Hand function in children and in persons with neurological disorders

Aspects of movement control and evaluation of measurements

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To God be the glory
for all He has done
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ABSTRACT

Hand function is of great importance in the many daily activities that require well-coordinated hand and arm movements. Measurement of hand function is an essential element in the rehabilitation process, in order to facilitate medical diagnosis and determine developmental stages, functional levels, and the efficacy of treatment interventions. Basic requirements for any measurement used in clinics are that they are easy to use, relevant to the function being assessed, and valid and reliable. When scrutinizing the literature on hand function, important gaps were found with regard to measurement. For example, the reliability of grip strength with the Grippit in children has yet to be determined, and there are few evaluations of hand function measurements in Charcot-Marie-Tooth disease (CMT). Furthermore, laboratory measurements of hand function, which have the potential to provide more detailed information and insight into hand control, such as the role of the cerebellum in reactive grip control – have not been fully explored.

The overall aim of the thesis was to achieve more knowledge on hand function; on the evaluation of measurements in different target populations; and on movement control of the hand. In the first study, the aim was to evaluate the test-retest reliability of the peak and sustained grip strength with Grippit in a sample of healthy children (n=58, 6-, 10- and 14- y-olds). This was followed by two studies examining hand function in an adult sample (n=20) diagnosed with CMT. The test-retest reliability of grip and pinch strength using Grippit, sensation with the Shape Texture Identification test (STI) and dexterity with the Box and Block Test (BBT) and Nine-Hole Peg test (NHP) were studied. The impact of the disease on daily life, measured with the Disability of the Arm, Shoulder and Hand questionnaire (DASH), and correlations between disability and various aspects of hand function, were also explored in this condition. The aim of the fourth study was to examine grip force response to unpredictable loadings of an object held in a pinch grip in subjects (n=9, 22-48 yrs) who had been diagnosed with a cerebellar lesion, compared with a healthy control group (n=11).

The first study showed that test-retest reliability was good for both peak and sustained grip strength in healthy children. The mean and best of three trials were equally reliable, but differences in reliability were detected within different age groups. For example, the peak grip strength, best of three trials, was more reliable for the 6-y-olds (intraclass correlation coefficient (ICC)=0.96, standard error of measurement in percentage (SEM%)=6.3) and 14-y-olds (ICC=0.96, SEM%=5.2) compared with the 10-y-olds (ICC=0.78, SEM%=12.5). In the second study, evaluating measurements of hand function in subjects with CMT, grip strength proved to be reliable (ICC=0.99, coefficient of repeatability (CR)=26.7 N, coefficient of variation (CV)=6.6 %), but pinch strength was
less reliable. The reliability was also good for the BBT (ICC=0.95, CR=11.5 blocks/min, CV=8.4%) and the NHP (ICC=0.99, CR=4.3 s, CV=3.9 %). However, a bias towards higher values was noted on the second test occasion with the BBT. The reliability of the STI test (kappa=0.87) was also very good in subjects with CMT. A limitation in this latter test was noted in terms of its ability to describe subjects either performing very well or very poorly. The results of the third study showed that hand function in CMT was reduced (p<0.001) to about 60% of that in healthy controls in each of the separate outcome measures, as well as by a constructed summary index of hand function. The median DASH score was 38.8 (range 0-66.7) and was clearly related to hand function (r=0.64-0.83). The results of the final study in subjects with cerebellar lesions showed that the ipsilateral hand had delayed and more variable response latencies e.g. 278±166 ms for loads delivered at 2 N/s, compared with healthy subjects (HS) 80±53 ms (p=0.005). The cerebellar subjects also used a higher pre-load grip force with the ipsilateral hand (1.6±0.8 N) than the HS (1.3±0.6 N (p=0.017)). Even the contralateral hand in subjects with unilateral cerebellar stroke showed a delayed onset of the grip response.

In conclusion: Grip strength assessment in children with Grippit results in good reliability for peak and sustained grip strength, although the 10-γ-olds were less reliable. In CMT the tested instruments can all be used to evaluate hand function, but certain factors, such as the number of trials used should be taken into consideration. The CMT subjects' hand function was reduced and correlated with their self-experienced disability. However, clinicians should be aware that patients might score lower than expected on DASH, possibly due to a long process of adaptation. Cerebellar lesions can impair the reactive grip control in both the ipsilateral and the contralateral hand. These investigations have thus, as intended increased the knowledge of hand function. The studies have evaluated some measurements in different samples, which will help clinicians testing hand function.

Keywords: cerebellum, disability, hand function, hereditary motor and sensory neuropathies, latency, motor control, reactive control, reproducibility, sensation, strength
Handfunktion är av stor betydelse vid många dagliga aktiviteter som kräver att hand och arm kan koordineras väl. Mätning av handfunktion är en viktig del av rehabiliteringsprocessen vid diagnosering, bestämning av funktions- och utvecklingsnivå samt vid utvärdering av behandling. Basala krav på mätinstrument som används i klinik är att de är lätt att använda, relevanta för den funktion som ska mätas och att de är valida och reliabla. Vid litteraturgenomgång identifierades viktiga luckor kring olika mätinstrument. Till exempel saknades reliabilitetstesting av handstyrka med Grippo hos barn och det finns få mätinstrument som värderar handfunktion hos personer med Charot-Marie-Tooths sjukdom (CMT). Dessutom kan mätningar av handfunktion i laboratorium ge mer detaljerad information och därmed insikt om hur handen kontrolleras t ex kring lillhjärnans roll vid reaktiv greppkontroll.

Det övergripande syftet med avhandlingen var att få fördjupad kunskap kring rörelsekontroll av handen samt att utvärdera metoder för att mäta handfunktion i olika grupper. Den första studien syftade till att värdera test-retest reliabiliteten hos Grippo för handstyrka i en grupp friska barn (n=58, 6-, 10- och 14-åringar). Därefter följde två studier som undersökte handfunktion hos vuxna personer med CMT (n=20). Test-retest reliabilitet av styrkan i handgrepp och pinchgrepp med Grippo, känsel med Shape Texture Identification test (STI) och koordination med Box and Block Test (BBT) och Nine-Hole Peg test (NHP) studerades. Självskattningsformuläret Disability of the Arm, Shoulder and Hand questionnaire (DASH) användes för att undersöka hur sjukdomen påverkade det dagliga livet. Dessutom studerades korrelationerna mellan DASH och några aspekter av handfunktion hos personer med CMT. Syftet med den fjärde studien var att undersöka gripkraftssvar vid oförutsägbara belastningar av ett föremål som greppades mellan tummen och pekfingret hos personer med stroke i lillhjärnan (n=9, 22-48 år) jämfört med en kontrollgrupp med friska personer (n=11).

Studie I visade att test-retest reliabiliteten var god för handstyrka hos friska barn, både maximal styrka och uthållighet. Medel och bättre av tre försök var lika reliabla men skillnader i reliabilitet upptäcktes mellan åldrarna. Till exempel var maximal styrka, bättre av tre försök, mera reliabelt hos 6-åringar (ICC=0.96, SEM%=6.3) och 14-åringar (ICC=0.96, SEM%=5.2) jämfört med hos 10-åringar (ICC=0.78, SEM%=12.5). I den andra studien undersökte reliabilitet vid mätning av handfunktion hos personer med CMT. Handstyrka var reliabelt (ICC=0.99, coefficient of repeatability (CR)=26.7 N, coefficient of variation (CV)=6.6 %) men styrkan i pinchgreppet var mindre reliabel. Reliabiliteten var också god för BBT (ICC=0.95, CR=11.5 kuber/min, CV=8.4%) och NHP (ICC=0.99, CR=4.3 s, CV=3.9 %). För BBT fanns dock en bias med bättre värden vid andra testtillfället. Reliabiliteten för STI test (kappa=0.87) var också
mycket god hos personer med CMT. En begränsning med detta test var förmågan att skilja mellan olika funktionsgrader. Hos personer med CMT var handfunktionen nedsatt (p<0.001) till ungefär 60% av kontrollernas handfunktion vilket resultatet från den tredje studien visar. DASH medianen som var 38.8 (range 0-66.7) korrelerade med handfunktionen (r=0.64-0.83). Studie IV visade att försökspersoner med skador i lillhjärnan hade fördöjda och mer varierade svarsutmaningar t ex 278±166 ms för belastningar som gavs med 2 N/s, jämfört med friska 80±53 ms (p=0.005). Innan belastningen startade greppade också personer med lillhjärnsskada med högre kraft med den ipsilaterala handen, 1.6±0.8 N jämfört med friska, 1.3±0.6 N (p=0.017). Hos personer med unilateral stroke i lillhjärnan var starten av gripkraftssvaret även fördöjt för den kontralaterala handen.

# ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>Amplitude set</td>
</tr>
<tr>
<td>BBT</td>
<td>Box and Block Test</td>
</tr>
<tr>
<td>CMT</td>
<td>Charcot-Marie-Tooth disease</td>
</tr>
<tr>
<td>CR</td>
<td>Coefficient of Repeatability</td>
</tr>
<tr>
<td>CS</td>
<td>Cerebellar Subject (s)</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
</tr>
<tr>
<td>DASH</td>
<td>Disabilities of the Arm, Shoulder and Hand questionnaire</td>
</tr>
<tr>
<td>GFMI</td>
<td>Grip Force Modulation Index</td>
</tr>
<tr>
<td>HFI</td>
<td>Hand Function Index</td>
</tr>
<tr>
<td>HS</td>
<td>Healthy Subject (s)</td>
</tr>
<tr>
<td>ICC</td>
<td>Intraclass Correlation Coefficient</td>
</tr>
<tr>
<td>ICF</td>
<td>International Classification of Functioning, disability and health</td>
</tr>
<tr>
<td>NHP</td>
<td>Nine-Hole Peg test</td>
</tr>
<tr>
<td>R</td>
<td>Rate set</td>
</tr>
<tr>
<td>SEM</td>
<td>Standard Error of Measurement</td>
</tr>
<tr>
<td>SEM%</td>
<td>Standard Error of Measurement in percentage</td>
</tr>
<tr>
<td>STI</td>
<td>Shape Texture Identification test</td>
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ORIGINAL PAPERS


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INTRODUCTION

General introduction
Hand function is an important part of the human movement repertoire, and is essential in many activities that demand well-coordinated hand and arm movements. The hand can be used to communicate through gestures and sign language, and can be used to show love. In daily activities like cooking, driving, or combing one’s hair, the hand enables us to manipulate different objects and use tools. At work, the hand function is essential, from the grip strength that builders need to the extremely fine coordination required for microsurgery. Nor can we forget the role of the hand in art like painting and playing music. How the hand works in healthy persons is not fully understood in detail, and it is an exciting challenge to understand how the nervous system can control such a complex system.

There is no consensus on the most appropriate theoretical models for studying hand function. Human hand function has been conceptualized by Lynnette and Lederman along a continuum ranging from activities that are essentially sensory in nature to those that have a strong motor component (1). This view has facilitated the understanding of the neurophysiological control of the hand - that is how much motor and sensory function can contribute to different activities. However, Kimmerle et al. developed a functional repertoire model of the hand that identifies four main components relating to hand function: personal constraints, hand roles, hand actions and task parameters (2). The model was developed to serve as a knowledge base to guide the clinician during the assessment process and in the development of therapies (2). Another way to conceptualize hand function assessment would be to use the World Health Organization’s framework, the International Classification of Functioning, Disability and Health (ICF) (3, 4). It is a broad classification that includes many components, from body structures to environmental factors, but the focus here will be on the ICF as applied in the evaluation of the Disabilities of the Arm, Shoulder and Hand questionnaire (5). The ICF addresses three dimensions of the consequences of a decrement in health, so-called disability: impairment, activity limitation, and restrictions in social participation (3). Impairments include problems in body function or body structure as a significant deviation or loss. Activity limitations are difficulties an individual may have in carrying out an activity. Participation restrictions are problems an individual may have in involvement in life situations. The three dimensions of the ICF framework are clinically applicable, and they can facilitate our understanding of the consequences of diseases or injuries affecting the hands. Another advantage of the ICF is that it is used more and more around the world, in
research and clinics. All models can contribute to our understanding of hand function, but the ICF framework is the focus of this work.

There is also no consensus on what an evaluation of hand function should include. Abilities that can be measured include coordination, grip and pinch strength, sustained strength, quality aspects when performing tasks, work abilities, sensation, timing, one-hand and two-hand activities, the experience of limitations in daily life, etc. The basic requirements for any measurement used in clinics are that they are easy to use, relevant to the function being assessed and valid and reliable. More detailed measurements of hand function, such as experimental laboratory measures of control and precision, can give additional information regarding the motor control of the hand. It is an advantage if the different qualities of the measurements are evaluated in specific groups like age-related and diagnosis-related groups.

Reduction of hand function through injury or disease can lead to decrement in health, resulting in activity limitations and restrictions in social participation. In neurological rehabilitation it is obvious that patients need hands that function well - for example, to manage personal care. Measurement of hand function is an essential element in the rehabilitation process, in order to facilitate medical diagnosis and determine developmental stages and functional levels, and to plan and evaluate treatment interventions.

Motor control of the miraculous human hand

Adequate motor control of the hand is crucial for different reasons, as exemplified in the beginning of the introduction. Motor control can be defined as the ability to regulate or direct the mechanisms essential to movement (6).

