Compared to TDC of the same age (Uda et al., 2015), the three children present similar FA values in the midbody and reduced values in the genu and splenium. This indicates that the intrahemispheric exchange is reduced between the prefrontal and the occipital regions. Unfortunately, no DTI results were obtained from subject #8. The participant exhibited uncoupling of the bimanual squeezing pattern in the fMRI task which might be an indication of a (partial) interruption of the transcallosal information exchange (Kennerley et al., 2002). The resting state fMRI based on seeds from the active task supports this assumption since the connections were only located within one hemisphere.

Children with Grey Matter Lesions

Participants with grey matter lesions on the MRI (subjects #1, #3 and #6) also presented the highest RS. In addition, motor impairments were comparably large (MACS II and III), which matches the results of larger scale studies (Arnfield et al., 2013). Scores on the JTTHF for the AH and CHEQ R1 also indicated poor uni- and bimanual function. Subject #6 also demonstrated reduced LAH functionality when looking at JTTHF scores. The participant was also reported as being able to perform only 10 out of the 29 tasks on the CHEQ independently (and only 6 of them with the help of his AH). The performance during the bimanual box-opening task revealed that this participant showed particular problems in the AHC with increased values of TC and TP, suggesting a strong bimanual interference when his AH was leading (Rudisch et al., 2016).

An investigation of the CMPP showed contralateral projections with slower CMCT to the AH in subject #1. Subject #3 exhibited ipsilateral projections from the less affected hemisphere to the AH, yet bilateral activation was found in the AH condition on the fMRI. Furthermore, this child did not show any evidence of MMs, contrary to the literature suggesting an association with ipsilateral CMPP and MMs. Markedly similar FA values in the CST of the affected and less affected hemisphere (which were even slightly higher in the affected hemisphere) were found in subject #3 despite the ipsilateral CMPP the TMS results revealed. These rather inconsistent findings may represent testing artefacts (i.e. variations in task demand with the TMS demanding a sustained grip pressure of the first dorsal interosseous muscle and the fMRI task demanding repetitive but minimal grip force changes) and differences in the MEP activation thresholds.

While no trackable connections to the AH were detected in subject #6, this might be due to the large size of the lesion or the immaturity of the CST (Nezu et al., 1997). Unfortunately, no fMRI or DTI results were obtained from subject #6, due to anxiety and fatigue, which might have helped to further investigate the patterns of activation or the structural impairments that might result in an extensive bimanual interference.

Child with Brain Maldevelopment

Only participant #5 presented a maldevelopment of the brain as the underlying pathology of the motor impairment. Motor impairments vary largely among individuals in this category and are often reported as more severe (Arnfield et al., 2013). The subject in this study appeared to have the lowest functional impairment within the group.

The participant did not show any major differences between hands in the performance of the fMRI motor task. Visually, one can clearly see large areas of activation around the central sulcus without any bilateral activation (Fig. 7.1). The number of active voxels is considerably higher in both hemispheres. Furthermore on the resting state fMRI, one can observe rather diffuse patterns of connectivity with the areas in the frontal and occipital lobes. It might be possible that motor functions are achieved by using functional connections more broadly across the cortex, due to the loss of grey matter occurring in children with polymicrogyria. Alternatively, additional learning difficulties influence strategies for learning and hence support or impede motor behaviour depending on the task requirements.

7.5 Summary and Reconciliation

It is far from being fully understood in what manner the different types of brain impairments evidenced in early childhood motor disorders affect bimanual hand use. Even though this chapter only explores a few single cases, a variety of different neuroimaging techniques, as well as neurophysiological and behavioural measures provide a rich dataset that makes it possible to understand the individual characteristics of bimanual impairment. While both the nature and the timing of unilateral brain insult can be seen to influence the severity of the unimanual function, the capacity to acquire and perform bimanual tasks appears to be influenced by multiple factors, including the inter-hemispheric connectivity as well as personal and environmental factors. The results obtained in this chapter may help identify additional factors for future research, particularly the interaction between brain injury, neuroplasticity and hand function. In addition, the study shows some of the shortcomings of the different methods used to investigate characteristics of the brain impairment. It was for example impossible to clearly determine the CMPP in 4 out of 9 participants. This shows the necessity of using various methods including neuroimaging, electrophysiological and behavioural measures to obtain a clearer picture about the characteristics of brain impairment. Further research is needed to explore how the different neuropathologies impact on the ability of the children to learn and acquire bimanual motor skills in order to provide more tailored interventions for children with uCP.

