BEHAVIORAL, MUSCULAR AND DYNAMICAL CHANGES IN LOW FORCE DEXTEROUS MANIPULATION DURING DEVELOPMENT AND AGING

by

Sudarshan Dayanidhi

A Dissertation Presented to the
FACULTY OF THE USC GRADUATE SCHOOL
UNIVERSITY OF SOUTHERN CALIFORNIA
In Partial Fulfillment of the
Requirements for the Degree
DOCTOR OF PHILOSOPHY
(BIOKINESIOLOGY)

August 2012

Copyright 2012 Sudarshan Dayanidhi

Epigraph

“The sheer versatility of the hand, its essential beauty, its contribution to everything we do and the devastation that results from loss of its control all justify the time, energy, resources and imagination that are needed to conclude a successful outcome to this quest.”

Roger N. Lemon (1999)

Dedication

To my parents and my brother for their love and support

Acknowledgements

A doctoral research presents one with many opportunities and difficulties, most of which are achieved and overcome not by one on their own but by help from many people. While this dissertation is my doctoral dissertation there are a large number of people whose presence in these PhD years have helped me achieve my personal goals. Additionally, while this dissertation presents successful outcomes to the research objectives the real learning has happened from the dead ends, the self doubts and the unsaid aspects of this process.

First and foremost I am very grateful to Professor Valero-Cuevas, who while recognizing that I was a nontraditional student never let me think that it would in anyway prevent me from entering a new domain of learning. As an adviser Francisco provided me with every resource I could ask for, always promoted my personal learning while managing to keep me grounded in reality and on track to finish up my PhD. In the course of the past 5 years I have had the opportunity to present our work in many conferences, attend meetings, meet numerous researchers, participate in various collaborative projects nationally as well as internationally, all of which have been an exceptional learning experience. Finally, I would like to thank Francisco, Erika, Marco and Eva for their wonderful hospitality during the many "annual" get togethers at their place as well as for the lab ski trip.

All of my guidance and dissertation committee members were a tremendous support and kept on challenging my thinking. Professor Winstein was a wealth of information and always managed to find time to meet with me as needed, in spite of having a very busy schedule. In addition, the opportunity to be a part of the Rehabilitation Engineering Research Center (RERC) at USC was a fabulous experience and for that I am very thankful. Professor Sanger brought in his encyclopedic resource about developmental aspects in children and in particular, I am very thankful to him for introducing me to the fabulous work done by John Martin's group. In addition, I am thankful to him for giving me the opportunity to be part of the Taskforce on Childhood Movement Disorders in 2008 and 2009. I would also like to thank Professor Schweighofer for taking the time to participate in my guidance committee and be a part of my qualifying exams.

Professor Hans Forssberg, although not officially in my dissertation committee was very instrumental in the design and development of the study in children. He was most gracious and kind with his time and advice during my many visits to Karolinska Institutet. Also I am thankful for his kind hospitality when I was in Stockholm. In addition, despite his busy schedule he made time to participate in my qualifying exams and his input was invaluable.

Professor Jason Kutch was very supportive and willing to share his AMPL facilities and time for me to do one of my dissertation studies. It turned out to be a very interesting study and I am thankful that I was able to do it. In addition, I would also like to thank him for all his advice for my postdoctoral work. Jason was also a friend, who provided a lot of good musical entertainment in many of the "annual" get togethers, in particular his rendition of the music of Nick Drake.

Dr. Åsa Hedberg is an equal contributing author on the first study and I am very thankful to her for all her time, hospitality and kindness shown during my many visits to Karolinska Institutet. In addition I would like to thank Dr. Elena Pavlova, Linda Junker, Isak Hägg and Novalie Lilja for their assistance. Many individuals from Rancho Los Amigos Rehabilitation Hospital were very helpful with recruitment and assistance in the RERC project. In particular I would like to thank Phil Requejo, Juan Garibay, Allison Chu, Kathleen Shanfield for all their help.

Professor Jim Gordon always had something nice and supportive to say to me whenever I have presented in his lab meetings or at the division seminar. The Division of Biokinesiology and Physical Therapy were very supportive with their generous support as were the discussions with my fellow BKN and DPT students.

Kornelius Ràcz and Manish Kurse, were my comrades in arms throughout the PhD process. Manish has been a good friend, a true motivator, an inspiration for camaraderie and organizer extraordinaire. He has been there for these past 5 years through the ups and downs of graduate education. Kornelius, likewise has been a good friend, always willing to discuss my data and suggest ideas for improvement. His minimalist (i.e primarily visual) approach to presentations has helped me a lot in my own presentations. Finally, the classes I took with both Manish and Kornelius without the pressure of trying to finish up my research were probably the most fun aspect of graduate school. I can honestly say that it would have been very difficult to complete my PhD without their friendship, discussions and support.

There are many other friends in the lab who contributed in ways which will not be acknowledged in research papers. I have to thank Brendan Holt for being a fellow public transport user and for introducing me to “A Song of Ice and Fire”, which helped maintain my sanity during a tough last year (*“Valar Morghulis”*), Alex Reyes for being a fellow microbrew aficionado and chess wizard, Josh Inouye for his amazing acronyms (*“Grazie Mille!”*), Na-Hyeon Ko for being a fellow pediatric therapist and social butterfly (*“Gambae!”*), Nora Nelson for her multi-lingual humor and discussions about the Karolinska project, Alison Hu for her help with the RERC project, discussions about my data and above all for asking me some very tough questions, Jon Weisz for his coding skills and rare kaiten sushi nights and Evangelos Theodorou for some very interesting philosophical, supportive discussions and for introducing me to some good music. Finally, all the other unnamed people in the lab were a great support and provided an excellent work environment.

Table of Contents

List of Tables

List of Figures

Abstract

This dissertation focuses on the change in low force ($< 3N$) dexterous manipulation capabilities across the lifespan. A simple device based on the mechanical properties of springs allowed us to systematically test the control and the change of dexterous manipulation skills across the lifespan over 240 participants from 4-89 years of age. Dexterous manipulation capabilities improve dramatically during early childhood and adolescence, followed by gradual declines from the middle age. Here we show that the timelines of development of dexterity are much longer than previously thought and continue well into late adolescence, matching known changes in neural development. In addition, these improvements appear to be poorly predicted by changes in strength and hand anthropometrics.

Muscle twitch properties of the hand muscles, specifically the time-to-peak of the first dorsal interosseous are shown to be slower in early adolescent children and peripheral changes could also be contributing to changes in dexterous manipulation. This was discovered by applying a previously developed noninvasive method, the EMG weighted average (EWA) used for the first time used in children. The parameters used by sensory modalities for dexterous manipulation appear to be different from those used for static tasks. Starting in the middle ages (45-65 years) there is a decline in both the control of fingertip force direction as well as the ability to overcome and postpone instabilities. By

observing the dynamics of the whole time series we are able to show that elderly people and young children share certain aspects of control of the dynamics of manipulation.

Chapter 1

Introduction

1.1 Background

1.1.1 Statement of the Problem

Manual dexterity can be defined as the control of fingertip force direction (Valero-Cuevas, Smaby, Venkadesan, Peterson & Wright 2003). The thumb and index fingers are the most independently controlled (Schieber & Santello 2004) and consequently, precision grip is considered a very dexterous task with specific direct neural control (Muir & Lemon 1983). The hand and the neural control associated with it has evolved over millions of years and in primates skill acquisition of dexterity is a feature of development (Kuypers 1962) and is a particularly protracted one (Armand 1982, Armand, Olivier, Edgley & Lemon 1997). Typically developing children grasp objects with whole handed movements around 2-3 months of age and show improvements in grasping to use the thumb and the index fingers (precision grasp) by around 10 months of age (Forssberg, Eliasson, Kinoshita, Johansson & Westling 1991). Children continue to show improvements in their precision grasp with adult-like behaviors starting around 6-8 years with refinements continuing into the second decade of life (Forssberg et al. 1991) These improvements are due to both neurological maturation as well as learning (Lawrence & Kuypers 1968a, Eliasson, Gordon & Forssberg 1991). Neuroimaging studies indicate the growth of the corticospinal tract and diffuse grasping network occurs well into early adulthood (Armand et al. 1997, Fietzek, Heinen, Berweck, Maute, Hufschmidt, Schulte-Monting, Lucking & Korinthenberg 2000, Lebel, Walker, Leemans, Phillips & Beaulieu 2008, Muller, Homberg & Lenard 1991, Paus, Zijdenbos, Worsley, Collins, Blumenthal, Giedd, Rapoport & Evans 1999) with decrements from the middle ages (Pieperhoff, Hömke, Schneider, Habel, Shah, Zilles & Amunts 2008). Consequently appropriate timelines matching structure and function for manual dexterity need to be elucidated in detail.

Perinatal cerebral palsy affects around 11,000 newborn children every year (Hirtz, Thurman, Gwinn-Hardy, Mohamed, Chaudhuri & Zalutsky 2007), with preterm infants having a 30-fold risk of developing cerebral palsy (Pharoah, Platt & Cooke 1996). Children with cerebral palsy have significant motor delays and lifelong difficulties in mobility and manipulation depending on the extent of the injury (Eliasson et al. 1991). Development of precision grip is severely impaired in these children, with 6-8 year old children demonstrating performance comparable to that achieved by age 1 in typically developing children (Eliasson et al. 1991). Hand rehabilitation in these children is very challenging and requires prolonged periods to show improvements. Importantly, cerebral palsy results in lifelong impairments that lead to poor quality of life and restricted participation in the society.

1.1.2 Phylogenetic Considerations for Dexterous Manipulation

Evolutionarily some motor systems are highly conserved across species; the Corticospinal Tract (CST) is present in all mammalian species (Nudo & Masterton 1990). Briefly the CST, a wide diffuse connection between multiple cortical areas and subcortical areas (Dum & Strick 1991), terminates onto the intermediate zone (dorsolateral & ventrolateral) and onto the alpha motor neurons of the spinal cord (Lemon 2008). Majority of the CST crosses over to form the lateral CST while a small percentage (10-15%) continues as the ventral CST. The CST works in parallel with brainstem pathways mediated via the corticobulbar tract (Lawrence & Kuypers 1968b).

Part of the CST has direct (monosynaptic) corticomotoneuronal connections onto the alpha motor neuron of the spinal cord (Bernhard & Bohm 1954). This system has been attributed to being responsible for fractionation movements in the hand (Lawrence & Kuypers 1968b) and has a specific role in fine control via precision grip (Muir & Lemon 1983). It has been shown that many of the monosynaptic connections project onto the alpha motor neurons related to the intrinsic muscles of the hand (Rathelot & Strick 2006). While the CST is not the only motor system responsible for dexterity, evolutionarily there appear to be two primary changes, namely: a) Increase in the size of the neocortex and the CST (Heffner & Masterton 1983) b) Increase in the projections of the monosynaptic Corticomotor (CM) system with it being very well developed in the primates and most so in the humans (Lemon & Griffiths 2005). While it is difficult to find causality in these changes they are believed to at least partly provide the neural substrate for dexterity in humans (Lemon 1999, Lemon 1993). Additionally there has also been an increase in the size of the lateral cerebellum (Matano & Hirasaki 1997), which has a role in development of neural representations (internal models) for skilled activities such as dexterity (Wolpert, Miall & Kawato 1998).