The hand is indeed a highly specialized part of the human body. It consists of 27 bones and 29 muscles (38 when subdivisions are counted) that control the hand (1). Voluntary movements require contraction and relaxation of muscles, recruitment of appropriate muscles, appropriate timing, and sequencing of muscle contraction and relaxation (7). When moving the hand, these aspects of this complex anatomical system need to be controlled, including all muscles and joints with more than 20 degrees of freedom. Experimental evidence indicates that the simultaneous motion and force of the fingers is characterized by coordination patterns that reduce the number of independent degrees of freedom to be controlled (8). The motor and sensory innervations of the hand are provided by the radial, median and ulnar nerves (9). The areas of the cerebral cortex that contribute directly to the control of hand movements include the primary motor cortex, the supplementary motor area, the presupplementary motor area, and the premotor cortex (1). The motor
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cortical areas receive inputs from subcortical motor areas such as the basal ganglia and the cerebellum (1). Finger movements are controlled by a highly distributed network in the brain rather than by functionally and spatially discrete groups of neurons controlling each finger (8).

A structure of particular interest is the cerebellum. It contains 10% of the total volume of the brain, but more than half of its neurons (10). Forty times more axons project into the cerebellum than exit from it (10). The cerebellum is involved with planning and executing movement, regulation of postural control, and serving in a comparator and corrector role (11). Its unique construction and connections allow it to upgrade and integrate information about the outside world continuously with information about body position, movement, and signalling along central motor pathways (12). However, the specific characteristics of the cerebellum, and how it contributes in detail to motor control, are still largely unknown. Two recent reviews conclude that there is no consensus on how the cerebellum operates (13, 14). In relation to control of the hand, the contribution of cerebellar regions to appropriate scaling and timing of the grip force profile is poorly understood (15). Recent studies indicate that, in addition to exerting a unilateral control, the cerebellum also controls contralateral movements (16-19).

The number of ways that objects of varying sizes and shapes can be grasped is nearly infinite; however, a broad classification system for grasp has evolved that makes it easier to observe (20). Prehension refers to those activities in which the hand reaches to grasp an object (1). Prehension can be categorized as either power grip or precision handling (20). There are three varieties of power hand grip: cylindrical, spherical, and hook grip (20). There are also varieties of pinch grips: key pinch (also named lateral pinch), tip pinch (also named two-point pinch), and three-point pinch (also named three-jaw chuck pinch or tripod pinch) (21). When studying grip control in experimental studies, the concept of prehension has been divided into reaching for and grasping an object (1). Reaching studies have focused on the kinematic features of the hand and arm movements but grasping studies generally start at the point of contact with the object and concentrate on analyzing how, as an object is grasped and perhaps lifted, the forces produced by the fingers are adapted to the properties of the object (1).

Cutaneous feedback is crucial to set, maintain and grade the grip control (22-24). The grip forces produced when lifting an object in the hand are precisely coordinated in space and time, and are strong enough to prevent the object from slipping between the fingers (25). Human grip reactions are dependent on the size, weight, and friction of the object grasped (26). A healthy grip force behaviour includes a) efficient force scaling to the intrinsic requirements of the manipulative intention and the extrinsic mechanical properties of the object to be manipulated, and b) precise temporal coupling between grip and load force profiles, with grip force
being modulated synchronously with the movement-induced load fluctuations (27).

Grip control differs between gripping and holding a passive object, and gripping and holding an active object (28, 29). In the first situation one relies on predictive control mechanisms (feedforward), but in the latter one relies more on reactive control mechanisms (feedback). Reactive control is thus more dependent on continuous sensory input due to unpredictable changes resulting from the object’s movements – for example, when holding a fishing rod (30).

**Measurements of hand function**

Clinical evaluation of the hand includes the integrity of the musculoskeletal system (range of motion and strength), sensory function, and functional capabilities of the hand (1). There is also value in measuring different dimensions according to the ICF, as has been shown, to model measurements of hand function (31). The aspects measured and the instruments used in our four studies are the focus in the sections that follow.

**Impairment dimension according to ICF**

**Strength**

The ability to generate sufficient force (strength) is essential to active upper limb movement and function (6). The regulation of grip force has a great impact on everyday activities such as unscrewing jars, zipping coats, or cutting with scissors (32). A loss in grip strength is associated with a number of different neurological and musculoskeletal conditions, and so an assessment of grip strength is generally included in hand evaluations (1). In research and clinical practice, grip strength is one of the most commonly assessed measures of function in health and disease. Grip strength testing is fast and easy to perform. It is recognized as a reliable method for strength evaluation, using various instruments in adults (33-36) and in children (37, 38). Two valuable reviews on grip strength testing are recommended: Innes 1999 (39) and Tyler et al. 2005 (40).

Apart from everyday clinical use, grip strength measures can also be used for health screening, since grip strength is positively correlated with fitness (41) and health (42). In children grip strength has been found to be positively correlated with motor function such as the ability to jump (43). Recently it has been shown that low grip strength in middle-aged and older adults was consistently associated with a greater likelihood of premature mortality, the development of disability, and an increased risk of complications or prolonged length of stay after hospitalization or surgery (44).
Many instruments can be used for measuring grip strength, such as hydraulic, pneumatic and mechanical instruments, and strain gauges (39). The hydraulic Jamar dynamometer is probably the most often used instrument for measuring grip strength, providing a cylindrical power grip (e.g. (35, 36, 38, 45, 46)). The Grippit dynamometer is a strain gauge instrument (cylindrical power grip) that is common especially in northern Europe, where it is frequently used in clinics and studies (47-51). While results from the Jamar and Grippit dynamometer are similar, the dynamometers are not interchangeable (52). One advantage of the Grippit instrument over the Jamar dynamometer is that it measures on a more sensitive scale, with the ability to discriminate better between individuals and between efforts (40). Another advantage of the Grippit instrument is that it provides endurance measures, estimating the sustained grip strength in 10 s. Most grip dynamometers only measure maximum grip strength. The reliability of grip strength with Grippit has not been evaluated in children, but it has been found to be good in healthy adults (51) as well as in patients with rheumatoid diseases (53) and strokes (49). Grippit can also be used to measure pinch strength when a thin handle is applied: however, the reliability of the Grippit instrument for pinch strength has not been previously addressed.

**Sensation**

Sensation testing can vary from simple screening tests to complex assessment of the type and distribution of sensory function (6). Since sensation strongly affects movement it is advisable to assess its integrity (6, 7). However, knowledge of the appropriateness of sensation tests is limited. There are, for example, not many studies on the psychometric properties of sensation tests. In one valuable review, however, the sensation tests were evaluated and classified into three groups (54).

1. Tests to assess the detection threshold. These tests address the question, “Can you feel the stimulus or not?”.
2. Tests to assess spatial discrimination. These tests assess the smallest spatial threshold at which localization or discrimination between different stimuli occurs.
3. Tests to assess object, shape or texture identification. These are tests that require identification of objects, shapes, and textures, and often require active movement for the tests to be done.

The only standardized tests where the psychometric properties had been evaluated were the touch threshold tests, Weinstein Enhanced Sensory Test (WEST), the Semmes-Weinstein Monofilament Test (SWMT), and the tactile gnosis test Shape Texture Identification (STI) test (54). However, the validity and responsiveness of the 2PD as a measure of spatial acuity was questioned (54).

Most clinical sensation tests have focused on the palmar surfaces of the distal phalanges because of the high concentration of tactile mechanoreceptors and the importance of this region to functional use of
the hand (1). This is also the case with the STI test, which was developed to quantify sensation in patients with peripheral nerve injuries (55). The reliability in persons with peripheral neuropathy was good (55).

**Dexterity**

A number of tests have been developed to evaluate the functional capacity of the hand, defined in terms of how the hand is used to perform a set of activities (1). The tests were developed after research showed that sensation tests could not be used to predict the functional capacity of the hand (1). Some functional tests, for example, measure the ability to pick up pegs (dexterity) at the ICF impairment level, but others evaluate the execution of everyday life activities of the hand at the ICF activity level (31). Dexterity is the ability to manipulate various objects using different prehension patterns quickly (6).

The Box and Block Test (BBT) is a simple, well-documented unilateral dexterity test that is easy to administer (56-58). The BBT’s reliability has been shown to be very good in elderly people with upper limb impairments (57) and in persons with strokes (58). A recent finding was that the BBT was the best predictor of the manual ability of children with cerebral palsy (59). The Nine-Hole Peg test (NHP) is one of the most commonly used tools for assessing dexterity (60). The reliability of the NHP has been evaluated in healthy people (60-62) and in persons with strokes (63) and Charcot-Marie-Tooth disease (64), with moderate to high results.

**Grip control experiments**

In order to understand in depth the motor control of the hand studies of the ability to grasp and manipulate objects are adequate. There are many ways and measures between which to choose. One point of view is to analyze the reactive grip control in experiments where a perturbation occurs in an unpredictable way, in contrast to the manipulative tests of passive objects such as BBT and NHP, or experiments evaluating predictive control – for example, when lifting a cup. To be able to analyze control of response latency, grip force, and changes in position, an apparatus that registers these aspects can be used. At the Department of Integrative Medical Biology, Section for Physiology in Umeå, many experiments have been done and the development of measurements and research continues. A testing apparatus, that make analyses of reactive grip control possible, has been constructed and used in many experiments e.g. (28, 65).
Impairment, activity and participation dimensions according to ICF

Apart from measuring strength, sensation, dexterity, and grip control at the dimension of impairment, it is important to measure the experience of limitation due to loss of hand function so that the therapist can better understand a patient. One such tool is the Disabilities of the Arm, Shoulder and Hand questionnaire (DASH) that was designed to quantify disability and symptom experience of people with upper-extremity disorders (66). Disability was defined by Verbrugge and Jette, in the context of the WHO’s International Classification of Impairments, Disability and Health (ICIDH), as difficulty in doing activities in any domain of life (67). The classification system of WHO has been developed from ICIDH to ICF. Recently DASH has been analyzed according to ICF (5). The DASH item scores were used to calculate separate scores for impairment, activity limitation, and participation restrictions, showing that all three dimensions are reflected in the questionnaire (5), thereby enabling a deeper insight into the results. DASH is a widely-used questionnaire for different populations of patients with injuries and diseases of the upper arm in many different countries. The Swedish version of the DASH is a reliable and valid instrument for patients with conditions that affect the upper extremity (68).

Evaluation of measurements

Reliability

The usefulness of measurements in clinical research and decision-making depends on the extent to which clinicians can rely on data as accurate, one important aspect is thus reliability (69). A reliable outcome measure is one that produces results that are accurate, free from error, consistent, stable over time, and reproducible (69, 70).

There are numerous ways to categorize and measure reliability, and the relative importance of each measure will vary according to the instrument (71) and the way it is intended to be used. The Standards for Educational and Psychological Testing, referred to in Kelly et al., list a variety of axioms on reliability, including two particularly important to clinical measurement: (1) a higher level of reliability is necessary when scores are to be used to make decisions concerning individuals rather than groups; and (2) a higher degree of reliability is necessary when scores are to be used to make decisions that have extreme and/or irreversible consequences (72). Both situations are common in clinics; reliability should thus be a key issue when selecting measurements. In research evaluating reliability, test-retest reliability intervals should be far enough apart to avoid fatigue and learning or memory effects, but close enough to avoid genuine changes in the measured variable (69). A retest score can
also be influenced by a subject’s effort to improve on the first score. This is especially relevant for variables such as strength, where motivation plays an important role (69).

One way to categorize the quantifiable reliability is to speak of relative and absolute reliability. Relative reliability examines the relationship between sets of repeated measurements and is measured with a correlation coefficient (73). A high correlation for scores across time would be indicative of low error and high reliability (74). Absolute reliability indicates the extent to which a score varies on repeated measurements (73). It is expressed in actual units or as a proportion of the measured values. In clinics, when judging whether a patient’s condition has changed, measures of absolute reliability are crucial. In reliability research it is important to have statistical measures of both relative and absolute reliability; however, often only relative reliability is calculated.

Validity

Measurement validity is the appropriateness, meaningfulness, and usefulness of the specific inferences made from test scores, not of the instruments or their scores themselves (72, 73). The validity of inferences is always a matter of degree, more accurate, or less accurate, but never perfect (71). Validity concerns whether the characteristic or theme is actually the one intended (74). Reproducible (reliable) results are necessary, but not sufficient, for valid inferences to be drawn (71).

As for reliability, the literature refers to many types of validity. In fact, validity is so complex that, over time, health services researchers have taken a seemingly endless variety of approaches to assessing it (72). Emerging paradigms replace prior distinctions of face, content, and criterion validity with the unitary concept ‘construct validity’ - the degree to which a score can be interpreted as representing the intended underlying construct (71). This approach underscores the reasoning that an instrument’s scores are only useful to the extent that they reflect a construct, and that evidence should be collected to support this relationship (71).

Hand function in the three samples

Any loss of function in the upper limb, regardless of the segment, ultimately translates into diminished function of its distal portion; the hand (20). Hand function is dependent on the nervous system functioning appropriately concerning both the sensory and motor nerves and the central control by the brain, cerebellum, and other regions. The nervous system can however ‘change’, either improving during development or being impaired due to disease/injuries like Charcot-
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Marie-Tooth disease or cerebellar stroke. These changes can affect the performance of the hand.

**Development of hand function in children**

Different theories of motor development have evolved over time, but current thinking suggests that development is a complex outcome of the maturation of multiple physiological systems in combination with the demands placed on children by the environment and by task-related experience (75).

To generate muscle force – e.g. grip strength in children – the nervous system’s recruitment of muscle fibers is a major factor, because the velocity of shortening depends on fiber-recruitment (76). Muscle fibers are activated by peripheral nerves. Already by the age of three, the myelin deposits in peripheral sensory nerves are at 90% of the adult level, and the nerve conduction velocities for the nerves that innervate arm muscles have reached 93-100% (77). However, even if the peripheral nervous system matures quite early, other factors are crucial for its development. Interaction is essential, between the neural and muscular components of the motor system (76), and between the brain, the body, and the environment (78). Equally important are questions such as why a particular movement is made, how the movements are planned, and how the children anticipate what is going to happen next (78). In addition, essential principles of motor development are a) that the development of motor skills generally proceeds in a cephalocaudal and proximodistal direction, b) that neural maturation is an important component of unfolding skill development, and c) that motor development appears, at least on the surface, to be more stage-like than continuous (75).