8 Overall Discussion & Conclusion

The overall goals of the present research project were directed towards a better understanding of the difficulties associated to bimanual coordination in children with uCP. The literature review (Chapter 2) has shown that bimanual coordination itself represents a special case of motor control relying heavily on the exchange of information between the two hemispheres (via the CC) and subsequent processing (e.g. in the supplementary motor area). Continuous bimanual in- and anti-phase finger movements have been used to prove the assumptions of the dynamical systems motor control theory. In daily life however, bimanual movements do not resemble these experimental models but rather have a role-differentiated nature. Nonetheless, the synergistic manner in which the two hands work cooperatively supports the assumptions of the dynamical systems theory. Guiard (1987) has hypothesised an asymmetric division of labour in which one hand, usually the non-dominant, acts as a frame of reference which the other hand adjusts to. During a bimanual box-opening task, it has been shown that with increasing age, the non-dominant hand is more likely to be used for the temporally earlier segment (Birtles et al., 2011; Kazennikov et al., 2002) indicating that the non-dominant hand provides a temporal frame of reference (i.e. the second hand is adjusted temporally to warrant a start of movement which is not too early and not too late).

In children with uCP, bimanual movement skills are often impaired as a consequence of a predominantly unilateral disorder (of a non-progressive nature) affecting the motor systems of the CNS (Chapter 3). These are attributed to a variety of pathologies affecting different areas of the brain (e.g. white matter or grey matter) to a varying extent resulting in differences in the characteristics of motor impairments. Various standardised assessments have been developed to investigate the manual function in children with uCP (Chapter 4). These predominantly assess the functionality of the AH in uni- or bimanual movement tasks. Experimental tasks measuring hand kinematics have been used to explore cooperative characteristics in children with typically developing children and those uCP (Birtles et al., 2011; e.g. Hung et al., 2004; Utley & Sugden, 1998). In order to investigate bimanual coordination and the extent to which children with typical development and those with cerebral palsy conform to Guiard's theory, the first study in this section defined a method of measurement of the kinematics of bimanual coordination. A bimanual box-opening task requiring role differentiated hand use (i.e. opening a box with one hand and pressing a button inside with the other) was thus adapted for this research project in order to investigate bimanual movement coordination in typical developing children and those with uCP as well as performance changes attributed to motor learning in children with uCP.

In a developmental study (Chapter 5), the bimanual box-opening task performance of children of different age groups, reflecting peak times in the development of the CC and prefrontal areas, was investigated. Performance was seen to stabilise from 7 years of age, a time which typically coincides with the end point of a phase of rapid development of the CC structures. This emphasises the importance of the interhemispheric transfer of information in order to facilitate the sequencing (or synergistic behaviour) of both hands. The improvement in spatial accuracy (during the bimanual task) was, on the contrary, especially pronounced in the group of adolescents (from 10 years of age); an age where maturation of the frontal cortex peaks (Gogtay & Thompson, 2010). This is indicative of an increased ability of the two hemispheres to process the afferent information (from the opposing side) without producing redundant movement (or bimanual interference). However, high performance variance within the different age groups may reflect considerable individual differences in the timing of development.