These studies on elucidating the role of the different pathways were performed in non-human primates (Lawrence & Kuypers 1968a, Lawrence & Kuypers 1968b, Nakajima, Maier, Kirkwood & Lemon 2000, Dum & Strick 2002) and differences exist between human and other species (Courtine, Bunge, Fawcett, Grossman, Kaas, Lemon, Maier, Martin, Nudo, Ramon-Cueto, Rouiller, Schnell, Wannier, Schwab & Edgerton 2007). The exact function of the phylogenetically older pathways in functional movements in humans remains unclear. It has been suggested that the C3-C4 propriospinal (PN) system mediated through the rubrospinal and reticulospinal tracts play a main role in control of the forelimbs in cats, but during evolution their influence over limb control was weakened and taken over by the CST, particularly the CM system (Nakajima et al. 2000, Lemon & Griffiths 2005). There have been a series of studies that have shown that the PN system might in fact be present in humans, but might be under inhibitory control by the cortex (Pierrot-Deseilligny 2002). However in people with stroke or spinal injuries this inhibition might be affected and could be of significant importance in neurorehabilitation (Burke 2001). In addition, while the rubrospinal tract can influence the alpha motor neuron it probably cannot take over the function of the CST after lesions (Nathan & Smith 1982). While there is an increased importance of the CM system in the control of the human hand, all the descending systems interact with each other in a concerted way to control movement (Kuypers 1964).

1.1.3 Ontogenetic Considerations for Dexterous Manipulation

In primates including humans the protracted period of development of hand control includes increased monosynaptic projections for the development of the CM system (Armand, Edgley, Lemon & Olivier 1994), maturation of the CST with increased myelination, conduction velocity and increase in axon diameter (Muller et al. 1991, Paus et al. 1999, Fietzek et al. 2000). While there are corticospinal projections at birth (Eyre, Taylor, Villagra, Smith & Miller 2001) during development there are a larger number of terminations in the spinal cord than that seen later in development and maturity (Martin 2005). There is a change in a cat model of the ipsilateral and contralateral terminations between an immature kitten and older mature cat with gradual elimination and increased contralateral specificity. In fact, one could argue that part of development is to eliminate transient terminations and increase specificity of actions by making it predominantly under the control of one hemisphere.

A number of studies have proposed the idea that the competition between hemispheres for control of the corticospinal projection during development is important for achieving this predominantly unilateral control of the limb (Eyre 2007, Friel & Martin 2007). Specifically, this competition is used to prune the exuberant ipsilateral projections and to increase the density of axon termination onto the spinal cord. Martin and colleagues (Martin, Friel, Salimi & Chakrabarty 2007) propose that this competition is activity-based and works along with the activity- independent processes during specific critical periods. It is important to note that many of the studies in development of the corticospinal (CS) connections as well as on plastic changes in the motor system, specifically in the spinal cord are performed in rats and cats.

This inter-hemisphere competition hypothesis was initially tested in kittens during postnatal CS refinement period, i.e. 3-7 weeks, when the terminations on the spinal cord are refined with elimination of the transient connections (Martin & Lee 1999). During this period unilateral inactivation of the sensorimotor cortex (with muscimol) demonstrated that the CS terminations from the silenced side were very limited (mainly to the contralateral side) while the active cortex maintained immature bilateral projections. Compared to controls the spinal gray area showed a substantial decrease in terminations from the silenced side along with an increase from the active side. These results suggest there is definitely a role of the activity of the neural cortex during this period on refinement of the transient terminations and more importantly the silenced cortex changes the organization of the terminations from both cortices.

In a follow-up study the role of bilateral versus unilateral inactivation was studied to flesh out the role competition between cortices & activation plays on the organization of the CS terminations (Martin & Lee 1999). Most interestingly they reported that bilateral inactivation showed that the transient terminations onto the spinal cord gray matter persisted and importantly were extensive than that seen with unilateral inactivation. These results provide some evidence to the hypothesis that activity-dependent competition between hemispheres during early development shapes the topography of the CS terminations on to the spinal gray matter. Impairments were seen in behaviors in the cats on the contralateral side to the inactivation (in the unilateral inactivation case) and to a less extent on both sides following this period for months in spite of training (Martin, Donarummo & Hacking 2000). More recently (Friel & Martin 2007) followed this idea with a cross-over design where the unilateral inactive M1 became the active cortex in a later post-natal period (week 7-11); the previously active cortex was inactivated. Their results showed a complete recovery of previously impaired motor movements reflecting an importance of bilateral interactions of the CS system for achieving a balance between the contralateral and ipsilateral CST connections.

In human studies (Eyre 2007, Eyre et al. 2001) TMS has played a role in elaborating on activity driven plasticity of the CS projections. (Eyre et al. 2001) tested a small (n=9) longitudinal sample along with a large (n=85) cross-sectional sample to characterize the development of the ipsilateral and contralateral projections of the CS connections on to the spinal cord. They show the presence of ipsilateral projections in neonates, which are withdrawn with competitive maturity. The withdrawal of the ipsilateral projections occurred between 3-18 months when the threshold for ipsilateral responses increased. This is believed to be due to activity-dependent corticospinal axonal withdrawal during development. While TMS provides us with indirect estimates of CS development, it cannot give us precise information as can be obtained from the animal models.

In primates including humans the protracted period of development of hand control includes increased monosynaptic projections for the development of the CM system (Armand et al. 1994), maturation of the CST with increased myelination, conduction velocity and increase in axon diameter (Fietzek et al. 2000, Muller et al. 1991, Paus et al. 1999). In a study exploring the effects of activity on development of the CST (and other white matter tracts) in pianists and non-pianists (Bengtsson, Nagy, Skare, Forsman, Forssberg & Ullen 2005), it was seen that there were increased white matter cytoarchitecture particularly in the posterior part of the internal capsule with both age of start of training and with number of hours practiced in childhood.

In children after a stroke at birth there is a significantly increased withdrawal of corticospinal axons from the infracted hemisphere although there might have been connections present at the time of the stroke (Eyre 2007). There appears to be at least an 18-month period over which this withdrawal occurs. In children with hemiplegia there is reorganization of the central motor pathways and a number of children have persistent ipsilateral CS projections (Carr, Harrison, Evans & Stephens 1993). Hand impairments seem to be worse in those children who only have ipsilateral projections than in those who have mixed control or only contralateral (lesioned) cortical control (Holmström, Vollmer, Tedroff, Islam, Persson, Kits, Forssberg & Eliasson 2010, Vandermeeren, Sebire, Grandin, Thonnard, Schlogel & De Volder 2003). Interestingly there are no monosynaptic (CM) connections in the ipsilateral CST (Muir & Lemon 1983), development of which might be essential for dexterity.

1.1.4 Development of Control

The role of development of anticipatory control is believed to be very important for dexterous manipulation. During grasping it has been demonstrated in adults there is feedforward control of force based on various parameters of the object (Johansson & Flanagan 2009, Johansson & Westling 1988). In children during development, it appears that after 2-3 years of age there is a change from feedback control to feedforward control (Forssberg et al. 1991). At younger ages children are unable to preprogram the forces required to pick up objects; they take longer duration in the phase before the object is lifted, in addition to having a poor scaling between load and grip forces. This is also seen for the use of specific parameters such as weight (Forssberg, Kinoshita, Eliasson, Johansson, Westling & Gordon 1992), tactile conditions (Forssberg, Eliasson, Kinoshita, Westling & Johansson 1995) and visual cues (Gordon, Forssberg, Johansson, Eliasson & Westling 1992) which is thought be related to development of internal models for dexterity.

Children with cerebral palsy have poor anticipatory control (Eliasson, Gordon & Forssberg 1992) and do not seem to be able to develop appropriate cues to information about weight but can adapt to some extent to tactile information (Eliasson, Gordon & Forssberg 1995). However with practice in a blocked fashion with longer number of trials they can adapt to both weight and tactile information (Eliasson, Gordon & Forssberg 1995) indicating that they do have the ability for sensorimotor transformations with anticipatory control. While children with typical development control fingertip forces similar to that seen in adults by the age of eight, children with cerebral palsy require higher amounts of practice in a predictable fashion, perhaps for use of error in learning internal models for eventual development of anticipatory control.

In summary, it can be concluded that the development of dexterity is based on a complex interaction of activity-independent factors and activity-dependent factors during childhood affecting neuroanatomical structures as well as neural control.

1.1.5 Assessment of Fine Motor Abilities & Manipulation

1.1.5.1 International Classification of Function, Disability and Health (ICF)

There are a large number of clinical metrics for evaluation of fine motor function and manipulation abilities as a means of planning and evaluating efficacy of intervention (Eliasson, Forssberg, Hung & Gordon 2006, Sakzewski, Boyd & Ziviani 2007, Gilmore, Sakzewski & Boyd 2009, van de Ven-Stevens, Munneke, Terwee, Spauwen & van der Linde 2009, Greaves, Imms, Dodd & Krumlinde-Sundholm 2010). However evaluating them using the International Classification of Function, Disability and Health (ICF) framework (Fig. 1.1) can provide a comprehensive and clear assessment of the utility and applicability in daily life of these tools as well as provide a means to understand impact of disablement (Nagi 1964), plan treatment, facilitate communication across disciplines and recognize their value for evidence based practice (Stucki, Ewert & Cieza 2002, Jette 2006).

Historically there have been a few models of disablement focused on medical, social and biopsychosocial aspects of disability (Jette 2006). The medical model focused on defining the individual based on their disability for professional intervention (correction or compensation) for the problem, while the social model aimed at defining the social factors causing the disability as means of political and environmental change. However, neither of these models worked for defining the impact of chronic conditions on the functional aspects of life of the people with disability. The biopsychosocial model integrates the two models and the Nagi (Nagi 1964) & ICF (WHO, 2001) are two commonly used frameworks in the field of rehabilitation.

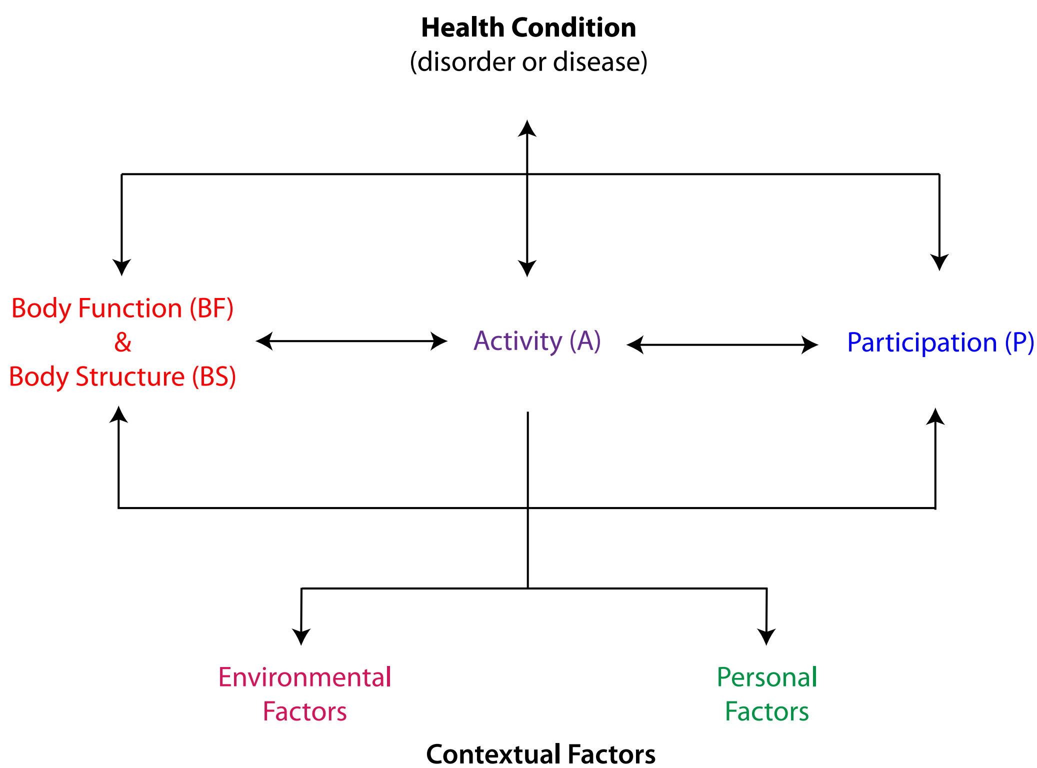

Figure 1.1: The International Classification of Function, Disability and Health (ICF) [modified from (Jette 2006)]

The ICF framework attempts to provide a view of the impact of the health condition on the person from a biological, personal and social perspective. The main relevant domains in this framework are:

1. Body Functions & Structure - Body Functions (BF) are physiological functions of body systems while Body Structure (BS) are anatomical parts of the body such as organs, limbs.