Infants as young as one week old show pre-reaching behaviours (6). At about four months, infants begin to gain trunk stability along with a progressive uncoupling of head, arm, and hand synergies, which allows the emergence of functional reach and grasp behaviour (6). The development of hand orientation begins to occur at the onset of successful reaching at about five months of age, and the pinch grip develops at about nine to ten months (6). Distance scaling is in place by age five, but integration of grasp with trajectory is not (79). Reaction time shows a progressive reduction with age, with sharper changes occurring up to the age of eight to nine years, followed by slower changes up to 16 to 17 years (6). Power and precision grip patterns expand with the neural development and the opportunity for exploration and practice (80). During development infants try out a variety of movement strategies that happen to occur to them, often accidentally, before readily selecting the safest and most economical one for the task at hand (75).

Research on development in children has shown that movement production in healthy children is characterized by a decrease in
movement variability as they grow older, in a variety of hand motor tasks such as handwriting (81), drawing movements (82), reaching and grasping coordination (77, 83), prehension movements (84), and sustained contractions with the index finger (85). The reliability of hand function could thus be poorer in younger children. When assessing muscle function in children, it is important to consider the differences between children and adults – for example, in reliability (86).

Charcot-Marie-Tooth disease (CMT)

In clinical work I have met CMT patients with reduced hand function. CMT is a slowly progressive neurological disorder with a prevalence of 5-40 cases in 100000 (87, 88). There are many subtypes of the disease; the two main ones are the demyelinating CMT type 1, with marked reduction of motor nerve conduction velocity; and the axonal CMT type 2, where the nerve conduction velocity is preserved or only slightly reduced (89). However, recent genetic studies emphasize the need for discussion about the ‘meaning’ of the subtypes of the disease, since a mutation of the same gene may result in either type (90). The longer nerve fibers are affected first and more severely (91). CMT patients typically present with distally accentuated motor weakness and sensory loss leading to significant and progressive clinical morbidity and impaired quality of life (92). The lower limbs are usually affected more and earlier than the upper limbs, and thus symptoms from the lower limbs have previously been the main focus of research and clinical practice (93, 94). Most patients, however, do indeed develop hand weakness and loss of manual dexterity (94). The median and ulnar nerves are usually affected more than the radial nerve (95). The intrinsic hand muscles are affected (palmar and dorsal interossei, thenar and hypothenar muscles), which can result in claw hands (96). Loss of thumb opposition was found in nearly 49% of subjects with CMT 1a (97). Paresis and deformities of the hand may thus hamper many daily activities (88) – for example, manipulating small objects, carrying a shopping bag, or opening a jar (94). Sensory signs are usually less prominent than motor symptoms, and the most frequent finding is loss of sensation to touch, pain and vibration (91). Neuropathic pain is seen, though uncommon (91). Cold intolerance is frequent and further contributes to impairment in severe climates (98). My clinical experience is that this is a common complaint during the winter. Research on hand function has recently been expanding (64, 99-102), but still little is known about the extent of the reduction of hand function, its impact on disability in persons with CMT, and appropriate measurements to use for evaluating hand function.

Cerebellar stroke

Patients with cerebellar stroke often complain of reduced hand function, such as coordination. The clinical symptoms of cerebellar stroke depend on what territory is involved. Lesions to the cerebellum can lead to, for
example, disrupted control of balance, eye, and limb movements; disruption of motor planning; prolonged reaction time; and impaired motor learning (10). The overall common result of cerebellar disorders is abnormalities in the execution of movements referred to as lack of coordination or ataxia (10) – an inability to perform smooth, directed movements (103). Upper limb control can be affected after cerebellar injury. Typical signs of upper limb ataxia are dysmetria and intention tremor at the end of reaching or pointing movements (104). The hand function is often affected in persons with cerebellar stroke, such as when picking up small objects (105) or performing the Nine-Hole-Peg test (106). Physiological findings associated with cerebellar lesions include, for example, disorganization of EMG, inappropriate amplitude and acceleration of muscle contractions, prolonged reaction time (12).

Most epidemiological studies do not differentiate between subgroups of stroke, so information about the frequency of cerebellar stroke is not easily obtained. The frequencies of cerebellar strokes were 5.2 to 8.8% of all strokes in a Japanese population (107), and cerebellar infarcts have been found to be 1.5 to 4.2% of initial strokes in different studies (108). The age-specific incidence of isolated cerebellar infarction has been reported to be 1.8/100 000 in northern Sweden (109). For a long time, study of the territory of cerebellar strokes has been neglected because neuro-imaging has generally failed to show the stroke, also, the sensitivity and specificity of clinical symptoms and signs in diagnosing cerebellar strokes were low (108). However, research during the 1990s showed that the cerebellar stroke syndromes were better defined (108). Research on cerebellar disease is also complicated because of the anatomical organization, which in most cases results in cerebellar disease affecting more than one cerebellar region, causing general cerebellar dysfunction (110). Even if the primary lesion is restricted to one region, other parts of the cerebellum may be secondarily involved by pressure, oedema, and/or circulatory disturbance, so that only a small number of lesions are restricted to only one part of the cerebellum (110).

Obviously changes in the nervous system due to development and disease can affect the ability to execute hand movements. Thus appropriate measurements of hand function in children of different ages, and in patients with neurological disorders, are crucial.

**Rationale for the studies**

**Reliability of grip strength in children**

As mentioned earlier, assessment of grip strength is common, easy to perform and correlates with other body capacities. In pediatrics reliable assessments are important to be able to follow the child’s development and to discover reduced abilities early. Developmental milestones are often related to the development of motor skills (76). Measurements
evaluated in adults have been used many times in children, but their reliability might not be as good in children. There are few studies on the reliability of grip strength measurements in children; there is no report, for example, on the Grippit. However, normative data using the Grippit in children aged 4-16 years have been presented (50). Sustained grip strength, which can be measured by Grippit, has to our knowledge not been evaluated at all in children. The reliability of hand measurements may vary with age in children, because of different maturity of sensory-motor development; yet it remains to be proved. To achieve a more correct reliability estimate when studying grip strength in children, relatively small age ranges are preferable.

Hand function in CMT

Hand function is often affected in persons with CMT. However, there are few reports on the amount of reduction and the appropriate measurements needed to assess hand function. At the start of this research there were only a few studies on the reliability of hand measurements in persons with CMT (e.g. strength (94, 111)) and no studies on the reliability of pinch strength, sensation and dexterity tests. Therefore plans were made to evaluate grip and pinch strength with Grippit, sensation with the STI test and dexterity with BBT and NHP. Recently the reliability of sensation (99), and dexterity (64, 87) have also been evaluated, which indicates that other researchers have come to identify the same need. When this research began, no-one had published data on DASH in CMT. DASH was chosen because it is a measurement that reflects the patient’s experiences. Now, other researchers have also used this instrument in persons with CMT. DASH was strongly correlated with wrist flexor and extensor strength (100) and with the Jebsen test (101), but its correlations with grip strength and sensation in persons with CMT have not been evaluated.

Reactive grip control in cerebellar stroke

Cerebellar stroke often leads to reduced hand function. However, how the cerebellum contributes to grip control is still poorly understood (15). A recent review confirms that the cerebellum is essential in predictive control (112). There are few and inconsistent studies on reactive grip control in persons with cerebellar disorders regarding, for example, response latency (normal (113, 114) – prolonged (115)) and grip force (normal (115) – increased (113)). This provides the motivation for a study design using sets of unpredictable grip perturbations to examine grip control in persons with cerebellar stroke, in order to investigate the cerebellar contribution to reactive grip control. Research indicates that, in addition to exerting a unilateral control, the cerebellum also controls contralateral movements (16-19). However, more research on whether and how a lesion in one side of the cerebellum may influence the motor performance of the contralateral hand is warranted.
Aims

AIMS OF THE THESIS

Overall aim
The overall aim of the present work was to gain more knowledge on hand function with focus on the evaluation of measurements in different target populations and also regarding the movement control of the hand.

Specific aims
To evaluate the test-retest reliability of peak and sustained grip strength using Grippit in healthy children. The analysis focused on comparing the reliability of the best and the mean of three test trials and the reliability of different age groups (6-, 10- and 14-y-olds). (Study I)

To evaluate the test-retest reliability of the Grippit instrument for grip and pinch strength, the sensation measurement Shape Texture Identification and dexterity with Box and Block Test and Nine-Hole Peg test in adult persons with Charcot-Marie-Tooth disease. (Study II)

To examine hand function and the impact of the disease on daily life measured with the Disability of the Arm, Shoulder and Hand questionnaire (DASH) in persons with CMT. The aim was also to explore the possible correlations between disability and various aspects of hand function. (Study III)

To investigate whether there were differences in grip responses between healthy controls and younger (22-48 yrs) persons with cerebellar stroke. It was hypothesized that the cerebellum would contribute to reactive grip control; differences would be found between the ipsilateral hand in cerebellar subjects and controls in e.g. levels of grip force; and the unilateral cerebellar lesions would have a negative influence also on the grip control in the contralateral hand. (Study IV)
Methods

Methods

Study designs

The first two studies were test-retest reliability studies, followed by a descriptive study and an experimental study (table 1).

Table 1 Overview of the four studies

<table>
<thead>
<tr>
<th>Title and design</th>
<th>Participants</th>
<th>Measurements</th>
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<tbody>
<tr>
<td>I. Grip strength in children</td>
<td>6-y-olds (n=19)</td>
<td>Gripita</td>
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<tr>
<td>- test-retest reliability using Grippit</td>
<td>10-y-olds (n=20)</td>
<td></td>
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<tr>
<td>Test-retest reliability study</td>
<td>14-y-olds (n=19)</td>
<td></td>
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<tr>
<td>II. Hand function in Charcot-Marie-Tooth – test-retest reliability of some measurements</td>
<td>CMT (n=20)</td>
<td>Grippitb, STI test, BBT</td>
</tr>
<tr>
<td>Test-retest reliability study</td>
<td></td>
<td>NHP</td>
</tr>
<tr>
<td>III. Hand function and Disability in Charcot-Marie-Tooth disease</td>
<td>CMT (n=20)</td>
<td>Gripitb, STI test, BBT</td>
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<tr>
<td>Descriptive study</td>
<td>HS (n=40)</td>
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<tr>
<td>IV. Reactive grip control in younger persons with cerebellar stroke</td>
<td>CS (n=9)</td>
<td>Unpredictable perturbations</td>
</tr>
<tr>
<td>Experimental study</td>
<td>HS (n=11)</td>
<td>Peg test</td>
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</table>

Grip strength. Grip and pinch strength.

Participants

Reliability of grip strength in children

The first study included 58 children, 26 boys and 32 girls, who were recruited from preschools and schools in northern Sweden (table 2A). In all groups the age was within +/- 3 months and SD 1 month. No children with medical diagnoses or other functional limitations that might have influenced the grip strength were included.

Hand function in CMT

All persons (20-75 years, n=24) with the diagnosis of Charcot-Marie-Tooth, registered at the neurological clinics in the counties of Västerbotten, Västernorrland and Jämtland in Sweden were offered to take part in study II-III. Subjects were not to have hand impairments
Methods

from other injuries or illnesses. Nine men and 11 women participated (table 2B). Eleven (55 %) were diagnosed with type 1, five (25 %) with type 2, one with type 4c while the subtype of the disease was unidentified in three subjects. All but one subject experienced hand symptoms. In study III the sample from study II was investigated, including healthy subjects matched by age and gender. Eighteen men and 22 women (aged 21-73 yrs) participated. The difference in age between the subjects and their matched controls was maximum 4 years. Exclusion criteria were injuries or illnesses causing hand impairments.

Reactive grip control in cerebellar stroke

The patients in study IV were recruited at the medicine and neurological clinics in Umeå. Four men and five women with cerebellar stroke (cerebellar subjects=CS) participated (mean age 38.2 yrs; range 22-48). They were right handed, and healthy prior to their focal cerebellar ischemic stroke that had occurred between 3 months and 5 years prior to the study. The types of lesions are shown in table 2C. Clinical examination by a neurologist (BK) was performed in the acute phase and prior to testing. All CS had exhibited symptoms of cerebellar involvement in the acute phase, e.g. reduced capacity to perform fine finger movements, dyscoordination, mild tremor, reduced oculomotor function or gait and balance deficits. All CS except one had clear symptoms at the time of the study, most commonly reduced control of fine finger movements. Healthy subjects (HS) without any history of neurological symptoms (four men, seven women, mean age 37.3 yrs; range 22-50) were also tested. The control group was chosen to get a comparable age spread and mixture of sexes.

Ethical approvals

All participants in the studies gave their informed consent according to the declaration of Helsinki and the studies were approved by the Regional Ethical Review Board, Umeå, Sweden (dnr 96-262, 99-407, 04-176M).
Methods

Measurements and procedures

Reliability of grip strength in children

The children were tested in a quiet room at preschools and schools. Body weight, height and hand length (50) were measured (table 2). The Edinburgh handedness test (116) was used to quantify hand dominance. Two children were left-handed. The children were seated on a chair with the Grippit in front of them on a table. The second test took place one week after the first and the test situations were kept as similar as possible (time of the day, location, instructions etc).