In a second study (Chapter 6), the performance of children with uCP on the box-opening task was investigated in relation to the individual levels of impairment and the measures of uni- and bimanual function. Performance was strongly affected by the extent of the functional impairment of the AH. Especially the condition where the AH was used to open the lid seemed to aggravate the formation of synergistic behaviour between the two hands. The more technically demanding a subtask for a movement (the lid-opening task is more demanding than the trigger press for these children), the more the task performance was affected by the level of impairment of the AH. It follows that appropriate bimanual coordination (e.g. using the non-dominant or AH as a frame of reference to facilitate cooperation) is only possible if both hands have the capacity to meet the demands of the task. As a consequence, focusing on the functionality of the affected hand, e.g. by applying a CIMT therapy approach in the beginning of a therapy, might be useful in order to initially increase the skills of the AH with the bimanual training following. Another finding that resulted from this study was that a subgroup of children showed excessive interference in their LAH when performing the more technically demanding lid-opening task with their AH. The resulting loss of control over the LAH seems to be a particular challenge for bimanual tasks. Two possible causal factors were hypothesized that lead to bimanual interference in these children: i) ipsilateral CMPP from the less affected hemisphere to the AH with crosstalk between the two regions due to close proximity of the areas innervating the AH and the LAH and ii) lack of suppression of interhemispheric crosstalk due to reduced functionality of the premotor cortex and supplementary motor area of the LAH.

In order to relate specific neuropathologies to the characteristics of bimanual motor problems, a multiple case study was conducted in which the results of multiple neuroimaging and behavioural measures were analysed simultaneously (Chapter 7). The results showed some interesting findings regarding the impact of the neuropathology type (i.e. white or grey matter lesions or maldevelopments) on motor impairment. Particularly children with impaired grey matter showed higher (uni- and bimanual) functional limitations than those with grey matter impairments. Only one child presented a brain maldevelopment. Contrary to typical presentation of more severe impariments in children with brain malformations, this child showed rather good functionality. Only one child in the study showed ipsilateral CMPP. However, this child did not show MMs in the fMRI motor task nor evidence of bimanual interference during the box-opening task; again contrary to the literature. None of the participants showed clear MMs during the fMRI squeezing task and only one child presented bimanual interference during the bimanual box-opening task. The child with bimanual interference did however not show any ipsilateral CMPP during the TMS nor were contralateral CMPPs tracked either, suggesting a high threshold for motor evoked responses for the AH. These findings are somewhat inconsistent with the hypothesis that ipsilateral CMPP are the basis of MMs in children with uCP (Balbi et al., 2000; Kanouchi et al., 1997). While this might be true for some individuals, other reasons are also conceivable such as the reduced capability to inhibit the excitatory information exchanged through the CC. It is thus necessary to further investigate the possible mechanisms for the existence of MMs in children with uCP.

8.1 Limitations

A number of limitations should be noted with respect to the studies in this thesis. Assumptions made about the developmental status of the CNS (developmental study in Chapter 5) were not directly measured. Development of the CC and prefontal cortex was rather assumed to follow typical trajectories and age ranges were selected that reflect peak periods of development. While the relation between age and peak periods of development might work on a group level, there is some intra-individual variability which might lead to an earlier or later development. Pairing measures of individual performance results with neuroimaging measures that evaluate the integrity of the networks attributed to the bimanual movements is thus important for future research.

The two distinct behavioural patterns shown in Chapter 6, i.e. presence and absence of bimanual interference, were assumed to be attributed to differences either in the reorganisation of the CMPP (i.e. ipsilateral vs. contralateral projection patterns) or by a lack of suppression of interhemispheric crosstalk. The finding of bimanual interference was not expected and was thus not systematically investigated e.g. by comparing neurophysiological and neuroimaging findings of those with and without bimanual interference. Indeed neither was the relation of neuropathologies and behavioural characteristics subject to investigation in Chapter 7. The small sample size and missing data only allowed for a multiple case investigation. Carefully selected larger samples are essential to confirm the preliminary findings from this study, but may be difficult to achieve.