2. Activity & Participation- Activity (A) is execution of a task/action by an individual while Participation (P) is involvement in daily life.

In addition A &P includes two important qualifiers: Capacity and Performance. Capacity is defined as the ability to perform an action or task (i.e. can do without the use of any assistance), while performance describes what an individual does (does do) in a real world environment (with the use of whatever assistive devices the individual uses daily, if any). So in essence the dimensions under which clinical tools should be evaluated are BF, BS, A&P capacity and A&P participation. Each of them provide relevant information and a true understanding of a persons disability should integrate these domains.

1.1.5.2 Clinical Assessment Tools

The commonly used clinical tools for assessment of hand function will be evaluated for both quality and for the dimension in the ICF that they test (Table 1.1). These do not include tests which are based on questionnaires of participation such as the Childrens Assessment of Participation and Enjoyment (CAPE), School Function Assessment (SFA) etc. because these do not test and measure participation but are scored based on general observation and information from children and caregivers [for a comprehensive review see (Sakzewski et al. 2007)].

1.1.5.3 Quality Analysis of Clinical Measurements

These clinical assessment scales were evaluated for quality (1-6) on the basis of studies showing validity (construct, criterion and content) and reliability (interrater, intrarater and test-retest), in addition to showing specificity and applicability in children and adults (if the test is used with both). Minimal quality was given if the studies were published in a peer- reviewed journal and were indexed on Medline. This is summarized in Table 1.2.

This classification of quality of clinical measures is subjective and not a meta-analysis considering levels of evidence. The scales with score 4 and higher were considered to have high quality and are compared in the ICF framework. Of the fifteen clinical measures considered five met this score of high quality, of which four are used in children and one in adults.

1.1.5.4 ICF-High Quality

The five tests were reviewed against which dimension in the ICF framework they test. This is summarized in Table 1.3.

Overall the highest quality tests measure performance and participation in daily life based on observation of a number of functional tasks which correlate well with the ICF framework. However these studies do not measure specific force or dexterity deficits,

Clinical Tools of Fine Motor Ability	**Target Population**
1.Range of Motion (Gajdosik & Bohannon 1987)	Adults/Children
2.Pinch Strength (Mathiowetz, Weber, Volland & Kashman 1984, Mathiowetz, Volland, Kashman & Weber 1985, Mathiowetz, Wiemer & Federman 1986)	Adults/Children
3.Muscle Tone-Modified Ashworth Scale (Bohannon & Smith 1987)	Adults/Children
4.Purdue Pegboard(Mathiowetz et al. 1986)	Adults/Children
5.Nine Hole Test (Kellor, Frost, Silberberg, Iversen & Cummings 1971)	Adults/Children
6.Box and Blocks (Mathiowetz et al. 1985)	Adults/Children
7.(Pediatric) Jebsen-Taylor (Jebsen, Taylor, Trieschmann, Trotter & Howard 1969, Taylor, Sand & Jebsen 1973)	Adults/Children
8.Assisting Hand Assessment (AHA) (Krumlinde-Sundholm, Holmefur, Kottorp & Eliasson 2007)	Children
9.House classification (House, Gwathmey & Fidler 1981)	Children
10.Shriners Hospital Upper Extremity Evaluation (SHUEE) (Davids, Peace, Wagner, Gidewall, Blackhurst & Roberson 2006)	Children
11.Manual Ability Classification (MACS) (Eliasson et al. 2006)	Children
12.Melbourne Assessment (Johnson, Randall, Reddihough, Oke, Byrt & Bach 1994)	Children
13.Quality of Upper Extremity Skills Test (QUEST) (DeMatteo, Law, Russell, Pollock, Rosenbaum & Walter 1993)	Adults/Children
14.Fugl Meyer (Fugl-Meyer, Jaasko, Leyman, Olsson & Steglind 1975)	Adults
15.Strength-Dexterity (Valero-Cuevas et al. 2003, Vollmer, Holmström, Forsman, Krumlinde-Sundholm, Valero-Cuevas, Forssberg & Ullén 2010)	Adults/Children

Table 1.1: Clinical instruments of fine motor ability in adults and children

Clinical Tools of Fine Motor Ability	Quality	Validity	Reliability	Specificity/ Norms	Comments
1.Range of Motion	2	-	(Gajdosik & Bohannon 1987)	-	Some reliability
2.Pinch Strength	2	-	(Mathiowetz et al. 1984)	(Mathiowetz et al. 1985, Mathiowetz et al. 1986)	Norms in children and adults but not reliability
3.Muscle Tone (Modified Ashworth)	1	Poor (Fleuren, Voerman, Erren-Wolters, Snoek, Rietman, Hermens & Nene 2010)	(Fleuren et al. 2010)	-	No validity, reliability in children
4.Purdue Pegboard	2	(Tiffin & Asher 1948)	(Tiffin & Asher 1948, Gallus & Mathiowetz 2003)	(Mathiowetz et al. 1986)	No validity in children, norms in14-19 year olds
5.Nine Hole Test	3	(Smith, Hong & Presson 2000)	(Smith et al. 2000)	(Oxford Grice, Vogel, Le, Mitchell, Muniz & Vollmer 2003)	norms in 5-10 year olds
6.Box and Blocks	3	(Platz, Pinkowski, van Wijck, Kim, di Bella & Johnson 2005)	(Platz et al. 2005)	(Mathiowetz et al. 1985, Platz et al. 2005)	No validity studies in children
7.Jebsen-Taylor	2	(Davis Sears & Chung 2010)	-	-	No reported validity, reliability studies in children

Table 1.2: Assessment of quality of clinical instruments for fine motor ability

8.Assisting Hand Assessment (AHA)	6	(Krumlinde-Sundholm et al. 2007)	(Krumlinde-Sundholm et al. 2007, Holmefur, Krumlinde-Sundholm & Eliasson 2007)	(Krumlinde-Sundholm et al. 2007)	Well tested for bimanual control in children with hemiplegia
9.House Classification	1	-	-	(House et al. 1981)	Not much information on reliability and validity
10.Shriners Hospital Upper Extremity Evaluation (SHUEE)	3	(Davids et al. 2006)	(Davids et al. 2006)	(Davids et al. 2006)	Only 11 children with hemiplegia were tested
11.Manual Ability Classification (MACS)	5	(Eliasson et al. 2006)	(Eliasson et al. 2006)	(Eliasson et al. 2006)	Good validity, reliability for a classification system.
12.Melbourne Assessment	5	(Johnson et al. 1994)	(Randall, Carlin, Chondros & Reddihough 2001)	-	Valid for use in children with cerebral palsy from 5-15 years of age
13.Quality of Upper Extremity Skills Test (QUEST)	4	(DeMatteo et al. 1993)	(DeMatteo et al. 1993)	-	Valid for use in children with cerebral palsy from 1.5-8 years of age
14.Fugl-Meyer	4	(Platz et al. 2005)	(Platz et al. 2005)	-	Valid for use in adults
15.Strength-Dexterity Test	3	(Vollmer et al. 2010)	(Valero-Cuevas et al. 2003, Vollmer et al. 2010)	-	Valid for use in typically developing children 4-17 years of age

Table 1.2, Continued

Test	**ICF BF BS**	**ICF A& P Capacity**	**ICF A&P Performance**	**Functions Measured**
1.Fugl-Meyer	*	*	-	Quality of movement
2.QUEST	*	*	-	Quality of movement
3.Melbourne	-	*	-	Speed of movement. Functional tasks like drawing
4.MACS	-	-	*	Participation in daily life. If assistance is required. Does not directly measure capacity.
5. AHA	-	-	*	Bimanual abilities in daily life. Daily life tasks like grasp & release, coordination.

Table 1.3: Clinical tests for fine motor ability in the context of the ICF

which in combination with one of these tests could provide more information for rehabilitation planning, intervention as well as follow-up. More studies are required evaluating the validity, reliability and specificity of measures of ICF BF BS and their correlations with the measures of ICF A&P.

1.2 Previous Work

In a series of innovative studies the development of precision grip in children with typical development (Eliasson, Forssberg, Ikuta, Apel, Westling & Johansson 1995, Forssberg et al. 1991, Forssberg et al. 1995, Forssberg et al. 1992, Gordon et al. 1992) and in children with cerebral palsy (Eliasson et al. 1991, Eliasson et al. 1992, Eliasson, Forssberg, Ikuta, Apel, Westling & Johansson 1995, Forssberg, Eliasson, Redon-Zouitenn, Mercuri & Dubowitz 1999) was elaborated using a stable grasp paradigm. Traditional methods of evaluating dexterity have been used to look at composite aspects of motor control and dexterity typically using tasks which use the whole upper extremity or with timed tasks (Gilmore et al. 2009, Johnson et al. 1994, Mathiowetz et al. 1986, Poole, Burtner, Torres, McMullen, Markham, Marcum, Anderson & Qualls 2005, Smith et al. 2000, Taylor et al. 1973). With all these methods the common underlying factor is that they have used stable objects while not specifically looking at the control of fingertip force direction. In the real world there is a significant cost associated with failure (like breaking objects) and dexterity depends on precision of task performance.

The manipulation ability of the hand is defined by the mechanical effect each of the fingertips can produced on the object being held (Valero-Cuevas et al. 2003). For effective manipulation the magnitude and direction of the fingertip forces are dynamically regulated. Based on this rigorous definition of the building blocks of dexterous manipulation the Strength-Dexterity paradigm was designed and developed to quantify the dynamic interaction between fingertip forces (strength) and directional accuracy (dexterity). The strength-dexterity paradigm is an innovative method of looking at hand function based on the principle of buckling of compression springs. Under this paradigm strength requirement is defined as the force necessary to compress the spring; the dexterity requirement is the ability to regulate the fingertip movement and consequently the direction of fingertip force vectors to compress the slender springs without buckling.