Grippit® (AB Detektor, Göteborg, Sweden, picture in (117)), an electronic grip strength dynamometer was used to measure grip strength in Newtons. Both the maximal value (peak grip strength) and the mean value (sustained grip strength) over 10 s of time are registered (53). Grippit consists of a strain gauge with two exchangeable handles (depth and width of 27 mm, depth of 45 mm width of 27 mm). The hand length determined the choice of handle; if the hand length was <16 cm the smaller handle was used, while the children with a hand length of 16 cm or more used the bigger handle. The grip device and an arm support to ensure standard grip position are mounted on a base. During testing, the palm and fingers were clasped around the handle. The position was standardized; shoulder adducted and in neutral rotated position, elbow in about 90° flexion, forearm semi-prone and wrist in neutral resting position (American Society of Hand Therapists (118)). The subjects were asked to squeeze as hard as possible for 10 s.

Hand function in CMT

The testing took place at the department or in hospitals/clinics in the participants’ city of residence. Retests were performed on each subject at the same time of the day one week later. The subjects were instructed not to perform strenuous activities before testing. The assessment started with a brief structured interview for background data including evaluation of handedness according to the Edinburgh handedness test (116), self rating of cold intolerance and impairment of tactile gnosis (table 2B). All subjects were right handed. Then followed measurement of physical performance, the Short Physical Performance Battery, including standing balance, walking 4 m and rising from a chair (119). Fifteen of the subjects walked 4 m without walking aids, two persons walked with aids and three subjects were not able to walk 4 m. With regard to cold intolerance and its' effect on hand function, hand temperature was measured with an infrared thermometer prior to the hand tests, 1) on the dorsal side of the index finger proximal to the nail and 2) at the distal groove of the volar wrist. At the first test occasion, the participants were required to stay indoors at room temperature (on average 22°C) for > 20 min. At the second test occasion, active hand movements were performed if finger tip
temperature was >2°C colder than in the first session. Five persons had to warm up prior to the second test session. The subjects were seated on a chair with the arms resting on a table in front of them. Seat height was adjusted when necessary. An anti-slip cloth was placed under the test equipment. The participants were offered to rest when needed during the testing. Then followed: two tests of dexterity; BBT and NHP, grip and pinch strength testing with the Grippit and test of tactile gnosis with the STI test. No pain problems were reported during testing. Finally, the subjects completed the Swedish version of the DASH questionnaire.

For the control group in study III, the experimental procedure was the same as for the CMT group for grip strength testing and dexterity tests. For tactile gnosis however, no testing was done since the STI maximum score of 6 points is considered as norm (55).

**Strength**

Grip strength in CMT was measured with Grippit, see p 28, but all subjects used the bigger handle.

Pinch strength was also measured with Grippit using a tip grip (tips of thumb and index finger) on a thin handle (width 15 mm, finger aperture 11 mm). The arm rested somewhat abducted on a wedged pillow with the elbow flexed (slightly > 90°). The wrist was held in neutral position. The index finger and the thumb were naturally flexed and the other fingers held flexed in the hand.

**Sensation**

*Shape Texture Identification test* (Össur Nordic AB, Uppsala, Sweden, picture in (120) p. 58) consists of three plastic disks where tactile identification of three shapes (cube, cylinder, hexagon) and three textures (1-3 raised metal dots placed in rows) was performed with the index finger without visual input (55). Three difficulty levels were presented for shape (size 15, 8 and 5 mm) and texture (distance between the dots 15, 8 and 4 mm) (55). To score one point the subject had to correctly identify all three shapes or textures at every level. The maximum score is six points which implies normal tactile gnosis. Testing was performed according to a standardized procedure (55).

**Dexterity**

*Box and Block Test* measures numbers of blocks (2.54 cm³) picked in one minute one at a time from one section of a box to the other (56).

*Nine-Hole Peg test* consists of a square board with nine holes and a container with nine wooden pegs (3.2 cm long, 0.64 cm Ø) (61). NHP is a time monitored test where pegs are picked up from the container one by one and put into the holes and then returned to the container as quickly
as possible. If a peg was dropped, the examiner quickly retrieved the peg or replaced it with a spare into the container (121).

Summary of and additional information on measurements and test procedure in study I-III are found in table 3.

**DASH**

*The Disabilities of the Arm, Shoulder and Hand questionnaire (DASH)* is a self-report questionnaire consisting of 30 items referring to activities in which a patient who has an upper-extremity disorder may face some level of difficulty. Each item has 5 response choices, ranging from “no difficulty/no symptom” to “unable to perform activity/ extreme degree of symptom”. A formula (DASH homepage (122)) is applied to the scores for all items in order to calculate a DASH score ranging from 0 (no disability) to 100 (severest disability). The optional sections of the DASH (four items concerning sports/music and four items on work activities) were omitted in the present study, in accordance with Selles et al. (100).
Methods

<table>
<thead>
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<th>Table 3 Information on measurements in study I-III</th>
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<td><strong>Grippit (Study I)</strong></td>
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<td><strong>Grippit (Study II-III)</strong></td>
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<td>Grip Hands alternated</td>
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<td><strong>Box and Block Test (Study II-III)</strong></td>
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<tr>
<td><strong>Nine-Hole Peg test (Study II-III)</strong></td>
</tr>
</tbody>
</table>
Methods

Reactive grip control in cerebellar stroke

The testing took place at Umeå University. Prior to the testing, the subjects washed their hands with soap and water. The testing started with the grip control experiments designed to evaluate the regulation of grip forces in response to changes in rate and load. After that a clinical peg test to detect fine manipulative symptoms followed then.

The subjects sat with their arm abducted (≈30°), their elbow flexed (≈100°) and the forearm extended anteriorly in mid-range pro-supination positioned in a vacuum cast. The tips of the thumb and index finger were used to grasp an instrumented manipulandum covered with fine sandpaper which was connected to a servo controlled force motor via two stiff beams (28). The motor produced loads in the distal direction tangential to the grip surfaces away from the palm. The subjects were instructed to restrain the manipulandum from moving when unpredictable load forces were applied, while not using excessive grip forces. The subjects performed an introductory test with the right hand, followed by two test sets with each hand, starting with the right hand. The order of the sets was counterbalanced across subjects. More information on the apparatus, the procedure and the sampling of signals are found in study IV.

Rate set (R): In the first set (n=40 trials) the sequence of trials was unpredictable with regard to load force rate. It was either: 2, 4, 8 N/s or a fast 'step like' rate increase of approximately 70 N/s. All the trials reached a load force amplitude of 4 N (average per finger), except for the fast 'step trials' which reached a value of 1 N, after which the load increased with a force rate of 4 N/s until the plateau of 4 N was reached. The diversity of this test set and the following amplitude set, were further obtained by randomly varying the duration of the plateau phase (2 and 4 s) and the inter-trial delay (1.5. and 3.5 s).

Amplitude set (A): In the second set (n=30 trials), all loads were delivered with the same force rate (4 N/s) but the sequence of trials was unpredictable with regard to load force amplitude. It was either: 1, 2 or 4 N (average per finger). To further diversify the presentation of the pulling loads intermingled in this test set but not analyzed were 3 fast trials, termed 'step load trials' (1 N, 32 N/s – peak rate ≈70 N/s).

For each trial the following measurements were derived for statistical analysis, figure 1.

Grip control before the perturbation: The pre-load grip force (N) was defined as the grip force at the onset of the load phase, ‘a’ in figure 1 (R and A). The distribution between fingers (%) was the distribution of grip force between the thumb and index finger (expressed as a percentage; the
force in the indexfinger / total force in index and thumb) here calculated from the pre-load grip force values (R and A).

**Figure 1** Measurements during a trial

![Figure 1](image)

a) Onset of load force, b) Onset of grip force response, c) Peak grip force rate, d) Grip force during the static hold plateau. The grip 'response latency' is defined as the time difference between 'a' and 'b'. The 'deviation of position' is defined as the position difference between 'a' and 'b'.

Grip control during loading: The grip *response latency (ms)*, was the time interval from the onset of the load phase to the start of the grip force increase (figure 1: R and A). The *peak grip force rate (N/s)*, was the maximum rate of grip force increase within a 1.2 s period starting at the onset of the load phase and following a grip force response, 'c' in figure 1 (R). The *static grip force (N)* during the plateau phase was measured 0.7 s after the start of the load force plateau, 'd' in figure 1 (A). The *distribution between fingers (%)*, described earlier, was also calculated from the static grip force values (A). The modulation of grip force to the demands of the load force amplitude during the loading was calculated as a grip force modulation index, *GFMI* (the difference between the static and the pre-load grip force expressed as the fraction of the static grip force (30) A). The *deviation of position (mm)*, was the difference in position during the onset of the load phase to the start of the grip force increase (R). The *frequency of slips (%)*, was measured as the number of trials in which the manipulandum slipped away from the fingers (R and A). A subject's *responsiveness (%)* was defined as the percentage of trials in which grip responses were observed with a grip force rate exceeding 5 N/s (R and A).

All subjects performed a peg test consisting of a square board with 25 holes and a container with 25 wooden pegs (3.2 cm long, 0.64 cm Ø). The task was to grasp and insert the pegs in the holes as fast as possible, with one hand at a time. The time (s) for the best trial out of three was registered.
Statistical analyses

All data were analyzed using SPSS (Statistical Package for Social Sciences) version 11.5, 13.0 or 14.0. Strengths of correlation coefficients were interpreted according to Munro (123). Level of significance was set at p<0.05.

Reliability statistics

There are many ways to calculate reliability. Today, there is a general agreement that a comprehensive set of statistical methods is required to address the reliability of measurements (124).

Relative reliability

The intraclass correlation coefficient (ICC) has become the preferred index, as it reflects both correlation and agreement (69). The ICC has several advantages: for example, it can be used with small samples and with data from more than two test occasions (124). There are different types of ICCs available for different study designs, but in practice, their values are often very similar (124). A major criticism of the ICC is the influence of between-subject variance on the ratio, i.e. if the true score variance is sufficiently large, reliability will always appear high (125).

Absolute reliability

The standard error of measurement (SEM) is calculated to evaluate how “true” a score is. There is a 68% probability that a person's true value would be within 1 SEM of the original measurement and approximately 96% of the time the true value would be within 2 SEM of the original measurement (126). SEM% can be calculated (SEM divided by the mean of the measurements from test 1 and test 2 and multiplied by 100) to make comparisons possible e.g. between different populations like age groups. The SEM is not affected by between-subjects variability (127).

The coefficient of repeatability (CR) represents the minimal detectable change between repeated measurements in the unit of the measurement, and can be calculated as 2,77 x SEM (126). The coefficient of repeatability can be defined as the value below which the absolute difference between test-retest scores may be expected to lie with 95% probability.

The average within-subject coefficient of variation (CV), expresses error as a percentage of the mean value and is applied to data in which the degree of agreement between tests does depend on the magnitude of the measured values i.e. heteroscedasticity is present (128). CV is calculated as (SD/mean x 100) for each subject and then averaged across the whole population (128). The calculation of CV is built on the assumption that with a 68% probability the differences between tests will lie within the CV
Methods

The use of CV can be wast when comparing different measurements with each other, since it is a dimensionless statistic.

Reliability of grip strength in children

ICC2,1, a two-way random effects single measure reliability (consistency) was used to reflect relative reliability. Absolute reliability analysis included calculation of SEM, SEM%, CR and CV. SEM was calculated from the two-way Anova (used when calculating ICC2,1), SEM%, CR and CV were calculated as earlier described. To evaluate heteroscedasticity, the correlation between the average of test I and test II and the absolute difference between test I and II was tested using Spearman’s rank correlation test. If there was heteroscedasticity CV was calculated. Because of heteroscedasticity in the whole sample CV was used, while the age groups didn’t show any heteroscedasticity; hence SEM, SEM% and CR were used. The hypothesis of zero bias between test occasions was tested using Wilcoxon signed rank test. Results are displayed only for the dominant hand since the difference in reliability between hands was negligible.

Hand function in CMT (Study II)

To reflect relative reliability ICC2,1 was calculated. The ICC were calculated for mean of three trials and best of three trials for the NHP test and for Grippit. The ICC’s were higher for the best of three trials for NHP test but for the mean of three trials for Grippit, hence all further analysis and the displayed results show the results of respective values. For STI, the linear weighted kappa was used to calculate the chance corrected agreement between the tests. The strength of agreement for the kappa value was interpreted according to Landis and Koch <0.2 poor, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 good, 0.81-1.00 very good (73). Absolute reliability was analyzed with the CR and CV. The CR was calculated by multiplying the standard deviation for the differences between test I and test II by two. The CV was calculated as earlier described. In addition, the limits of agreement were generated to illustrate absolute reliability, however, these results are not displayed in the thesis, but can be found in study II. The hypothesis of zero bias was tested using Wilcoxon signed rank test. To estimate the normal distribution, Kolomogorov-Smirnov test was used. To evaluate heteroscedasticity, the correlation between the average of test I and test II and the absolute difference between test I and II was tested using Spearman’s rank correlation test. The results of the right hands are displayed in the thesis but the results from the left hand can be found in the article.
Methods

Hand function in CMT (Study III)

Both hands were tested but only data for the right hand was analysed, since the right hand was dominant in all subjects. Mann-Whitney U tests were used for group level comparison of the results on each hand function test. A hand function index (HFI) summarizing three aspects of hand function; grip strength (Grippit), tactile gnosis (STI) and dexterity (BBT), was constructed. All three aspects were considered to have equal importance for hand function. Thus, the HFI for each subject was the sum of the three aspects where each aspect was expressed as the quotient between the obtained result and the norm value. For Grippit and BBT a mean of the results from two healthy controls matched for age and gender was considered as norm for each of the subjects with CMT, and for STI the maximum score of 6 points was considered as norm. After conversion of the index scores (0-3.0) to percentages, a maximum of 1.0 would indicate normal hand function. Relative DASH scores for impairment, activity and participation, respectively, according to ICF, were calculated from summaries of different item scores using syntax files presented by Dixon et al (5). Spearman’s rank correlation was used to evaluate possible correlations between aspects of hand function and upper limb disability. A multiple regression analysis was used to estimate the relative contribution of hand strength, tactile gnosis and dexterity (BBT) to the DASH score. The significance of R² was determined with an F-test.