8.2 Future Directions

This thesis focuses on the development of bimanual coordination and the implications of unilateral motor disorders form a dynamical systems perspective. Especially with respect to motor learning based therapeutic interventions (such as CIMT or HABIT), incorporating this perspective, including study of the dynamical interaction between the child's capabilities, task demands and environmental contexts, might provide a useful basis to investigate changes in motor skills in children with uCP. Observing the different time-scales in which learning occurs (e.g. within session, between sessions) can help identifying individual learning rates and goal achievement. This would require frequent measurement of performance. Such individual indicators of motor learning can then be related to neuropathological characteristics. Possible relations between the two might facilitate more development of more individualised therapy interventions in the future.

8.3 Conclusion

In conclusion, this thesis provides additional evidence of the interaction between the two hands in the control of bimanual tasks and impact of maturation and neuropathology on bimanual coordination. Changes in performance in typical children were seen to correspond to the maturation of the CC and prefrontal cortex for control of bimanual movement. It was also shown that uCP does not necessarily have a particularly detrimental effect on bimanual skills, especially in children with lower levels of impairment of the AH where the coupling of the two hands can be very similar to that of TDC. Poor control of the AH in children with increasing levels of impairment however, also seems to have an impact on the control of the LAH in bimanual situations, severely limiting the ability to perform bimanual tasks.

One of the main insights that follow the study of individual neuropathologies emphasises the individuality across the various cases of individuals affected by uCP; reflecting more singularities than communalities. This should be acknowledged in research as well as for therapy planning. A wider range of differential diagnoses within uCP is important to identify variables that increase understanding of the various singularities and identify communalities for the categorization of subgroups in the future.

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APPENDIX A Relevant Publications

A-1: Rudisch J, Butler J, Izadi H, Birtles D, Green D (accepted for publication on 04.12.2016 in Journal of Motor Behaviour). Developmental Characteristics of Disparate Bimanual Movement Skills in Typically Developing Children

A-2: Rudisch J, Butler J, Izadi H, Zielinski IM, Aarts P, Birtles D and Green D (2016) Kinematic parameters of hand movement during a disparate bimanual movement task in children with unilateral Cerebral Palsy. *Human Movement Science* 46: 239–250

APPENDIX B Ethical Approvals

B-1: Oxford Brookes University Research Ethics Committee (Ref 130713) Approval for Collecting Data on the Bimanual Box-Opening Task in Typically Developing Children

OXFORD
BROOKES
UNIVERSITY

Julian Rudisch
PhD Student
Department of Sport and Health Sciences
Faculty of Health and Life Sciences
Oxford Brookes University
Marston Road Campus

16 March 2015

Dear Julian

UREC Registration No: 130713
Bimanual Motor Development in Children – identifying patterns of typical motor co-ordination

Thank you for your email of 16 March 2015 requesting an amendment to the original study approved by UREC on 12 March 2013.

I confirm that Professor Jenny Butler will also be gathering data for the study during the Science Bazaar and I give Chair's approval for this change. The UREC approval remains the same as the original study, so until 12 March 2016.

Should the recruitment, methodology or data storage change from your original plans, or should any study participants experience adverse physical, psychological, social, legal or economic effects from the research, please inform me with full details as soon as possible.

I wish you continued success with your research.

Yours sincerely

Hazel Abbott
Chair of the University Research Ethics Committee

cc Louise Wood, UREC Administrator
Jenny Butler, Co-investigator
Dido Green, Supervisory Team

UNIVERSITY RESEARCH ETHICS COMMITTEE, FACULTY OF HEALTH AND LIFE SCIENCES

Headington Campus Gipsy Lane
Oxford OX3 0BP UK

Tel: 01865 482639
heabbott@brookes.ac.uk

B-2: National Research Ethics Committee (ref 10/H0804/40) Approval for the Hand-Arm-Bimanual Intensive Therapy Study in the UK Including Ethical Approval for Collecting Data on the Bimanual Box-Opening Task, Neuroimaging, Transcranial Magnetic Stimulation and Behavioural Assessments

NRES Committee London - London Bridge
Skipton House
80 London Road
London
SE1 6LH