The mechanical independence of the strength and dexterity requirements in a spring was used to create a set of springs with different strength and dexterity requirement, where each spring has a specific pair of requirements. In other words each spring represents a point on the strength-dexterity plane. This plane was approximated by a kit with 87 springs with different combinations of stiffness and slenderness. The original kit has 8 dexterity levels (A-H) with the dexterity index values ranging from 0.28 (the spring will never buckle even with both sides free to rotate and shift) to 2.33 (the spring can buckle even when both ends are held parallel to each other) and 14 strength levels (from 1 to 92 N). The dexterity index is defined by the mean diameter of the spring, spring constants depending on material properties, springs free length, and the maximum distance the spring can be compressed before reaching solid length (Valero-Cuevas et al. 2003). This version of the SD paradigm has been found to be repeatable and sensitive in the elderly (Valero-Cuevas et al. 2003).

The SD paradigm was the basis of a subsequent study evaluating sensorimotor capabilities for dynamic manipulation in adults using a single finger (Venkadesan, Guckenheimer & Valero-Cuevas 2007). Bifurcation theory provides methods to analyze the behavior of very complex nonlinear dynamical systems (Venkadesan et al. 2007), such as dynamic fingertip forces. By using bifurcation theory they were able to quantify how the limits of dynamic fingertips forces are reached. Analyzing the nonlinear dynamical behavior of how participants delay or prevent spring buckling provides vital information about how neuro-muscular-skeletal interactions produce dynamic manipulation. A clear transition to instability (bifurcation) is observed in 3-D position data past a critical compression load. In addition, the projection of the position data close to the instability onto a horizontal plane lies along a straight line ($R^2 \geq 0.8$), which is indicative of reduction of dimensionality characteristic of bifurcated systems. Importantly, this work also showed that compressing such springs utilizes, and is informative of, a sensorimotor integration process but not a passive peripheral strategy. The maximal compressive force was similar across healthy people regardless of their hand strength, and was sensitive to the integrity of sensory signals.

Subsequent work further confirmed that the SD paradigm can be used as a means to quantify cerebral sensorimotor processes that produce dexterous manipulation. Given the complex interaction between the central nervous system and manipulation, a critical question is whether the musculoskeletal properties of the periphery dominate this behavior, or if there is significant cortical involvement associated with controlling dexterous manipulation in the SD paradigm. Three published studies (Mosier, Lau, Wang, Venkadesan & Valero-Cuevas 2011, Talati, Valero-Cuevas & Hirsch 2005, Holmström, Lennartsson, Eliasson, Flodmark, Clark, Tedroff, Forssberg & Vollmer 2011) show significant cortical involvement when using the SD paradigm. Specifically there are different networks associated with Strength/Stable tasks and with Dexterity tasks. Importantly, this cortical involvement is very sensitive to the sensory conditions and small changes in the mechanical requirements and stability characteristics of the SD spring used. Therefore, the SD paradigm is an effective means to bilaterally engage a wide variety of sensorimotor networks in the brain, and is therefore, uniquely suited to assess the integrity of brain function specific to dexterous manipulation.

In children with typical development the SD paradigm has demonstrated internal scale validity as a means to measure improvement of fingertip dexterity with age (Vollmer et al. 2010). In addition the correlation of the SD paradigm with gross manual dexterity (Box and Blocks test) and pinch strength was examined. The SD paradigm has a significant non-strength, non-box and blocks variance, which reflects sensorimotor integration for dexterity. In essence the SD paradigm is indicative of a latent sensorimotor performance trait that improves with age and is different from, and complementary to, strength and gross hand-arm function. Importantly this test demonstrated some evidence for sensitivity to hand impairment in children with cerebral palsy and with refinement can be made into a clinically useful metric of fingertip force coordination.

This landmark study demonstrates the use of an unstable grasp paradigm in children with typical development. However by using the first version of the SD paradigm it evaluates a combined performance of strength and dexterity and not all of the tested springs demonstrate instability. Secondarily while informative of development of hand function in children, it is not necessarily informative specifically of development of dexterity. Additionally it requires children to be tested on a large number of items; upwards of at least 60 that have varying strength and dexterity requirements, for which a binary score is computed (1 or 0 i.e. successful in compressing the spring or not). The composite score in and of itself might or might not be informative of control of fingertip force direction. Finally the use of that setup does not allow an understanding of the dynamical behavior at the limits of performance, which might yield insights into directional control.

1.3 Significance of Research

These innovative results indicate that the strength-dexterity paradigm is an ideal system for challenging the developing neuromuscular system to be able to quantify the development of dexterous manipulation. In particular, there is a need for appropriate measurement of dexterity during development and in children with cerebral palsy. Not only can such a system help measure impairments in children with disabilities but also can help plan treatments specifically focused on challenging the system for skill acquisition. A primary goal of this dissertation is to elaborate on the specific timelines and test the processes involved in the improvements of dexterous manipulation during the course of development and in aging. It is anticipated that the results of this work will significantly advance the current state of knowledge regarding acquisition of manual dexterity in children, elderly people as well as promote methods for rehabilitation in children with cerebral palsy and in people aging with and into a disability.

1.4 Dissertation outline

1.4.1 Chapter 2

This chapter is about the development of dexterous manipulation abilities in children (4-16 years of age). This was done in collaboration with Karolinska Institutet, Sweden. Professors Hans Forssberg and Valero-Cuevas have guided the project with Dr. Åsa Hedberg and I being equal contributors to this study. Part of this work has been presented at the 35th annual meeting of the American Society of Biomechanics in 2011 and at the 22nd Annual Meeting of the Society for Neural Control of Movement in 2012.

1.4.2 Chapter 3

This chapter elaborates on the study looking at muscle twitch properties with the use of the EMG weighted average (EWA) in early adolescent girls. This work was done in collaboration with the Applied Mathematical Physiology Lab (AMPL) at USC under the guidance of Professors Jason Kutch and Valero-Cuevas.

1.4.3 Chapter 4

This chapter looks at the influence of different surface and vision conditions on dexterous manipulation abilities. This pilot work was done under the guidance of Professor Valero-Cuevas and was presented at the 19th Annual Meeting of the Society for Neural Control of Movement in 2009.

1.4.4 Chapter 5

This chapter looks at the change in low force dexterous manipulation in adults (18-89 years of age). This was done as part of the Rehabilitation Engineering Research Center (RERC) on Technologies for Successful Aging with Disability at USC and Rancho Los Amigos National Rehabilitation Center under the guidance of Professor Valero-Cuevas. Part of this work and some earlier forms have been presented at the Annual Conference of the Rehabilitation Engineering and Assistive Technology Society of North America in 2009 and at the 35th annual meeting of the American Society of Biomechanics in 2011.

1.4.5 Chapter 6

This chapter looks at the change in dexterous manipulation capabilities across the lifespan by combining data from Chapters 2, 3 and 5. This was done under the guidance of Professor Valero-Cuevas and part of the work has been presented at the 35th annual meeting of the American Society of Biomechanics in 2011.

Chapter 2

Development of Dexterous Manipulation in Childhood

2.1 Abstract

Neural control of dexterous manipulation is attributed to specific neuroanatomical structures whose connectivity and function are known have a prolonged period of development into late adolescence. In contrast, functional improvements in dexterous manipulationas measureable by current developmental and clinical milestonesshow few changes past the age of eight because most measures of hand function saturate. We now show that an extension of our prior work bridges this apparent discrepancy and establishes a novel and clear link between known neuroanatomical development and dexterous manipulation well in to late adolescence. Importantly, musculoskeletal growth and strength are poorly correlated with these functional improvements in dexterity. These results begin to clarify the behavioral benefits of such neural maturation, enable the systematic study of specific neuroanatomical structures, their connectivity, and plasticity. For example, neuroimaging studies to disambiguate the differential roles and contributions of maturation of the corticospinal tract vs. the emergence of fronto-parietal and cortico-striatal-cerebellar

networks. Clinically, this extends the ages for which therapeutic interventions can be considered fruitful, and provides a clinically-practical means to chart functional development of dexterous manipulation in typically developing children, and children with neurological conditions.

2.2 Introduction

Dynamic control of fingertip force magnitude and direction is the paramount requirement for manipulation of small, deformable and fragile object. Neural control of dexterous manipulation is attributed to a distributed network of control for small force, precise dexterous manipulation; specifically the primary sensory motor cortex, the dorsal premotor area (PMd), the ventral premotor area (PMv) and the supplementary motor area (SMA) (Bernhard & Bohm 1954, Ehrsson, Fagergren & Forssberg 2001, Muir & Lemon 1983, Porter 1985, Rathelot & Strick 2006, Bonnard, Gallèa, De Graaf & Pailhous 2007, Davare, Andres, Cosnard, Thonnard & Olivier 2006, Ehrsson, Fagergren, Jonsson, Westling, Johansson & Forssberg 2000, Gallèa, de Graaf, Bonnard & Pailhous 2005, Holmström et al. 2011, Kuhtz-Buschbeck, Ehrsson & Forssberg 2001, Mosier et al. 2011), all of which form a part of the CST. Their connectivity and function are known have a prolonged period of development into late adolescence (Armand et al. 1997, Fietzek et al. 2000, Lebel et al. 2008, Muller et al. 1991, Paus et al. 1999). In contrast, the functional improvements in dexterous manipulation — as measured by current developmental and clinical milestones — show few changes past the age of 8 (Deutsch & Newell 2001, Deutsch &

Newell 2002, Eliasson, Forssberg, Ikuta, Apel, Westling & Johansson 1995, Forssberg et al. 1991, Forssberg et al. 1995, Forssberg et al. 1992, Gordon et al. 1992).

The Strength-Dexterity Test (SD) provides an innovative way to dynamically test the control of dexterous manipulation (Mosier et al. 2011, Valero-Cuevas et al. 2003, Venkadesan et al. 2007), defined as the ability to control fingertip force magnitudes and directions (Valero-Cuevas et al. 2003). Recently, this paradigm was shown to capture the development of a latent behavioral trait of dynamic fingertip force coordination in typically developing children through adolescence (Vollmer et al. 2010) over a range of voluntary force magnitudes. That study was the first to demonstrate behavioral correlates in dexterous manipulation to known neural maturation throughout adolescence but, by testing over the range of voluntary force magnitudes, the latent variable we detected is a compound of both sensorimotor processing and finger strength. Most importantly, the change in the ability to control small forces that require a high amount of precision was shown to be the area in manual skills that displays large switch during development (Fig. 2.1).

This study focuses on clearly establishing the relationship between the known timelines of neuroanatomical development and this novel means to grade behavioral improvements in dexterous manipulation. We extend the previous work by (i) specifically focusing on a subset of the Strength-Dexterity Plane informative of dexterous manipulation capabilities requiring low strength; (ii) removing the enslaving effects between the index and middle finger by only testing index-thumb precision pinch; (iii) using a brief (<15 min), clinically-practical version of the Strength-Dexterity Test; (iv) uniformly sampling performance in 130 children spanning 4-16 yrs years of age; and (v) demonstrating an empirical metric of the development of dexterous manipulation that has sensitivity through adolescence, and which has also been shown to be associated with specific fronto-parietal and cortico-striatal-cerebellar networks.

2.3 Methods

130 children (4-16 yrs, 76F/54M) participated in this study. Ethical approval was obtained from an institutional review board and all subjects and parents consented to participate in this study.