Reactive grip control in cerebellar stroke

For one subject with bilateral lesion with no clinical symptoms at the test occasion, only data for the right dominant hand were included. For the other subject with bilateral lesions data for both hands were included, because both presented symptoms. ‘Ipsilateral hand’ group refers thus to seven subjects of which two had bilateral lesions (table 2C). ‘Contralateral hand’ group refers to the five subjects with unilateral cerebellar stroke (table 2C). Data from those two CS with additional lesions are treated separately and is not included in the statistics but used only in some comparisons when so indicated in the text. Data were first averaged for the sets (40/30 trials) for each subject at each force rate/amplitude when applicable, then means for the groups were calculated. For comparisons between CS and HS, non-parametric statistical tests, Mann-Whitney U test, were used. Repeated measures ANOVAs with mixed design were used for comparisons of more than two independent samples after checking assumptions regarding normality distribution of the residuals and interaction. When these assumptions were not met, non-parametric statistics were used. For HS, data for the dominant hand were used (there were no significant differences between the dominant and non-dominant hand in the HS). To analyze the variation of performance, the CV was calculated as earlier described. Population estimates are presented in the form of means ±SD values unless otherwise stated in the text.
RESULTS

The main findings from these studies on hand function are:

Grippit has a high test-retest reliability when measuring peak and sustained grip strength in children. Measurements of grip strength were more reliable in 6- and 14-y-old children compared to 10-y-olds.

In persons with CMT strength, tactile gnosis and dexterity, are markedly reduced, only ~60% of normal function, causing various degrees of limitations in daily life measured with DASH. The test-retest analysis demonstrated that the analyzed measurements are reliable in CMT. However, there are advantages and disadvantages that need to be considered. The DASH score was clearly related to hand function.

Unpredictable loadings trigger grip reactions in persons with cerebellar stroke that differ from healthy. The ipsilateral hand in CS showed delayed and more variable onset of response and a higher pre-load grip force. Prolonged onset of grip response was found even for the contralateral hand in unilateral CS. Cerebellar lesions can thus impair the reactive grip control both in the ipsilateral and contralateral hand.

Reliability of grip strength in children

The best and mean of three trials

For peak grip strength the best of three trials showed slightly higher reliability than the mean of three trials, both when all children were analyzed and in the age groups, except in the 6-y-old group where no such differences were seen. However, the best of three trials was systematically higher at the second test occasion in the whole age group (table 5). For sustained grip strength however, the mean of three trials showed higher reliability compared to the best of three trials both when all children were analyzed and in all age groups. Most of these statistics are displayed in the article, not in the result section of the thesis.

Reliability for the different age groups

The test-retest reliability of both peak and sustained grip strength were very good in the 6-y-olds and the 14-y-olds. Very high relative reliability was found and the absolute reliability was good also (e.g. SEM% 5.2-8.4%; table 5). The reliability of peak and sustained grip strength were similar for the 6-y-olds (table 5). For the 14-y-olds however, the reliability was higher for peak grip strength than for sustained grip strength (table 4).
Results

For the 10-y-olds the reliability was not as satisfactory. The relative reliability between test occasions was high (ICC 0.72 and 0.78) but the 95% CI of the ICC were wide (e.g. CI 0.54-0.91 for peak grip strength; table 5). The reliability was higher for peak grip strength than for sustained grip strength (table 5). The SEM% were 12.5 and 15.5%, about twice as high as in 6- and 14-y-olds.

The ratio of sustained grip strength in percentage of peak strength differed between the age groups. In the first trial at the first test occasion, the mean ratios of sustained strength in percentage of peak strength (sustained/peak x 100) were 70% for the 6-y-olds, 83% for the 10-y-olds and 87% for the 14-y-olds. The best peak value was seen at the third trial in 13% (6 y), 31% (10 y) and 16% (14 y) respectively.

Hand function in CMT

Results of hand measurements (Study III)

All subjects with CMT, except one, demonstrated quite evident reduction in hand function (figure 2). The CMT subjects scored significantly lower on all of the four hand function tests (Grippit, STI, BBT, NHP; p<0.001 in all cases) compared to age- and gender matched controls. Strength and sensation results are found in table 4. For STI, median of the CMT subjects was 4 p (range 0-6 p). The CMT subjects also reported self rated impairment of tactile gnosis and cold intolerance (table 2B). The HFI compiles three aspects of hand function: grip strength (Grippit), tactile gnosis (STI), dexterity (BBT). The median index value was 0.62 (range 0.12-0.91).

All CMT subjects, except the asymptomatic person, experienced difficulties in their daily life because of reduced upper limb function. The median DASH score was 38.8(range 0-66.7); where a higher score indicates a greater disability. Analysis of the DASH item scores according to the dimensions of ICF showed that the medians and ranges were; for impairment 40.0(0-80.0), for activity limitation 35.8(0-91.7) and for participation restriction 37.5(0-62.5).

Reliability of measurements (Study II)

The test-retest reliability of grip strength assessed with the Grippit was good. The relative reliability for both peak and sustained grip strength was very high (table 6). The results of the absolute reliability measures (table 6) were good. The correlation between test occasions was very high for pinch strength (table 6). However, the CR was quite large (e.g. 8.5 N compared to mean of ≈ 28 N) and there was a bias for peak and sustained pinch strength showing better performance the second test occasion.
Table 4 Strength and sensation values in CMT

<table>
<thead>
<tr>
<th></th>
<th>CMT (n=20)</th>
<th>Number (%)</th>
<th>Measured values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grip strength</td>
<td></td>
<td>2 (10%)</td>
<td>&lt; 40 N</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 (30%)</td>
<td>&lt; 100 N</td>
</tr>
<tr>
<td>Grip strength, compared to HS</td>
<td>14 (70%)</td>
<td>&gt; 100 N weaker</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>18 (90%)</td>
<td>&gt; 35 N weaker</td>
</tr>
<tr>
<td>Pinch strength</td>
<td></td>
<td>3 (15%)</td>
<td>&lt; 10 N</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 (35%)</td>
<td>&lt; 20 N</td>
</tr>
<tr>
<td>Shape Texture Identification test</td>
<td>16 (80%)</td>
<td>&lt; 5 p</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 (35%)</td>
<td>= 0 p</td>
</tr>
</tbody>
</table>

Figure 2 Hand function in CMT and healthy subjects (HS)
Results

The CVs were higher indicating a less stable performance for pinch strength compared to grip strength. The subjects scored best at the second trial for grip and pinch (42% and 37% respectively) followed by the third (36% both conditions) and the first (22% grip and 26% pinch) trial.

Sensation assessed with Shape Texture Identification test showed a very good agreement between tests, a linear weighted kappa coefficient of 0.87 (CI 0.79-0.95). The maximum difference between test occasions was two points. There was no difference between tests in 67.5% of the tests (both hands).

Reliability analysis of dexterity tests showed a very high test-retest correlation and good results of the absolute reliability analyzes for the Box and Block Test (table 6). However, there was a significant bias of 4.7 blocks improvement between tests. Also the Nine-Hole Peg test showed very high relative and good absolute reliability (table 6). The best score of three trials occurred in 46% of the total tests in the third trial, while in 28% in the second and 19% in the first trial.

Correlation of DASH to hand function measurements (Study III)

A high degree of upper-limb disability (DASH) was highly correlated to a reduced hand function in three of the separate hand function tests, as well as for hand function summarized in the HFI (table 7). A moderate correlation was shown found between DASH and BBT (table 7).

Multiple linear regression showed that while hand strength (p=0.002) and tactile gnosis (p=0.021) each contributed significantly, dexterity did not (p=0.919) further explain the DASH score. The degree of explanation was 0.77 in the model.

Table 7 Correlations between DASH scores and hand function in CMT

<table>
<thead>
<tr>
<th>DASH and:</th>
<th>$r^a$ (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grippit</td>
<td>-0.72 (-0.94 - -0.50)</td>
<td>0.001</td>
</tr>
<tr>
<td>STI</td>
<td>-0.79 (-0.99 - -0.60)</td>
<td>0.001</td>
</tr>
<tr>
<td>BBT</td>
<td>-0.64 (-0.89 - -0.39)</td>
<td>0.002</td>
</tr>
<tr>
<td>NHP</td>
<td>0.83 (0.69 - 0.97)</td>
<td>0.001</td>
</tr>
<tr>
<td>HFI</td>
<td>-0.71 (-0.92 - -0.50)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

$a$Spearman correlation.
Results
Results

Reactive grip control in cerebellar stroke

Frequency of slips and responsiveness in the sets

The frequencies of trials in which the manipulandum slipped away from the fingers for the CS were 6.3% for the CS ipsilateral hand and 5.5% for the contralateral hand in unilateral CS in the rate set. In the amplitude set, the frequencies of slips were 8.0% for the CS ipsilateral hand and 7.3% for the contralateral hand in unilateral CS. The HS lost the object in only a couple of trials. In as much as 21% of the trials, the object slipped away for one subject with an additional lesion (nr 9).

The frequency of trials with a clearly detectable response (responsiveness) was close to 100% for HS in both sets. In contrast, the responsiveness for the CS was 86.6% for the ipsilateral hand and 87.2% for the contralateral hand in the rate set. In the amplitude set, the responsiveness for the CS was 92.5% for the ipsilateral hand, but 93.8% for the contralateral hand. Subject (nr 8) with an additional lesion showed grip force responses in only 25% of the trials in the amplitude set.

Pre-load grip control in the two sets

The CS used higher pre-load grip force with their ipsilateral hand compared to the HS (p=0.017) in the amplitude set (table 8). In this set, one CS (nr 8) with an additional minor lesion had a very high pre-load grip force, 6.5(1.9) N. In the rate set, however, there was no significant difference in pre-load grip force between the CS ipsilateral hand and HS (table 8). There were no differences between the contralateral hand in unilateral CS and HS in either set (table 8).

In neither of the two sets were there any significant differences in distribution of pre-load grip force between the fingers between the ipsilateral or contralateral hand in CS compared to HS (table 8).

Effect of different load forces rate on grip control

In the rate set the CS responded with delayed response latencies with the ipsilateral and the contralateral hand compared to HS (table 9). The performance was more varying in the CS ipsilateral hand (CV: 2N/s; 60%, 4N/s; 33%, 8N/s; 23 %, 32N/s; 25%) compared to HS (CV: 2 N/s 30%, 4N/s; 25%, 8N/s; 26 %, 32N/s; 9%). These differences were significant for two of the load force rates (2 and 32N/s).

The peak grip force rate and the deviation of position were similar between both the ipsilateral hand in CS and HS and between the contralateral hand in unilateral CS and HS (table 9).
Results

Effect of different load force amplitudes on grip control

Also in the amplitude set the CS responded with delayed response latencies with the *ipsilateral* hand, 169(50) ms compared to HS 132(38) ms (p=0.017). The response latency in the unilateral CS *contralateral* hand was 160(52) ms. The most prolonged response latency, 345(95) ms, was seen for the CS (nr 8) with an additional lesion.

The static grip force during the plateau phase, the distribution of static grip force between the fingers and the modulation of grip force (GFMI), were similar between the *ipsilateral* hand in CS and HS, and between the *contralateral* hand in unilateral CS and HS (table 9).

Peg test

The CS needed considerably more time with their *ipsilateral* hand to perform the peg test 46.4(8.7) s than the HS 36.2(3.8) s (p=0.003). The *contralateral* hand in unilateral CS was also clearly slower; 42.4(5.3) s than HS (p=0.041).
Table 8 Pre-load grip control for cerebellar subjects (CS) and healthy subjects (HS)

<table>
<thead>
<tr>
<th></th>
<th>CS</th>
<th>HS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Set Ipsilateral</td>
<td>Contralateral</td>
</tr>
<tr>
<td>Pre-load grip force (N)</td>
<td>R 1.7 (0.8)</td>
<td>1.6 (0.7)</td>
</tr>
<tr>
<td></td>
<td>A 1.6 (0.8)*</td>
<td>1.6 (0.8)</td>
</tr>
<tr>
<td>Distribution of grip force (%)</td>
<td>R 51.6 (7.6)</td>
<td>51.3 (5.7)</td>
</tr>
<tr>
<td></td>
<td>A 53.1 (6.4)</td>
<td>51.0 (4.7)</td>
</tr>
</tbody>
</table>

R=rate. A=amplitude. Ipsilateral n=7, contralateral n=5, HS n=11. Values are means (SD). *Significant difference with Mann Whitney.