Tel: 0207 972 2559
Fax: 0207 972 2592

27 May 2014

Dr Dido Green
Honorary Consultant Paediatric Occupational Therapist/Lecturer in Occ Therapy
Honorary, Guy's St Thomas' NHS Trust/ Tel Aviv University
Evelina Children's Hospital, 6 Floo
St Thomas' Hospital
Westminster Bridge Road
SE1 7EH

Dear Dr Green

Study title:	**A study of the effectiveness of a Hand-Arm Intensive Bimanual therapy (HABIT) using magic tricks for children with hemiplegia**
REC reference:	**10/H0804/40**
Amendment number:	**Am02: Inclusion of new members**
Amendment date:	**05 May 2014**
IRAS project ID:	**52541**

The above amendment was reviewed at the meeting of the Sub-Committee held on 27 May 2014.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation to include new members to your research team with two additional investigations.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering letter on headed paper		12 May 2014
GP/consultant information sheets or letters	Summer Camp letter v1	26 April 2014
Notice of Substantial Amendment (non-CTIMP)		05 May 2014
Other [List of revisions]		05 May 2014

Other [CV's of new research staff x 6]		
Other [Updated Parent Letter]	1	26 April 2014
Participant consent form [Updated]	1	26 April 2014
Participant information sheet (PIS) [Patient]	2	26 April 2014
Participant information sheet (PIS) [Updated Child (MRI)]	1	26 April 2014
Participant information sheet (PIS) [Updated Parent and Child (Additional EEG)]	1	30 April 2014
Participant information sheet (PIS) [Updated Parent (MRI)]	1	26 April 2014
Participant information sheet (PIS) [Child]	1	26 April 2014
Research protocol or project proposal	revised	05 May 2014

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

10/H0804/40:	**Please quote this number on all correspondence**

Yours sincerely
PP

Professor David Bartlett
Chair

E-mail: nrescommittee.london-londonbridge@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Dr Jean-Pierre Lin, Guy's and St Thomas' NHS Foundation Trust*

NRES Committee London - London Bridge

Attendance at Sub-Committee of the REC meeting on 27 May 2014

Committee Members:

Name	*Profession*	*Present*	*Notes*
Professor David Bartlett	Honorary Consultant	Yes	
Mrs Tamsin Brownell	Lay Member	Yes	

B-3: Sint Maartenskliniek Nijmegen Research Ethics Committee (ref 2014/12/011B/MV/eb) Approval for Collecting Data on the Bimanual Box-Opening Task in Children with Unilateral Cerebral Palsy in NL

gespecialiseerd ziekenhuis voor
orthopaedie • reumatologie • revalidatiegeneeskunde

Revalidatiecentrum

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Aan:
Mw. dr. P. Aarts, senior onderzoeker, hoofd PE PRB
Peuters en ZOOM-IN

Datum	Referentie	Doorkiesnummer	Contactpersoon
17 december 2014	2014/12/011B/MV/eb	(024) 3659188	rmt.secretariaat@maartenskliniek.nl

Betreft
"Bimanual Motor Development in children : **identifying patterns of typical motor coordination**"

Geachte mevrouw Aarts,

De Toetsingscommissie van het revalidatiecentrum is op 8 december jl. bijeen geweest. Tijdens deze bijeenkomst is het door u opnieuw ingediende onderzoeksvoorstel "Bimanual Motor Development in children : identifying patterns of typical motor coordination" besproken.

De toetsingscommissie heeft op basis van de aan haar toegezonden informatie de verschillende criteria doorlopen. Naar aanleiding hiervan heeft er op 15 december een gesprek met u plaatsgevonden. De toetsingscommissie heeft besloten in te stemmen met de start van het onderzoek op voorwaarde dat er een controlegroep wordt meegenomen in het onderzoek zodat de onderzoeksvraag adequaat beantwoord kan worden. U gaf aan dat dit wordt gedaan door de partners in Engeland.

Veel succes met de uitvoering van het onderzoek,

met vriendelijke groet,
namens de Toetsingscommissie Revalidatie,

Dr. M. Vos-van der Hulst,
Voorzitter Toetsingscommissie Revalidatie

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