2.3.1 Instrumentation for Dexterity Instrument

Four custom-made springs (Century Springs Corp., Los Angeles, CA) that require low force for complete compression and have the same stiffness (k=0.49 lb/inch) were used (Table 2.1). These four springs were chosen to provide higher resolution in dexterity while maintaining a low strength requirement identified from (Vollmer et al. 2010) (Fig. 2.1). In addition the following criteria were used: less 4 N of force (Ehrsson et al. 2001) and length between 2-4 cms. Pilot studies confirmed that the properties of the custom-made springs would possibly cover the dexterity range for the ages 4 to 16 years.

Two compression load cells (ELB4-10, Measurement Specialties, Hampton, VA) were mounted at the spring endcaps (Fig. 2.2). The load cells were connected to a signal-conditioning box, an USB-DAQ (Measurement Computing, Norton, MA) sampled the data at 400 Hz using a custom written MATLAB program (Natick, MA) and a deadweight calibration procedure was used for conversion from voltage to force.

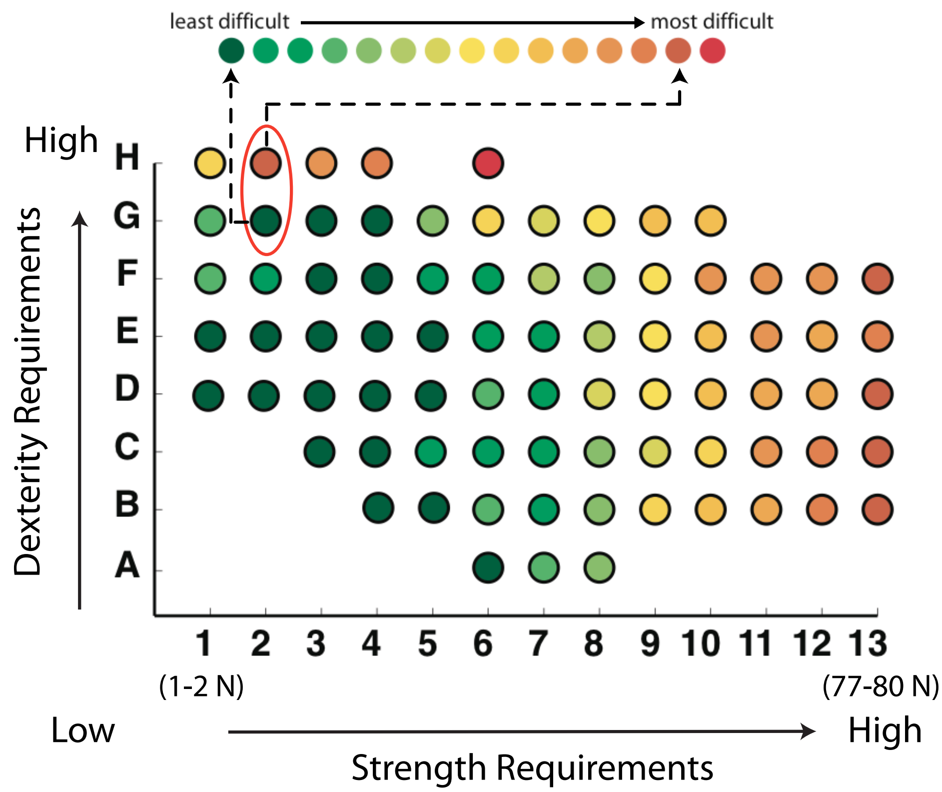

Figure 2.1: The Strength-Dexterity plane (Valero-Cuevas et al. 2003) created to have increasing strength requirements along the x-axis and increasing dexterity requirements along the y-axis. The results from (Vollmer et al. 2010), color-coded for difficulty, demonstrate the large switch in difficulty in performance in children when they go from item G2 to H2, implying that a higher resolution in this transition could provide a better gradation of changes in dexterity. The strength requirements in this column 2 is only between 2.2 -2.7 N.

2.3.2 Experimental Procedure

The aim of the task was to keep a sustained compression, with the index finger and the thumb of their dominant hand, for at least three seconds at the highest individual level of control of force magnitude and force directions. After a brief familiarization with

	Spr 1	Spr 2	Spr 3	Spr 4
Free Length (cm)	3.96	3.6	3.24	2.90
Solid Length(cm)	0.69	0.69	0.69	0.69
Force Range(N)	0-2.84	0-2.5	0-2.19	0-1.89

Table 2.1: Spring specifications of the experimental setup. The four springs used had the same stiffness (k= .8581 N/cm) but different length and low forces were required for full compression of the springs.

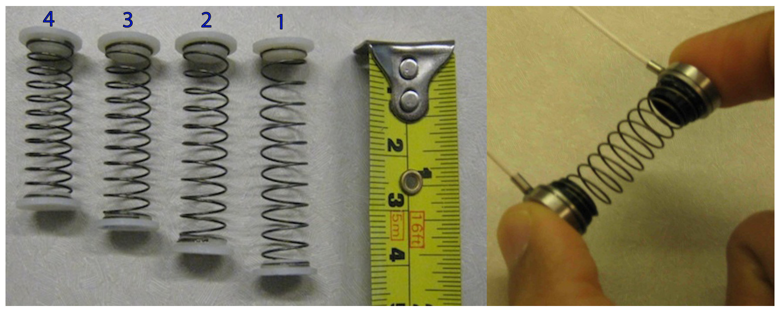

Figure 2.2: Strength-Dexterity Setup demonstrating the four springs and the hardware for force data capture. The springs were custom made such that the spring stiffness was maintained the same (k=0.86 N/cm) across all the four springs. The lengths of the springs varied from 2.90- 3.96 cm, while the maximum force required for compression of the springs ranged from 2-3 N of force. Compression load cells were mounted on custom ABS plastic endcaps with double-sided tape. The springs were presented in a sequential order from the shortest, i.e. spring 4 and the test spring was chosen such that it was the first spring the subject was not able to compress fully, i.e. the minimally-impossible-to-compress spring. The figure on the right shows an example compression and hold.

all springs and the task, the springs were presented in order, starting with the shortest (Spring 4) to identify a spring the subject could not compress fully, i.e., Spring 3, 2 or 1. This spring was identified as the test-spring. After test-spring identification, the subjects were asked to firstly compress their test-spring to the point at which the device would slip out of their hand, in order to identify their level of control. They were then asked to compress the spring as close as possible to that point and maintain that compression at a steady level for at least three seconds (Fig. 2.2). At least three successful compression holds were collected per subject.

Pinch strength with the index finger and the thumb of the dominant hand using a tip-to-tip pinch was measured using pinch gauge (B&L Engineering, Tustin, CA, USA). The subjects were asked to compress the pinch meter with maximum force for a couple of seconds and the maximal value of two attempts was used. Fine motor precision was tested using subtest one for Fine Manual Control of the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2). The summed raw scores of the subtest were used to confirm typical fine motor development in the population.

For anthropometrics measures, the dominant hand was photographed in three positions; dorsal view, palmar view and radial view. This data were obtained only in 94 subjects. Anthropometric data were extracted regarding thumb length, index finger length, hand size as well as 22 other measures.

2.3.3 Data Reduction

A custom written MATLAB © (Mathworks, Natick, MA) program was used to visually identify (ginput) the sustained compression phases based on the force and force rate. To facilitate this in the presence of high frequency dynamic changes in the force, we used a loess smoother with a span of 10% before the force rate was computed. We defined a sustained compression phase when the rate was bounded within 1 standard deviation of the mean force rate. The start was identified when the rate was close to zero and the end when the rate went out of bounds and the force dropped towards baseline. The sustained compression phase data were downsampled to 100 Hz, low pass filtered at 25 Hz while maintaining phase (Butterworth, filtfilt). The average of the two finger force time series were computed to create a representative force.

The springs were weighted such that for each subject a Dexterity score was computed by summing the maximum force of each spring they could compress fully, plus the maximal force they could keep in their test-spring, normalized to that maximally possible over the four springs. In addition dead band of force between the springs were removed. So if a child were able to compress spring 1 completely they would get a score of 100%. For most children in our study Spring 1 or 2 were used as the test-spring (three children of the age of four used Spring 3). In order to characterize the dynamics of how children control the dexterity device during the sustained compression we examined the data in state space. We calculated the normalized sum of Euclidean distances of the trajectories through the time series of the hold phase.

2.3.4 Statistical Analyses

The independent variables of interest were age and gender while the dependent variables were a) the Mean of the three maximal holds, b) Maximal hold, c) Dexterity score during maximal compression and d) Dynamics during maximal hold compression. The dexterity score was computed as a weighted average based on the mean hold force on the impossible-to-compress spring and normalized to the maximal possible value. In addition dead band in forces in the high and low ranges were removed for the springs. Regression analyses were performed to look at shared variances between pinch strength and maximum performance in dexterity as well as between hand size and maximal performance in dexterity.

2.4 Results

2.4.1 Improvements in Individual Spring Forces

There is a consistent increase in the ability to overcome instability as seen with the increased force in both spring 1 & spring 2. Statistical differences ($p<0.05$) are seen in the average of the best 3 hold phases across the ages as seen in the boxplots (Fig. 2.3).

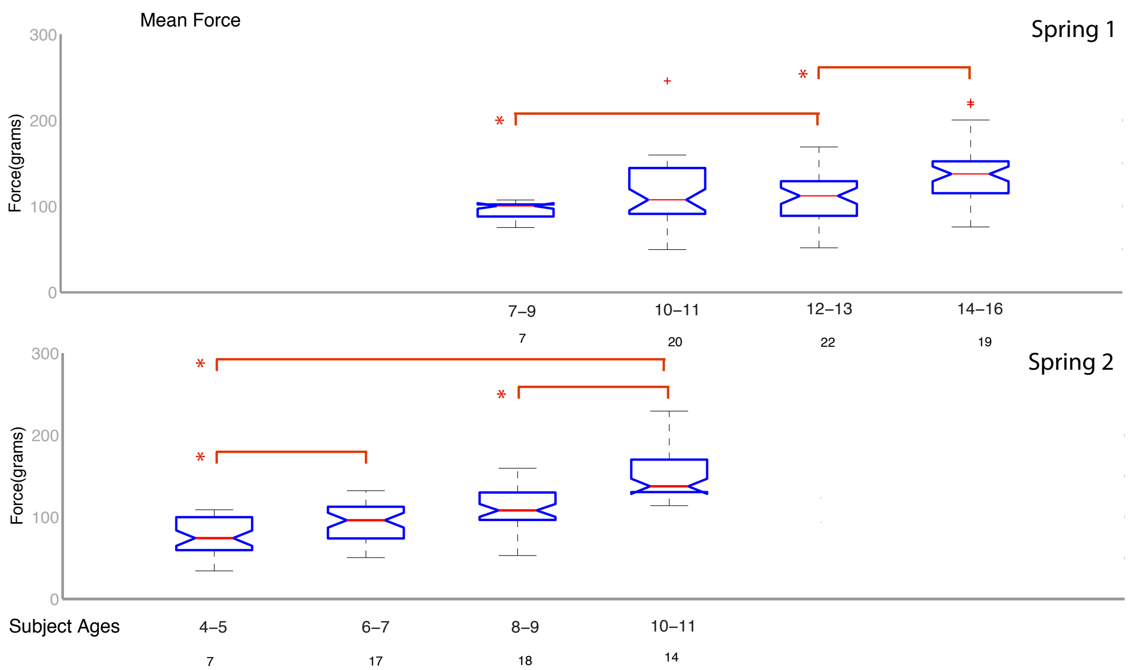

Figure 2.3: The median hold force children are able to generate for spring 1(Top) or spring 2 (Bottom). The children (n=126) used either spring 1 or spring 2 as their minimal impossible-to-compress spring. The difference in length between the two springs is 0.36 cm. The x-axis is childrens ages while the y-axis is the force in gram force (0-300 gmf). Significant differences indicated with an asterisk, are based on a 95% confidence interval around the median values for the age groups and show changes throughout childhood and adolescence.