Table 9 Grip control during load force perturbation for CS and HS

<table>
<thead>
<tr>
<th></th>
<th>CS</th>
<th>HS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R (N/s) Ipsilateral</td>
<td>Contralateral</td>
</tr>
<tr>
<td>Grip response latency (ms)</td>
<td>2 278 (162)a</td>
<td>285 (117)b</td>
</tr>
<tr>
<td></td>
<td>4 141 (48)</td>
<td>166 (47)b</td>
</tr>
<tr>
<td></td>
<td>8 113 (27)</td>
<td>119 (31)b</td>
</tr>
<tr>
<td></td>
<td>32 95 (3)a</td>
<td>96 (22)b</td>
</tr>
<tr>
<td>Peak grip force rate (N)</td>
<td>2 13.5 (9.5)</td>
<td>12.4 (7.4)</td>
</tr>
<tr>
<td></td>
<td>4 23.6 (11.9)</td>
<td>23.3 (11.0)</td>
</tr>
<tr>
<td></td>
<td>8 48.6 (39.7)</td>
<td>48.6 (30.9)</td>
</tr>
<tr>
<td></td>
<td>32 38.0 (30.4)</td>
<td>33.5 (16.5)</td>
</tr>
<tr>
<td>Deviation of position (mm)</td>
<td>2 0.83 (0.67)</td>
<td>0.89 (0.50)</td>
</tr>
<tr>
<td></td>
<td>4 0.82 (0.46)</td>
<td>1.02 (0.38)</td>
</tr>
<tr>
<td></td>
<td>8 1.30 (0.57)</td>
<td>1.67 (0.62)</td>
</tr>
<tr>
<td></td>
<td>32 1.29 (0.52)</td>
<td>1.56 (0.51)</td>
</tr>
<tr>
<td>A (N) Distribution between fingers (%)</td>
<td>1 3.0 (1.4)</td>
<td>3.1 (0.9)</td>
</tr>
<tr>
<td></td>
<td>2 4.5 (1.5)</td>
<td>4.8 (1.3)</td>
</tr>
<tr>
<td></td>
<td>4 7.3 (1.8)</td>
<td>7.8 (1.2)</td>
</tr>
<tr>
<td>Distribution</td>
<td>1 56.8 (3.6)</td>
<td>54.5 (2.7)</td>
</tr>
<tr>
<td></td>
<td>2 59.1 (3.8)</td>
<td>55.8 (2.7)</td>
</tr>
<tr>
<td></td>
<td>4 59.7 (3.1)</td>
<td>57.3 (2.1)</td>
</tr>
<tr>
<td>GFMI</td>
<td>1 0.37 (0.27)</td>
<td>0.47 (0.20)</td>
</tr>
<tr>
<td></td>
<td>2 0.59 (0.15)</td>
<td>0.64 (0.15)</td>
</tr>
<tr>
<td></td>
<td>4 0.75 (0.12)</td>
<td>0.77 (0.10)</td>
</tr>
</tbody>
</table>

Explanations, see table 8. *The ANOVAS showed significant interaction, hence Mann-Whitney was used, and was significant. bSignificant difference with ANOVA. No other significant differences were found.
DISCUSSION

Results of hand function measurements

Children

As expected, hand strength in children differed between children according to age; the oldest were about four times stronger than the youngest (table 2A, c.f. (50)). There was also a difference by age in their ability to sustain grip strength for 10 s. The ratio of sustained strength in percentage of peak strength was 17% higher in the 14-y-olds compared with the 6-y-olds. This could be due to the youngest children’s lower ability to stabilize the motor output, due to the immaturity of the nervous system.

Charcot-Marie-Tooth disease

In the CMT sample, the grip strength was about 50% of the grip strength of the HS (figure 2). In other studies, grip strength in persons with CMT was somewhat higher – about 67% (94) and 65% (129) of that of healthy controls. Impaired tactile gnosis was found in as many as 80% of the CMT subjects and 35% had a severe reduction (table 4). Other studies have also reported impaired sensation in persons with CMT: in 54% (130, 131) and in 74% (99). The frequency of sensory symptoms may vary between different types of CMT. Sensory loss was more common in CMT type 1 than type 2 – for example, marked sensory loss (88) and thermal and vibratory thresholds (132). However, positive sensory symptoms were also shown to be more frequent in CMT 2 (75%) compared with CMT1 (20%) (130). Varying study samples or methodological differences might explain this. Dexterity was also reduced (figure 2). Accordingly, impaired dexterity was found in 94% of CMT subjects with the Sollereman sum score (87). The studies reviewed show that subjects with impaired sensation have great problems when transporting objects or using tools, even under visual conditions (27).

To obtain an overall picture of a patient’s hand function, the three important aspects of strength, sensation and dexterity were summarized in a total HFI score (c.f. Rosen and Lundborg (133)). The HFI showed a reduction to approximately 60% of normal hand function. It may be a good estimate of overall hand function in persons with CMT, in terms of the ICF dimension of impairment. A regression analysis showed that dexterity did not contribute to the experienced limitation (DASH score). This indicates that grip strength and sensation are the key components of hand function in this population. It has recently been shown that both strength and sensation were predictors for dexterity in CMT (99). Dexterity might thus be redundant in a summarized index for hand
Discussion

function; however, dexterity is valuable because it measures time aspects in addition to strength and sensation.

Knowledge of the development of impairment of hand function in CMT is sparse. One study suggested that the clinical signs of sensory and motor loss do not develop equally, since only 7% of the subjects had normal muscle function while 26% had normal sensation (99). This is supported by our study, where normal grip strength (less than 35N weaker than controls) was found in 10% of the subjects, but 20% had normal tactile gnosis. In another study, following persons with CMT during 10 years, the only strength measures that declined during this period were pinch, grip, and neck flexion strength (129). However, decline in sensation was not evaluated (129).

The median DASH scores in our study were similar for all three dimensions of ICF – impairment, activity limitation, and participation restriction – and for the total DASH score. This indicates that in persons with CMT the total DASH score can be understood to represent all three dimensions of the ICF equally. The present CMT subjects reported a higher level of disability than in a sample in which a median of 13.3(2.7-48.1) was found (101), and a slightly higher level than in another sample with a mean of 28.7±17.8 (100). In patients evaluated with DASH after amputation of a finger and corresponding metacarpal bone, a median of 29.2(3.3-74.2) was found (134). However, the reduction of grip strength was minor in these patients (27% (134)) compared with the CMT subjects (50%). In addition, reduced sensation was found in 80% of the CMT subjects, but was not reported in the amputees. Higher DASH scores could thus have been expected among the CMT subjects because of the greater reduction in this slowly progressive disease. When testing, I was also surprised at the low level of experienced disability in some subjects who had large reductions in, for example, strength. Perhaps the CMT subjects have gradually adapted to a life affected by disease and therefore score a lower level of disability than expected, considering their poor performance on the hand function tests. Acceptance of an injury can aid in reducing the level of disability, since persons with brachial plexus injuries proceeding to amputation, who might have accepted the long-term dysfunction, scored much lower on DASH (mean 39) compared with persons who did not proceed to amputation (mean 66) (135). During the development of DASH, disability was defined by Verbrugge and Jette, who emphasized that disability is a gap between personal capability and environmental demand (67). Perhaps persons with CMT have not only accepted the situation, but also made efforts to adjust their level of activity, modify the environment, or get external support; and this could be a reason for the low level of experienced disability. When interpreting DASH scores it is important for clinicians to be aware that a gradual adaptation to loss of function caused by a slowly progressing disorder might lead to unexpectedly low scores on the DASH.
Cerebellar stroke

Subjects with cerebellar stroke (CS) complained that they felt clumsy, and thus showed reduced dexterity. They needed more time to perform the peg test – which matches another study where all the CS performed abnormally on the Nine-Hole Peg test (106). When comparing results from grip control studies in cerebellar patients, certain difficulties appear. The many different ways to study the complex grip control, and the different ways in which lesions affect the cerebellum – unilaterally, bilaterally, or generally, often affecting additional brain regions – may influence the interpretation.

Effect on ipsilateral grip control following cerebellar lesion

Prolonged response latency (table 9) was found in the CS ipsilateral hand. In contrast to our result, normal response latency was found in a reactive grip study in subjects with various kinds of damage to the cerebellum (stroke and degeneration) when an unexpected load perturbation (2 N, at 3 rates: 8, 32, 200 N/s) was imposed on an object held in a precision grip 4-6 cm above the table (114). Preserved response latencies of ≈100 ms were also found in subjects with degenerative cerebellar disorders when an unexpected load perturbation was imposed on an instrumented object held in a precision grip (113). One reason for these different results could be that the unexpected load in our experiment had less impact and gave less sensory input because of slower force rates and because our subjects did not carry the object and its full weight. Cutaneous feedback is indeed crucial for grip control (1, 23, 24). The slowest force rate of 2 N/s resulted in the most prominent difference between CS and HS, probably giving rise to less distinct sensory input. This rate was slower than the force rates in the previously mentioned study (114). In the two other reactive control studies in CS, the object’s weight was carried by the subjects (113, 114) but in our experiment the arm rested in a vacuum cast and the manipulandum’s weight was not lifted by the subjects. The afferent signals from the arm were most likely more prominent in the other studies than in ours. A recent study showed that afferent signals from the arm contribute to reactive grip control (136). If we had chosen a more slippery surface material, giving even less sensory input, a further distinction may have been seen between the CS and the HS. However, the CS might lose the object, or as a consequence therefore, just increase the force and grasp hard enough not to risk any slips; that would have resulted in no modulation at all. Already in more trials the CS did not have a robust grip reaction (responsiveness), than in the HS. When performing an active voluntary movement with a grasped drawer, the onset of the EMG response and time from impact of the drawer to peak grip force were prolonged in subjects with bilateral cerebellar dysfunction, compared with controls, and this supports our results (115). However, the reactive component in that study occurred during an active movement (115), not during a passive grip.
The variability was larger for response latency in CS compared with HS, which indicated an absence of stability in motor performance. The variability increased with decreasing force rate in CS but also in HS. In line with this, variability was higher with lower force levels (finger abduction 0.4-4N) in healthy subjects (137). The relatively high variability of the response latencies in our study might have to do with the design of the experiment. Efforts were made to create unpredictable reactions, in both sequence and time. In addition, no visual feedback was allowed.

The pre-load grip force in the amplitude set was significantly increased in CS (table 9). Peak grip force rate, static grip force and GFMI did not differ between CS and HS (table 9). Previous studies on predictive control in CS show exaggerated grip force (138-141). However, studies on reactive grip control in CS are contradictory regarding both grip force and response latency. For example, the reactive grip force was found not to be increased in CS (115), but other CS generated clearly increased grip forces compared with the controls (113). Given the earlier findings of exaggerated grip force, and our experience of patients with cerebellar lesions, we hypothesized that exaggerated grip force levels would be found. Generation of excessive forces is frequently found in various forms of motor disability, suggesting a general control strategy to ensure grasp stability (15, 27, 30). Though only pre-load grip force was significantly increased in this study, for some parameters small but insignificant differences were found (e.g. static grip force and GFMI, table 9) which another study also demonstrated (114). These differences might be more evident in larger samples.

**Effect on contralateral grip control following cerebellar lesion**

The grip control of the contralateral hand in subjects with unilateral cerebellar stroke was reduced compared to HS, with prolonged response latencies, a higher frequency of slips of the manipulandum, and longer times to complete the peg test. There are few studies on motor control of the contralateral hand in subjects with unilateral cerebellar damage. Consistent with our results, slower movements and longer time lags in the contralateral hand were found during pointing movements (17). However, these aspects of motor control were predictive rather than reactive. Bilateral activation of the cerebellum (fMRI) has been found in sequential finger movements (18) and during transporting tasks (19). Based on other studies (though none on reactive grip control), we hypothesized that unilateral cerebellar lesions may influence the grip control in the contralateral hand negatively; this too was found. However, to our knowledge this is the only study that includes analysis of reactive grip control in the contralateral hand in subjects with unilateral cerebellar lesions, and more research is needed.
Evaluation of hand measurements

Reliability statistics

The evaluation of reliability can be confusing because of the different jargon used in the context of reliability – terms like ‘consistency’, ‘precision’, ‘repeatability’, and ‘agreement’ (127). Another confusing aspect is the many different procedures used to evaluate reliability. It has certainly not been easy to identify the best analytic tools to use for assessing reliability.

There is no consensus about what constitutes a clinically acceptable level for the correlation coefficient (127). Interpretation of correlation coefficients can be done in four ways (126). Apart from looking at the strength according to different levels, the coefficient of determination can be calculated, statistical significance can be calculated, or the CI can be evaluated (126). Strength has been interpreted according to certain levels. Portney & Watkins suggest <0.5 as poor reliability, 0.5-0.75 as moderate reliability, and >0.75 as good reliability (69). Another scale was suggested by Munro: 0.00-0.25 shows little if any correlation, 0.26-0.49 is low correlation, 0.50-0.69 is moderate correlation, 0.70-0.89 is high correlation, and 0.90-1.00 is very high correlation (123). In a recent review, 0.85 was chosen as a satisfactory reliability level for the evaluated studies (142). The statistical significance of a correlation coefficient does not mean that the correlation represents a strong relationship; it only indicates that the observed value is unlikely to be the result of chance (69). In recent articles the CI interval has often been used for the ICC value. However, only one article suggests how to interpret the CI interval: a meaningful agreement is attained if the lower limit of the 95% CI is at least 0.75 (143). Interpretations are complicated by another two factors: which version of the ICC is used, and the fact that the ICC is dependent on the variability in the data (127). What is ‘acceptable reliability’ is thus a choice between different statistical views and the way the reliability is to be used (for individuals/groups, etc. (72)). In the interpretation of our results we have chosen to use the levels according to Munro and the CI intervals of the coefficients.

The interpretation of absolute reliability statistics is also complicated. First, the terminology can be confusing: different names, such as CR, SDD (smallest detectable difference), or SRD (smallest real difference) can mean the same, or nearly the same. Second, the different assumptions regarding probability levels can be confusing: they sometimes use 68%, sometimes 95%. Third, there is no help to be found in strength levels (as, for example, for the ICC) for SEM% and CV that can be compared between different measurements. In one study, quite arbitrarily, an analytical goal of the CV being 10% or below was selected (128).
It has been suggested that internationally acceptable methods need to be established for how reliability research should be performed and reported \((144)\). This is a great need, since it is still common to report only the ICC value. However, to my knowledge no such agreement has been reached.