2.4.2 Improvements in Dexterity on Dexterity Score

The change in combined dexterity score is best represented by a Fourier fit with a plateau phase achieved in late adolescence (Fig. 2.4, top). Statistically significant differences ($p<0.05$) are seen throughout childhood and adolescence (Fig. 2.4, bottom).

2.4.3 Relationship between Strength & Dexterity

The maximum strength a child can produce does not appear to be predictive of their performance during dexterous manipulation, with low r^2 values for both spring 1 ($r^2 = 0.18$, Fig. 2.5, Red) & spring 2 ($r^2 = 0.185$, Fig. 2.5, Blue).

2.4.4 Change in Dynamics

The dynamics of control during the hold phase improves with age as seen by the reduction in the normalized Euclidean distance in the state space (F-$\dot{F}$-$\ddot{F}$). Fig. 2.6 (top) shows representative children for each of the age groups (4-6, 7-9, 10-12, 13-16). The greatest reduction is seen in early childhood between 4-6 and 7-9, however there are also significant changes ($p<0.05$) in late adolescence (Fig. 2.6, bottom).

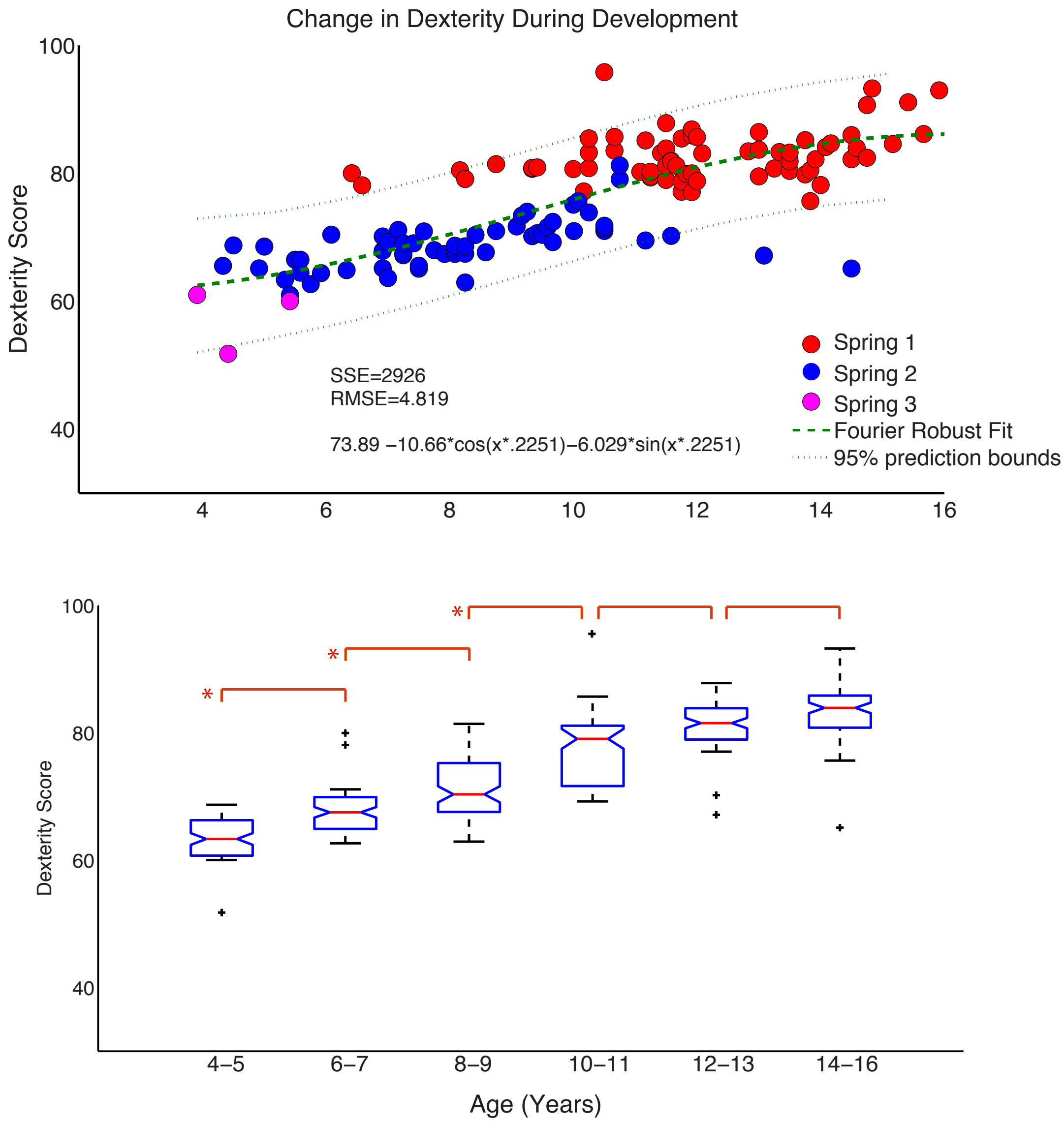

Figure 2.4: Dexterity Score throughout childhood and adolescence. The dexterity score was computed as a weighted average based on the mean hold force on the impossible-to-compress spring and normalized to the maximal possible value. In addition dead band in forces in the high and low ranges were removed for the springs. A regression line (± 95% prediction bounds) based on a Fourier robust fit showed the best fit for the Dexterity Score with respect to age (Top). The test spring is colored for spring 1 (red), spring 2 (blue) and spring 3 (magenta). Significant differences indicated by asterisks, based on 95 % confidence levels around the median are seen in adjacent age bins across childhood and adolescence.

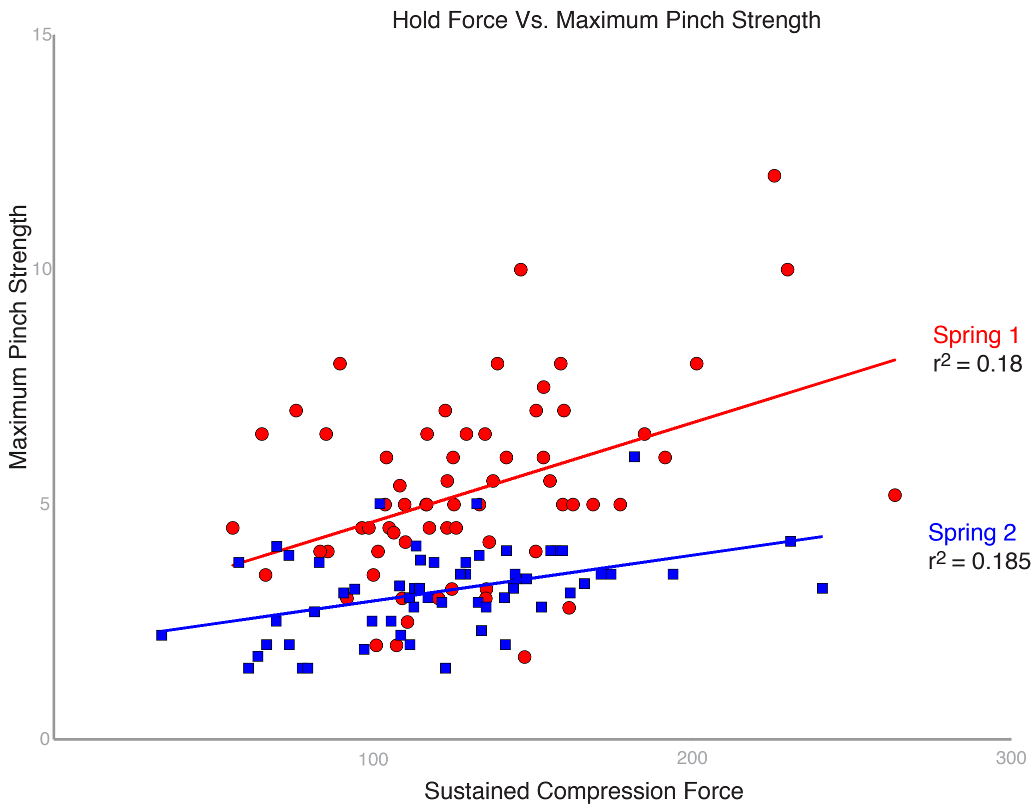

Figure 2.5: Regression between maximum pinch strength and maximal hold phase for spring 1 (red circles) and spring 2 (blue squares). Pinch strength does not appear to be predictive of ability in dexterous manipulation with only 18% of the variance being explained by strength.

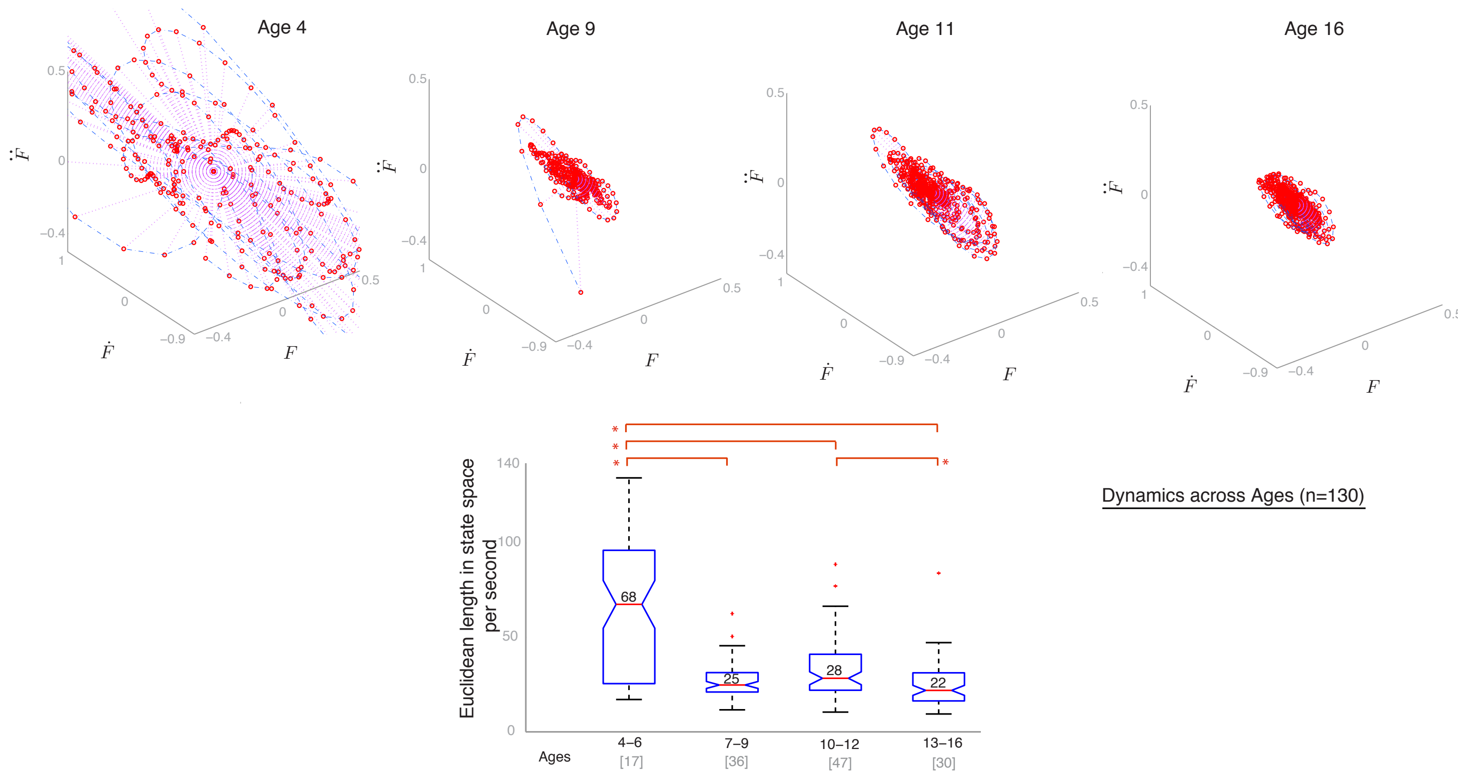

Figure 2.6: Changing dynamics of control quantified by Euclidean length in the state space. Representative children for each age range show improvements across childhood and adolescence (Top). Median values are significantly different, indicated by the asterisk in the earlier age range (4-6 years) as well as the end age range (13-16 years) (Bottom). The highest rate of change is in the earliest years, i.e. 4-6 years.

2.4.5 Relationship between hand anthropometrics and dexterity

The length of the hand, length of the thumb and the index finger in itself does not appear to be entirely predictive of ability to perform dexterous manipulation. Pearsons correlation of coefficient between dexterity and thumb length, index finger length and hand length for spring 1 was 0.24, 0.26 and 0.34 respectively, while for spring 2 this was 0.48, 0.55 and 0.62 respectively. A multiple regression with interaction effect was performed to evaluate the predictive relationship of the hand anthropometric variables on dexterity. The adjusted coefficient of determination (R^2) for this multi-linear regression model was 0.19 (spring 1) and 0.32 (spring 2). Fig. 2.7 and 2.8 show the regression of the finger lengths with respect to the ability to perform dexterous manipulation. The variance in the hand length could be explained by the other anthropometric variables (R^2=0.74, R^2=0.88), but not entirely (Fig. 2.9, Fig. 2.10).

2.5 Discussion

Development of dexterous manipulation abilities shows improvements well into late adolescence as seen by higher maximal hold phases, as well as normalized Euclidean distances being achieved by the children in the 14-16 year olds. We are able to provide a link between known timelines of neuroanatomical changes and behavioral improvements in dexterous manipulation well past the age of eight, independent of changes in strength. These developmental changes parallel known exponential increases in the structure of the corticospinal tract where changes are observed till the early 20s (Lebel et al. 2008, Paus et al. 1999). Region specific changes are seen in the CST with extensive practice of

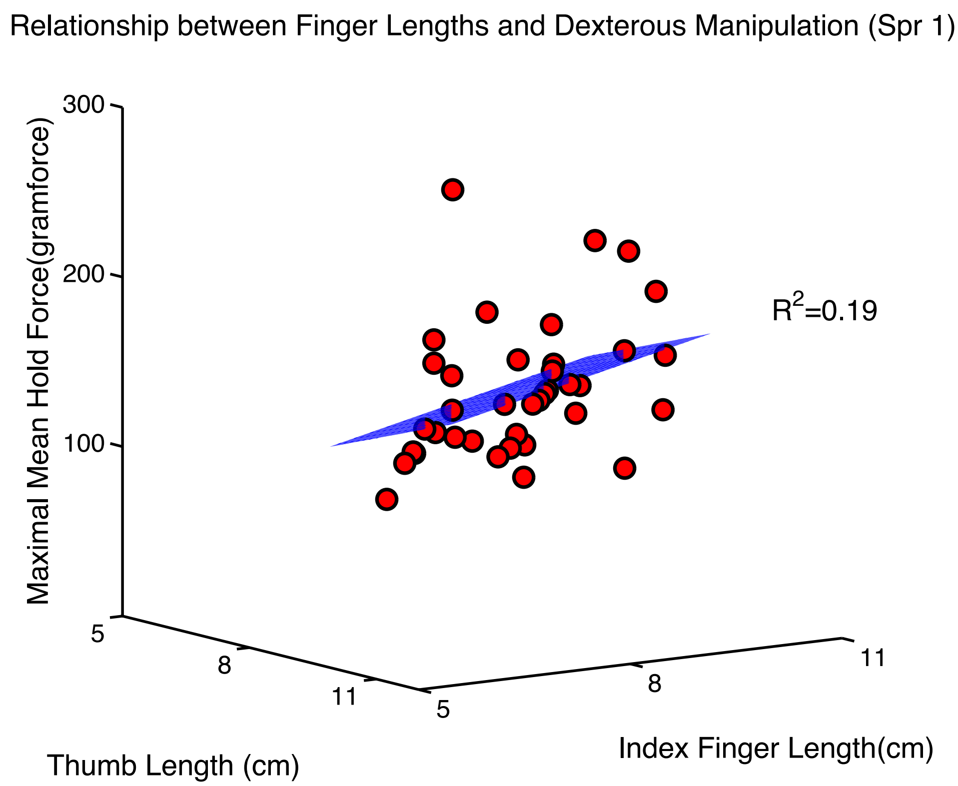

Figure 2.7: Multiple regression between finger lengths and dexterous manipulation for spring 1. Individual lengths do not appear to be predictive of dexterous manipulation ability with combined variance in finger lengths only accounting for 19% for spring 1.

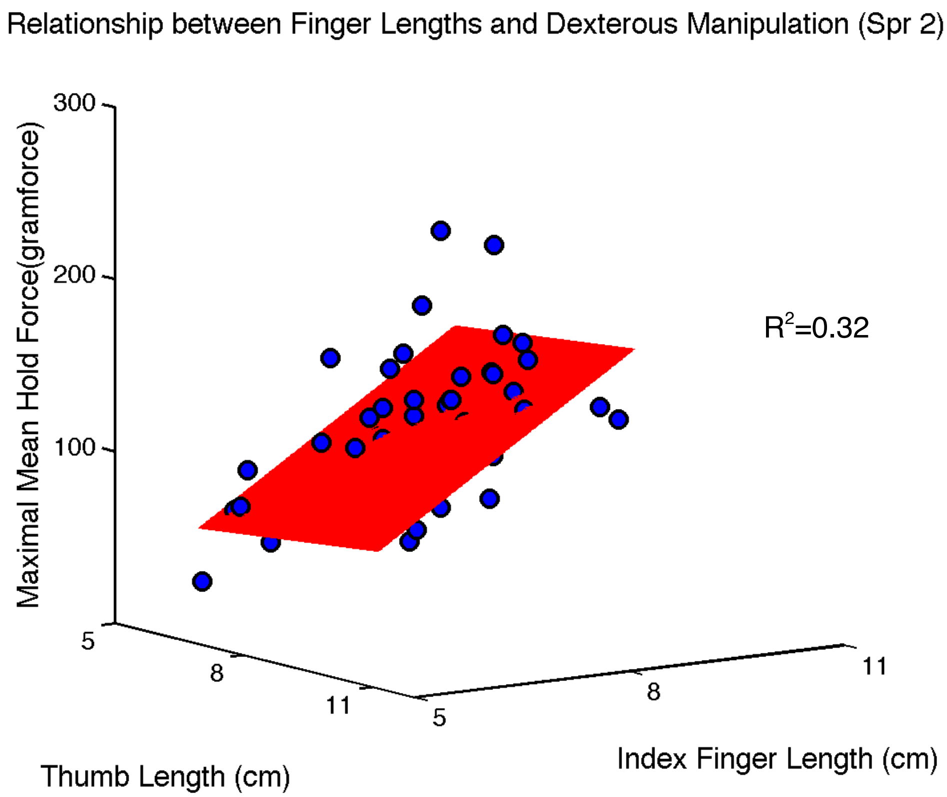

Figure 2.8: Multiple regression between finger lengths and dexterous manipulation for spring 2. Individual lengths do not appear to be predictive of dexterous manipulation ability with combined variance in finger lengths only accounting for 32% for spring 2.

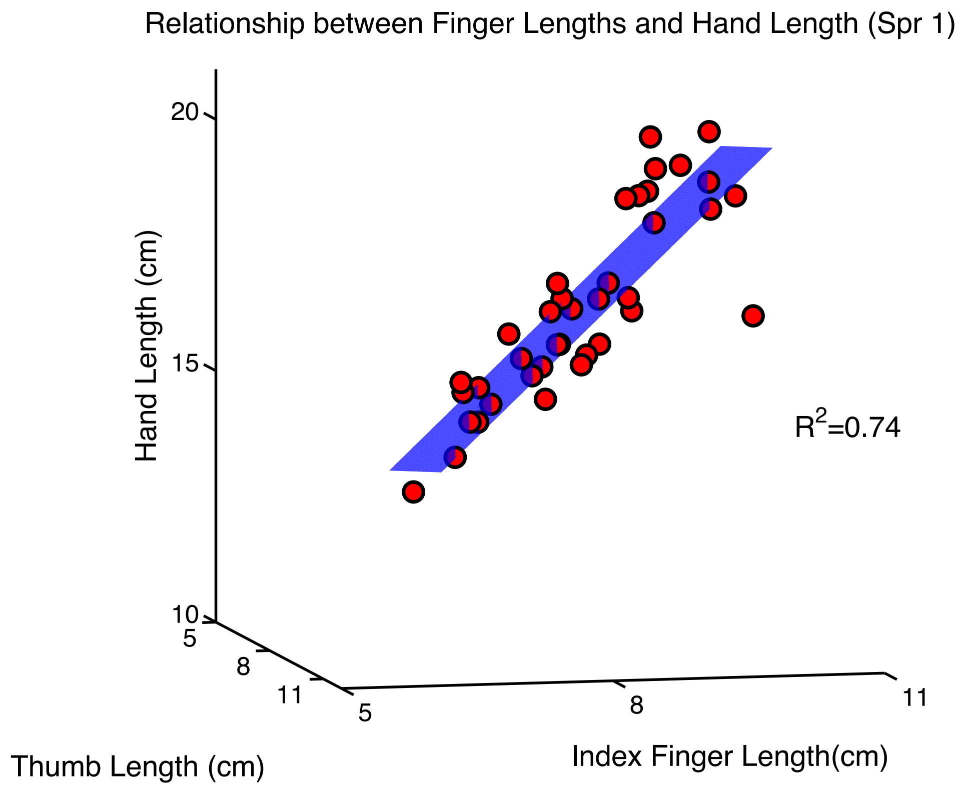

Figure 2.9: Multiple regression between finger lengths and hand lengths for spring 1. Combined variance in finger lengths account for 74% variance in hand length.