**Reliability of strength**

Grip strength in children measured with Grippit was considered reliable except for in the 10-y-olds. The absolute reliability for e.g. SEM between 3-5 N for the 6-y-olds and 17-21 N for the 14-y-olds is considered good. Others reported SEM between 1.6-2.7 kg in children aged 13-17 years \((145)\) which is comparable to our 14-y-olds. The CR ranged between 9-57 N in our study. No other estimate of CR for grip strength in children was found.

Grip strength in persons with CMT was considered reliable because of very high ICC values, good absolute reliability statistics (CR and CV table 5), and no bias. Other studies confirm high ICCs for grip strength \((36, 51, 53, 146)\) in CMT also \((64, 94)\). The CRs indicate that a difference between test occasions should exceed \(\approx 27-29\) N to be regarded as a true change. Only relatively large changes can be adequately detected between consecutive measurements – for example, the limits of agreement for peak grip force in persons with CMT were \(-39-28\) N \((94)\) and for the paretic stroke hand, the CR was 48.2 N \((49)\). The CV for grip strength was \(\approx 6.5\)% \((table 6)\) indicating a low variation, compared with the Jamar dynamometer \((CV 10\%-12\%)(39)\) or the paretic stroke hand using the Grippit \((CV 9.8\%(49))\).

**Number of test trials**

Grip strength testing was performed in three trials in our studies, as well as in previous ones. In healthy adults, the best result occurred in only 1% in the third trial \((51)\). However, the best peak grip value occurred more often in the third trial in children \((13-31\%\) of the trials) and in subjects with CMT \((36\%\) of the trials). Children can exhibit greater learning effects due to developmental processes and the novelty of the task \((86)\). Over the course of the trials they may learn a better technique, or dare to squeeze harder. The motor and sensory loss in person with CMT may make it more complicated to optimize performance immediately. For persons with strokes who also have limited motor and sensory function, the highest value occurred more often in the third trial 29.2% \((49)\) than in healthy adults \((1\%,\ (51))\). So a minimum of three test trials is recommended when maximal grip strength is targeted in both children and in persons with CMT.

**Learning effect**

No significant improvement of grip strength between occasions was found in subjects with CMT. In children, however, there was a systematically
better performance during the second test across the whole sample, but this was less evident in the separate age groups (table 5). This is confirmed by other studies of children (145, 147). One submaximal trial, used for familiarization in study I, might not be enough in children. We suggest that, when testing grip strength in children, more than one submaximal trial should be performed prior to testing.

**Mean or best of three trials**

There is no consensus in the literature regarding the optimal test procedure. It has been suggested that test-retest reliability of grip strength is highest when using the mean of three trials (39, 49, 148-150). However, equally high reliability of the best value and the mean of three trials (37, 51), as well as between only one trial and the best and the mean of three trials (35), has been found.

Reliability analysis in children demonstrated that the best of three trials was slightly more reliable than the mean of three trials for peak grip strength. However, for sustained grip strength the mean of three trials showed slightly higher reliability than the best of three trials. Similar results of high relative reliability with the ICC were found for both the mean and the best of three efforts for maximal grip strength in children (37). In persons with CMT the relative reliability was slightly better for the mean of three trials than for the best of three trials. Our studies thus suggest that these measures are equally useful.

**Peak grip strength and sustained grip strength**

In children peak grip strength was slightly more reliable than sustained strength (table 5). Similar reliability was found between peak and sustained grip strength in persons with CMT (table 5). Other studies of grip strength in adults show diverging results for the reliability of peak and sustained grip strength. Peak grip strength was more reliable than sustained grip strength in several studies (34, 36, 51). However, more reliable sustained grip strength has also been found (53).

**Age differences**

The relative and absolute reliability were lower in the 10-y-olds compared with the other age groups (table 5). At the start of study I, no other studies were found that evaluated reliability of grip strength in different age groups. However, another reliability study of grip strength in children was published recently (38). This study also showed differences between the age groups. The relative reliability (ICC) of both the Lode dynamometer and the Martin vigorimeter were lowest for 7-9-y-olds (Lode: 0.78(0.62-0.88) Martin: 0.46(0.17-0.69)) compared with 4-6-y-olds (Lode: 0.91(0.81-0.96), Martin: 0.76(0.55-0.88)) and 10-12-y-olds (Lode: 0.92(0.85-0.96), Martin: 0.70(0.48-0.83)) (38). The SEM for Lode dynamometer, which measures in N and can be compared with our result, was 6.7 N for 4-6-y-olds, 12.2 N for 7-9-y-olds and 14.6 N for 10-12-y-olds
When comparing Grippit to Lode dynamometer, the reliability of Grippit was better for 6-7-year-olds than for 4-6-year-olds, but the reliability of Lode dynamometer was better for the 10-12-year-olds compared with our 10-year-olds. Perhaps the smaller handle used with the Grippit was one reason for the better reliability in the youngest children; the grip width of the Lode dynamometer was 46 mm. Differences in mood, motivation and attention between test occasions or biomechanical factors such as hand size in relation to handle size might have influenced the performance of the 10-year-olds. In our study the use of the two handles differed between the age groups. All of the younger children used the smaller handle and all of the older used the larger handle. However, of the 10-year-olds, seven used the larger handle (hand size ≥16 cm) and the remaining 13 children used the smaller one, which might have been too small. Not having an optimal handle size might also explain the about twice as high frequency of the best performance in the third trial in this age group. In adults, when using the Jamar dynamometer the reliability was lower for the smallest of five different handles (150). Careful selection of handle size is suggested, but further studies are needed to evaluate the possible contribution of handle size to reliability across different age groups.

As mentioned in the introduction, research on development in children has shown that movement production in healthy children is characterized by a decrease in movement variability with increasing age. Thus, it could be expected that the reliability would be lowest in the youngest children, due to the maturity of the nervous system. This was not found, however, in either our study or the study on Lode dynamometer and Martin vigorimeter (38). Other tasks that are more complex – for example, where discrimination ability is important (which improves until the age of eight years (151)) or includes timing (which improves with age (6)) – might have shown other differences in reliability between ages.

A statistical note on ICC is worth mentioning. The limitation of ICC – that it is dependent on the variability of the sample – was obvious in both our study and the study by Molenaar et al. (38). Analysis of all children increased the ICC level in each study, and masked the lower reliability that was found when analyses were made in age groups (c.f. Lode dynamometer whole sample ICC 0.97(0.95-0.98) (38)).

**Pinch strength**

Pinch strength with a tip grip measured with Grippit in CMT subjects showed very high ICC values. The reliability of the Grippit instrument for pinch strength has not been previously studied. Reliability of three-point pinch has been evaluated in CMT with a hand-held dynamometer (Citec CT 3001) showing an ICC value of 0.95(0.94-0.98) (64), which is comparable to our ICC. The CRs in the present CMT sample were nevertheless high – about a third of the mean strength value (table 6). A bias also existed between the tests, indicating a better performance on the second test occasion. This highlights the confusion about the
Discussion

interpretation of reliability statistics. If only the ICC was focused on, the reliability was very high; but when valuing the CR as well, the reliability was not as satisfactory. Comparing our results with the other study, where CR and CV were not calculated, is thus also problematic. The result from study II indicates that pinch testing in CMT should be interpreted with caution. One reason for the unstable measurements could be the difficulty of obtaining a good finger position and retaining it for 10 s. A better approach in evaluating pinch strength in weak persons could be to use key pinch, which could be easier to standardize and would give higher strength due to a shorter lever arm for the thumb. The peak forces generated with the key pinch grips are about 40% greater than those produced with the tip pinch (1). In addition, some CMT patients are likely to use a pinch that is more lateral than the normal one used in daily life, because the former is stronger; and, in time, they may develop contractures that do not permit a normal pinch between the pulps (102). However, when evaluating the correlation between motor axon loss and three different pinch grips in subjects with CMT, the three-point pinch correlated most strongly (97).

Reliability of sensation

The agreement between tests was very good for the Shape Texture Identification in CMT subjects. A slightly lower kappa value of 0.79 was found in subjects with peripheral neuropathy (55). The STI test showed limitations in terms of how well it can describe the CMT subjects either performing very well (20%) or very poorly (35%) – the so called floor (the scores bottom out) & ceiling (the scores top out) effects – and there was a small distribution across the scale. In persons with severe nerve injuries, though, the raw data of the STI test showed a good distribution on the scoring scale (152). The STI test can most likely be used in CMT subjects to screen sensation deficits, but is not optimal to evaluate changes in sensation because of its limited scale and the floor and ceiling effects.

Reliability of dexterity

The relative reliability was very high for the Box and Block Test in CMT subjects (ICC table 5), as was also found also in elderly people with upper limb impairments (ICC=0.97(0.93-0.98)) (57) and persons with stroke (ICC=0.98) (58). Nevertheless, in CMT subjects, there was a bias towards a better performance in the second test. We chose to do the BBT only once because of the risk of fatigue during the hand testing, which included several measurements. The mean of three trials has been used in persons with stroke, resulting in a ICC of 0.98 (58) – that is, somewhat higher than the present results. The observed bias in study II would perhaps not have existed if the BBT had been performed three times. The CR of 11.5 blocks is considered acceptable when judging changes between test occasions in CMT subjects. No other estimates of CR for the BBT have been found.
Discussion

In CMT subjects the relative reliability of the Nine-Hole Peg test was very high (table 6) – about the same as in a recent study in CMT (ICC 0.95(0.89-0.97) (64). We argue that the CR was acceptable; many people with CMT perform the test slowly, and a time difference of ≈4 s is proportionately small. In another recent study in subjects with multiple sclerosis, a considerable learning effect was found with the NHP test when compared with healthy controls (153). A small learning effect was seen during the three trials in subjects with CMT: the best result occurred most often in the third trial (46%); however, in one week no significant differences were found. The motor and sensory loss in person with CMT may make it more complicated to optimize performance immediately. All four subjects who took longer than 50 s to perform the test had poor sensation (i.e. score 0-1 on the STI test). We chose to let the subjects continue if they dropped a peg; the tester put in another one. This enabled some of the subjects to complete the test within the chosen time limit of 3 min without fatigue, whereas having to restart every time a peg was dropped would have taken longer and caused fatigue. Allowing different techniques, – such as pushing the peg to the corner to get a good grip – also made it possible for some CMT subjects to perform the test. Nevertheless, this test was too difficult for two of the CMT subjects to complete. We recommend that the test be performed three times, that the tester be permitted to add a new peg if the subject drops a peg, and that differing techniques be allowed when the NHP test is used in persons with CMT, and possibly also in other patients with impaired strength and sensation.

Validity of DASH

An instrument’s scores are only useful inasmuch as they reflect a construct, evidence should thus be collected to support this relationship (71). The degree to which DASH could be interpreted as representing some part of the intended construct was evaluated by correlating DASH with the measurements of hand functions at the dimension of impairment according to ICF. DASH was highly correlated with reduced grip strength, tactile gnosis and dexterity (NHP) – that is, the subjects with the most reductions displayed the highest level of disability (table 7). A moderate correlation was found between DASH and dexterity (BBT) (table 7). In line with our results, it was shown in persons with CMT that wrist flexion strength (r= -0.71, p<0.001) (100) and dexterity with the Jebsen (r= 0.61, p<0.05) (101) correlated with DASH. It has been estimated that a grip force of approximately 40N is sufficient for performing up to 90% of daily activities, and that a pinch force of 10N is adequate for accomplishing most of the simple grasping activities that involve the digits (1). The grip strength in our sample was less than 40N in 10% of the subjects, and the pinch strength was less than 10N in 15% of the subjects. This implies that some of the subjects would indeed have difficulty performing the activities measured in DASH due to weakness. However, with even less reduced
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hand strength (70% of CMT > 100N weaker than HS), some activities in DASH – like heavy household chores, gardening or yard work, and carrying a heavy object – would be difficult. In addition, 80% of the CMT subjects had impaired sensation, which might have increased the disability. No further studies on the validity of DASH in persons with CMT were found. However, DASH has been thoroughly evaluated – mainly in patients with musculoskeletal disorders – concerning different aspects of construct validity in addition to test-retest reliability and responsiveness (154); and the research continues (e.g. (155)).

When assessing construct validity the comparison should be with a measurement of similar construct, and a similar trend in score would be expected. A recent study linking DASH to ICF found that, of the 30 items in DASH, 27 were classified according to ICF (5). Five of the items were purely impairment items, 15 were purely activity limitation items, two were participation items, and five items measured both activity limitations and participation restrictions (5). The construct validity evaluated in our study was only in respect of measurements of impairment, which should be reflected in only 5 of 27 items. This is a limitation of the validated aspects. However, measured dexterity might resemble activities in DASH that depend on good finger/hand control, such as writing or turning a key. It would be useful if the construct validity of DASH could be evaluated in persons with CMT, with further measurements at the level of activity and participation according to ICF – especially activity, which represents most of the items included in the questionnaire.

Methodological considerations

Participants

The samples in our studies are all relatively small. Despite this, there are certain factors that strengthen our results. Our sample of children was smaller than the sample in Molenaar et al. (104 children), where grip strength reliability was also assessed in age groups (38). However, they measured reliability in age groups of children with a broader range of ages (e.g. 4-6 yrs), which can affect the ICC value (127). Also our ICC values were very high and stable for the 6- and 14-y-olds, which suggests that we had enough subjects. However, the broad CI ranges in 10-y-olds does imply that the result is not stable. All 24 CMT subjects in three counties of Sweden were offered to take part in studies II and III, resulting in 20 participants. It was not possible to cover a larger geographical area at that time. The CMT sample thus represents almost an entire population of persons with CMT. The CMT subjects showed a wide range of functional levels, which might have contributed to the high correlations. In comparison, other recent reliability studies in persons with CMT have included 15 (99) or 40 subjects (64). A further statistical note on reliability studies is that there is no consensus on how many subjects are
required to get adequate stability for the ICC and SEM (127). The number of subjects in study IV was also limited. However, other studies on reactive grip control in cerebellar subjects have used similar numbers (n=5(113), n=5(115), n=6, 8, 12(114)).

Measurements

Choice of measurements

In the first three studies, the choice was based mainly on the previous use of the measurements in clinics and research, the reliability in earlier studies, and of course the availability and cost of the measurements. An additional aspect was that the test should be mobile, and easy to use in new environments. It is helpful that the Grippit instrument has now been evaluated in two different samples. Using two dexterity tests was shown to be important, since CMT subjects with large reductions of hand function did not manage to complete the more difficult NHP test, – a very common clinical test, and the first choice.

Grip force analysis is a highly sensitive method to document even subtle impairments of finger force control, and may be used both as a diagnostic tool and for the objective evaluation of treatment in neurological disorders (27). The subjects in our study used a pinch grip, in which the cerebellum is activated (156). A reactive control experiment was planned instead of a predictive experiment, because this is a less studied aspect of grip control, which is important in many daily activities. In addition, reactive control is particularly important in persons with cerebellar lesions, due to the suggested role of the cerebellum as a monitor of sensory input; indeed, 40 times more axons are projected into the cerebellum than exit from it (10). The reactive grip control experiment in our study might be considered a ‘simple’ experiment that does not resemble the reactive control needed in real life situations. For example, the subject was sitting still even with the arm in a cast, and the manipulandum was drawn in the same direction. To be able to compare the results between patients and controls, there is a need to standardize the perturbation; that is why reactive studies that resemble real life situations are not easy to design. In our study, however, efforts were made to attain unpredictable reactions, with the forces delivered in an unpredictable sequence at unpredictable points in time. Other reactive grip control studies have designs that are similar to ours. In the future, more complex reactive movements could most likely be evaluated.

The reliability of the apparatus used in the reactive experiment has not been evaluated, which is a limitation. The literature on reliability of techniques used for movement analysis is sparse, but probably growing. For example, kinematic analysis of upper-limb movements (hand-to-mouth/reaching) in healthy subjects showed high relative test-retest reliability for movement duration, but low reliability for angle at elbow
However, the absolute reliability and the reliability in subjects with stroke were not evaluated (157). By way of comparison, the role of motion analysis in elite soccer has been reviewed recently, concluding that measurement precision and reliability of systems have not been satisfactorily demonstrated (158). Intra-session and inter-day measurement reliability of neuromuscular performance (such as peak force and onset latency) of the knee flexors has been evaluated (159). Results showed greater variability of performance across several days compared with intra-sessions assessments; the SEM% indicated limited capability to discriminate performance changes based on single-trial assessments (159). However, the mean of two to 25 trials improved precision (159). Since repeated trials can improve the stability of kinematic measurements, the mean of 10 trials used in study IV may strengthen this result. I agree with the conclusions in two of the studies, that there is indeed a need for researchers to investigate the efficacy and scientific legitimacy of the measurements used for movement analysis (158, 159).

Measurements at the dimension of impairment according to ICF were mostly used in the present investigations. However, a broader perspective was sought by using DASH in the evaluation of hand function in CMT. Some advantages of measurements of impairment after stroke have been discussed (160). They were closely related to the volume of brain loss, and are probably the best markers of prognosis; in addition they can be the most sensitive to change, and have the greatest capacity to differentiate between treatment groups (160). Still, there is a need to measure more on the activity and participation levels according to ICF. At the activity level tests exists, such as Jebsens test. However, the development of measures that capture participation has just begun (160), and there is a growing interest in measurements at this level when hand function is the focus. The use of the DASH, for example, which includes some aspects of participation (5), has indeed increased since the start of our studies.

Bimanual actions represent a complex, highly-coordinated skill category that may need to be assessed, as the majority of activities of daily living are typically executed bimanually (getting dressed, cooking, etc.) (2). Many daily activities are indeed hard to perform with only one hand, even when it functions properly in every aspect. None of our studies looks at the hand roles – a limitation that should be addressed in future studies.

Test procedures

When testing grip strength, verbal encouragement was allowed in study I, but not in study II. It was argued that to maintain the motivation in children they would need verbal encouragement. The amount of verbal feedback has been found to correlate to the level of biceps strength (161), and effort on the treadmill test (162), and to have both objective and subjective influence on the grip strength performance (163). These results indicate that verbal feedback affects performance, probably in children
too. It is important for the clinician to be aware that the amount of feedback might affect the performance. In CMT subjects no verbal encouragement was used, because it was easier to standardize the tests without it.

Type of test property evaluated
Assessment of scores on two or more repeated administrations of a test is often called test-retest reliability (73). This type of reliability was analysed in studies I and II, using the same rater. When a measurement – whether a new measurement or in a new population – is evaluated for the first time, it is natural to start with intra-rater reliability. If this is unsatisfactory there is not much point in continuing the evaluation. The reliability of Grippit in children was never previously analysed, and reliability was not evaluated for the instrument used in the CMT sample either. Another reason for using intra-rater reliability in the CMT study was the geographical spread of the subjects. Since DASH had not been used in CMT subjects before, it was interesting to see whether the results of measurements of strength, sensation, and dexterity were reflected in the DASH. However, this is not considered to be a profound evaluation of the validity of the DASH in subjects with CMT.

Clinical applications
Hand function measurements
Strength, tactile gnosis and dexterity were markedly reduced in this sample of persons with CMT, compared with age- and gender matched controls. For physical therapists it is important to be aware of this when, for example, prescribing walking aids. The three aspects of hand function summarized in an index might be relevant for patients, as a percentage that represents 'remaining hand function'. A regression analysis showed that dexterity did not contribute to the DASH score. This indicates therefore that grip strength and sensory function are the key components of hand function in this population, and in urgent cases should be measured first.

In CS there were reductions in the reactive grip control in both the ipsilateral but also in the 'unaffected' contralateral hand, which is an interesting finding. In rehabilitating patients with CS, an awareness of this possible limitation of reactive grip control is important, especially when exercising in unpredictable environments.

Evaluation of measurements
This thesis could be useful for clinicians when judging different measurements. The results of SEM and CR can be applied in the clinical
setting to estimate measurement error; and the thesis may enhance the understanding of the statistical results from evaluation of measurements.

The evaluation of Grippit showed that both peak and sustained grip strength are reliable in subjects with CMT, and in 6- and 14-y-old children, but are less reliable in 10-y-olds. In children, it is suggested that one submaximal trial should be performed prior to testing, to limit learning effects. At least three trials should be used when maximal strength is targeted in both children and persons with CMT, since the best value often occurred in the third trial. Caution is also suggested when choosing handle size for children. Results from pinch measurements with Grippit in subjects with CMT should be interpreted with caution.

The STI test can be used for tactile sensation screening in subjects with CMT, but it is not suitable for detecting differences between tests because of floor and ceiling effects.

The test-retest analysis of dexterity tests in CMT showed that both the BBT and NHP tests were reliable; however, there was a bias in the BBT. We recommend that the NHP test be performed three times; that the tester be allowed to add a new peg if the subject drops a peg; and that differing techniques be allowed when the NHP test is used in subjects with CMT.

Using DASH in subjects with CMT can be suggested. Disability measured with DASH was highly correlated with reduced function at the dimension of impairment. When interpreting DASH scores it is important for clinicians to be aware that a gradual adaptation to loss of function caused by a slowly progressive disorder such as CMT might lead to unexpectedly low scores on the DASH.

**Considerations when choosing measurements**

The purposes of outcome measures could be regarded as discriminative, predictive, or evaluative (6, 160). When choosing an instrument, it is important to reflect on the purpose of a measurement, preferably in relation to a theoretical framework – such as the ICF. It is also essential to consider the cost and availability of the measurements, but also whether the test is practical. An outcome measure should, whenever possible, be simple, not be time-consuming, and need little special training, because it will improve the patient (and user) compliance (70). For example, a peg was added when one was dropped, making the NHP test less time-consuming. The experience of using the DASH was that the time needed to answer the questions was reasonable. Other aspects of practicality might be that manuals are easy to follow, instructions are clear, the equipment is standardized and moveable, and so on. An advantage with the Grippit is the arm support, which makes it easier to standardize position. For the tester, a test is practical when the results are easy to get
(time to enter responses, scoring, calculating means, etc.). If, for example, the best and mean of three trials are equally reliable, e.g. for grip strength in children, the most practical clinical application is to use the best value. It is also important to keep in mind the level of function in a patient in order to avoid floor and ceiling effects (6). One advantage with the BBT test, used in CMT subjects, was that all were able to finish it, independent of hand status. Another aspect that is valuable to consider is communicability. An outcome measure should provide results that can easily be interpreted by others (70), other members of the clinical team, and above all the patient who is being measured and her/his loved ones.

Clinical measurements should be evaluated regarding reliability, validity and so on, in order to provide meaningful and adequate results. Results from such studies can help in interpretation. Absolute reliability values are crucial for clinical application. SEM can be used when evaluating the error of one test (e.g. when comparing with normal values), and CR when evaluating changes between test occasions (e.g. before and after treatment). When results are interpreted, it is also helpful if normal values exist, for example, for different sexes and ages.

**Implications for future research**

Which aspects of hand function should we measure?

The most evident lack of knowledge concerns sensation tests; there are few standardized tests. Other areas where research is sparse include tests of hand function at the dimension of participation according to ICF and on how the roles of the hands are affected, e.g. from a slowly progressive disease like CMT. An interesting finding when comparing the DASH values in subjects with CMT with the values in another population, was that subjects with CMT scored lower than expected. The reason for this would be interesting to explore, to discover whether aids, or assistance, or the patients’ mental adaptation influenced the experienced level of disability most. There is also a need for further evaluation of the value of summary scores on hand function, as well as the weighting of the including aspects. The best way to evaluate pinch strength in persons with CMT should be targeted in future studies. Pinch grips are crucial in daily life, because loss of thumb function may severely restrict tool use (2).

The cerebellar contribution to grip control of the contralateral hand remains to be researched further. Another interesting area for future study is the possible value of movement analysis in clinics to monitor treatment and rehabilitation (27). A recently-published study showed that upper-limb kinematics were sensitive in assessing motor recovery after constraint-induced movement therapy in subjects with stroke, suggesting that the method could be used in the future for evaluating conditions such as ataxia (157). One advantage with kinematic analysis is that it offers
insight into the mechanisms responsible for the loss of motor control in different neurological disorders.

How should the properties of measurements be evaluated?

Test-retest reliability and some aspects of validity have been investigated. It is valuable to start with the evaluation of reliability and validity when new instruments are developed, or when existing instruments are used in new populations. In the case of reliability, it is to gain knowledge of the stability and error of performance. In the case of validity, it is to know that we are targeting what we intend to measure. When reliability is assessed in children, analysis should preferably be done in groups with small age ranges because of the variability between ages. In addition, more research is warranted to support or contradict our finding with the 10-y-olds. Further reliability testing of the BBT to find methods for limiting bias is also encouraged, but also to explore whether to use the best or the mean of three trials. It would be useful if the construct validity of DASH could be evaluated in persons with CMT, with further measurements at the level of activity and participation according to ICF.

There are, however, other essential properties. In clinics, for example, it is important also that the inter-rater reliability is satisfactory, since sometimes different clinicians test the same patient. In addition, a measure should be able to discriminate between irrelevant changes and clinically meaningful changes, i.e. responsiveness to change (70, 160). Certainly in persons with neurological disorders that can lead to lasting reductions, like CMT and cerebellar stroke, evaluation of responsiveness has great value. Clinicians and patients would benefit if future studies addressed this perspective.

There would seem to be an endless amount of work if every measurement were evaluated for all properties in every population. However, this research shows that studies on the properties of measurements are valuable in specific conditions and can yield relevant clinical applications. Properly examined measurements are indeed crucial for evaluating rehabilitation, which is an important goal of physical therapy. A recent Cochrane review on treatment of CMT also recognizes that there is certainly a need for well-designed trials in CMT, using appropriate measurements (164).
CONCLUSIONS

Grippit is a reliable instrument for measuring peak and sustained grip strength in children and persons with Charcot-Marie-Tooth disease (CMT). The best and the mean of three trials were equally reliable. Measurements of grip strength were more reliable in 6- and 14-year-old children, compared with 10-year-olds. Three repeated trials in both children and in persons with CMT are recommended. In children more than one submaximal test trial is suggested. Pinch grip strength was not as reliable as grip strength in CMT.

The Shape Texture Identification test can be used for tactile sensation screening in CMT, but it is not suitable for detecting differences between tests because of floor and ceiling effects.

The reliability of the Box and Block Test and the Nine-Hole Peg test was good in persons with CMT – except that the performance was systematically better at the second test occasion for the Box and Block Test. Three repeated trials, and putting in a new peg if one is dropped, are recommended for the Nine-Hole Peg test.

The CMT subjects’ hand function was reduced and clearly correlated to their self-experienced disability (Disabilities of the Arm, Shoulder and Hand questionnaire; DASH). Clinicians should be aware that patients might score lower than expected on DASH, possibly due to a long process of adaptation.

Cerebellar lesions can impair the reactive grip control in both the ipsilateral hand, e.g. delayed and more variable onset of response and a higher pre-load grip force, and in the contralateral hand, e.g. prolonged onset of grip response. This suggests that the cerebellum plays an important role in reactive grip control.
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