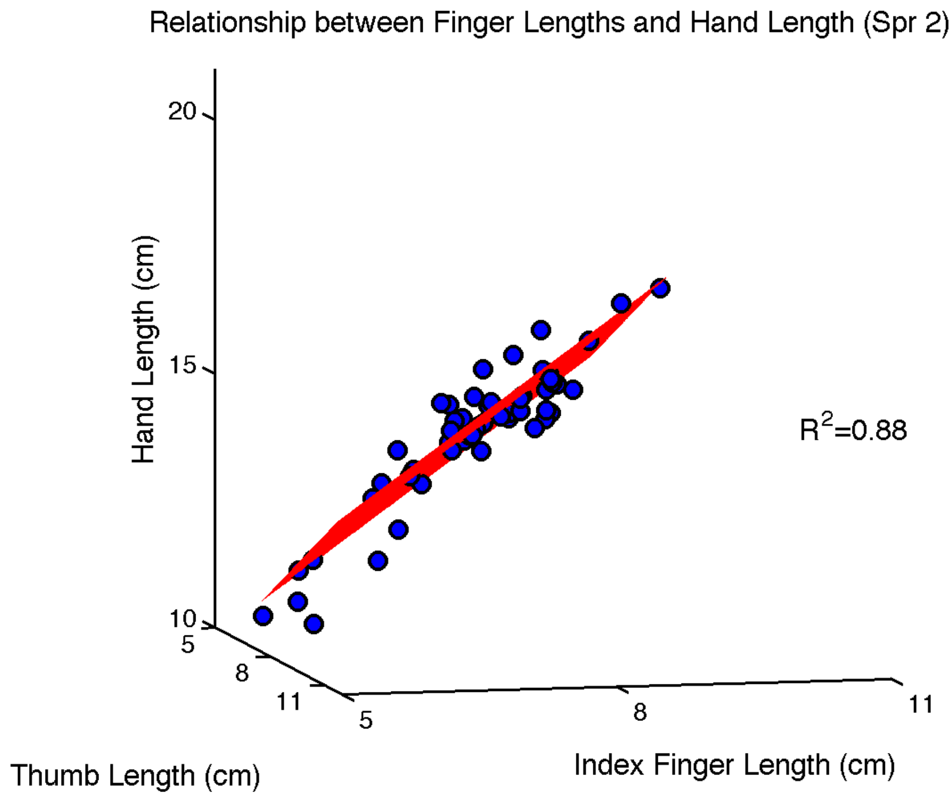

Figure 2.10: Multiple regression between finger lengths and hand lengths for spring 2. Combined variance in finger lengths account for 88% variance in hand length.

manual skills (Bengtsson et al. 2005) and impaired ability to coordinate fingertip forces are seen in children with congenital hemiplegia (Forssberg et al. 1999) , which is highly correlated with CST dysgenesis (Duque, Thonnard, Vandermeeren, Sebire, Cosnard & Olivier 2003).

Here we are able to extend the previous work (Vollmer et al. 2010) to show changes in dexterous manipulation abilities with a high resolution for small forces that span the age range from 4-16. In addition by using only the thumb and index finger; the two most individuated fingers in the hand (Häger-Ross & Schieber 2000) that can be controlled independently during manipulation (Edin, Westling & Johansson 1992) we are eliminating any influence of enslavement effects over the middle finger on the task. The change in the normalized Euclidean distance provides an innovative way to quantify the control during dexterous manipulation. The dynamics of control seen in our study show the greatest change in the initial years, 4-6 years similar to the changes seen in white matter density in the internal capsule (Paus et al. 1999). Interestingly, while improvements in tactile spatial resolution and in dexterity do not appear to be associated, maximum change in sensory acuity is seen in the 4-6 year range (Bleyenheuft, Wilmotte & Thonnard 2010).

It is important to note that the musculoskeletal changes in hand size as well as strength increases are not predictive of dexterous manipulation capabilities with low values for coefficient of determination. This reinforces previous work (Venkadesan et al. 2007) that the use of such a paradigm allows one to measure changes in neuromotor performance and processing. Additionally while it is known that the increase in hand strength is highly correlated with changes in anthropometrics such as hand length in children from 4-16 years of age (Häger-Ross & Rösblad 2002) it appears that the rate of development of dexterity is relatively independent from that of strength or hand anthropometrics.

The method presented in our current work provides a simple, brief (<15 min) and yet clinically-practical version of the Strength-Dexterity Test (Valero-Cuevas et al. 2003). Other clinical metrics for dexterity (Mathiowetz et al. 1986, Poole et al. 2005) are timed tasks that require sequencing, motor planning, utilizing the whole arm and do not necessarily provide specific information about coordination of fingertip forces while they might have shown changes in children past the age of 8-10. Recently it has been argued (Steenbergen & Utley 2005) that this specific information could be relevant and informative for planning of rehabilitation in individuals with neurological injuries. Here we propose that the prolonged period of development of dexterity in typically developing children- longer than previously known- provides a larger window for rehabilitation in children with neurological injuries. In children with hemiplegia there is an improvement in hand function even in adolescent years following specific rehabilitation (Bonnier, Eliasson & Krumlinde-Sundholm 2006, Eliasson et al. 2006, Gordon, Schneider, Chinnan & Charles 2007, Kuhtz-Buschbeck, Sundholm, Eliasson & Forssberg 2000).

Finally while the CST development has been attributed to provide the neural substrate for dexterity, recent evidence has shown a diffuse cortical network for dexterous manipulation (Bonnard et al. 2007, Davare et al. 2006, Ehrsson et al. 2000, Gallèa et al. 2005, Holmström et al. 2011, Kuhtz-Buschbeck et al. 2001, Mosier et al. 2011). Ehrsson et al. have demonstrated that there is a greater activity in the fronto-parietal sensorimotor areas during the control of smaller forces than larger forces, implying that during dynamic manipulation, there is a high modulation of control of objects requiring low strength that is different from the control required for increases in force magnitude. Force magnitude and direction appear to be controlled by different aspects of the grasping network (Holmström et al. 2011) with poor modulation of the control of force direction by the M1. The cortical representation for the control of force vectors differs from that of grip strength and require modulation by cortical-striatal-cerebellar networks (Mosier et al. 2011). Importantly, Mosier et al. have shown that different neural circuitries are associated with grasping stable and unstable objects with a significant involvement of the basal ganglia modulation of the premotor and motor areas in the presence of instabilities. All of these studies have tested adults where the sensorimotor system has matured and in order to get a deeper understanding of neural control of dexterity, the developmental aspects of control of unstable objects needs further exploration.

2.6 Acknowledgements

We acknowledge the assistance of Elena Pavlova with data collection, Jonathan Weisz, Nora Nelson and Linda Junker with technical assistance during the initial stages. Veronica Santos and Ruben Wong, from Arizona State University extracted the hand anthropometric information from the photographs. Åsa Hedberg and Sudarshan Dayanidhi contributed equally to this study. NSF EFRI, RERC Grant 84-133E2008-8 to FVC.

Chapter 3

Characteristics of Muscle Twitch of the First Dorsal Interosseous (FDI) in Children and Adults during Submaximal Contractions

3.1 Abstract

During childhood and adolescence improvements in dexterous manipulation abilities have been attributed to myelination and maturation of the corticospinal pathways. It is not known if there are any peripheral changes in the muscle structural properties and if these could contribute to improvement in manipulation. In order to answer this we use a previously developed non-invasive technique, the EMG weighted average (EWA) to study the muscle twitch properties of the First Dorsal Interosseous (FDI) in early adolescent girls and in young adults. Children appear to have a slower muscle twitch as seen by a slower time-to-peak compared to young adults. In addition we were able to show again that there are differences in the manipulation abilities between children and adults. It is not clear if the slower muscle twitch properties are related to dexterous manipulation abilities and longer cross-sectional studies are required. However we clearly show that

there could be a peripheral component of the developing system which could also play a role in improvement of low force dexterous manipulation skills.

3.2 Introduction

During the course of development the improvements seen in dexterous manipulation abilities in childhood and adolescence are primarily attributed to changes in the central nervous system; specifically the corticospinal tract (CST) (Armand et al. 1997, Fietzek et al. 2000, Lebel et al. 2008, Muller et al. 1991, Paus et al. 1999). The high degree of modulation required for manipulation tasks can be achieved by changing the corticospinal excitability to either the first dorsal interosseous or the opponens pollicis (Bonnard et al. 2007). Finer adjustments of low force dexterous manipulation also require appropriate firing of motor units with more than 50 % of the motor unit pool of the first dorsal interosseous being potentially activated for just 2N force output (Milner-Brown, Stein & Yemm 1973*c*, Fuglevand 2011). Recent work has shown that there are behavioral improvements in dexterity well into late adolescent years (Dayanidhi, Hedberg, Hägg, Lilja, Forssberg & Valero-Cuevas 2011, Vollmer et al. 2010), contrary to the idea that there are few significant changes past the age of ten (Deutsch & Newell 2001, Deutsch & Newell 2002, Eliasson, Forssberg, Ikuta, Apel, Westling & Johansson 1995, Forssberg et al. 1991, Forssberg et al. 1995, Forssberg et al. 1992, Gordon et al. 1992). While strength gains are a dominant feature of muscular changes in the pre-pubescent and pubescent years currently it is unclear if there are any peripheral contributing factors for the observed improvements in dexterous manipulation.

Muscular development is a significant aspect of change in pre-pubescent and pubescent children with a dramatic, three-fold increase in hand strength after the age of 10 (Häger-Ross & Rösblad 2002). The increases in muscle strength during adolescent years have been attributed primarily to increases in physiological cross-sectional area (PCSA), moment arm length and activation level but not to changes in specific tension of the muscles (O'Brien, Reeves, Baltzopoulos, Jones & Maganaris 2010). Direct measurements of temporal properties of motor units in children have been few and far due to the invasive nature of such studies and have focused on different aspects such as the firing rates of motor units and recruitment over a wide age range in people with developmental disabilities (Rose & McGill 2005) or have used maximal level activation (Belanger & McComas 1989) which might not be informative of submaximal twitch characteristics. Importantly all of the studies have focused on lower extremity muscles. The developmental aspects of muscle twitch properties in hand muscles and their role, if any in improvements in dexterous manipulation are not known.

Spike-Triggered Average (STA) is a commonly used invasive technique to study properties of muscles (Milner-Brown, Stein & Yemm 1973*a*, Thomas, Ross & Stein 1986). First developed by (Stein, French, Mannard & Yemm 1972), while invasive it has become the *de rigeur* for evaluating single motor unit properties and performed over a number of motor units to create an average STA. Electromyography Weighted Average (EWA) is a recent noninvasive technique developed by (Kutch, Kuo & Rymer 2010) to extract the spatiotemporal characteristics of average motor unit firing, including the time-to-peak (similar to contraction time). Conceptually the information about the average motor unit characteristics obtained by this method is similar to that from the averaged STA (Kutch et al. 2010). Importantly the EWA might be a noninvasive way to extract information about muscle twitch properties such as contraction time and be used in children with relative ease. The goal of this study was to utilize the EWA to evaluate if there are any differences in muscle twitch characteristics, specifically the time-to-peak between children and adults as well as to observe if there is an association between the time-to-peak and dexterous manipulation capabilities.

3.3 Methods

Thirty six subjects; twenty three adults (28.3 $\pm$ 2.7, 13 F, 1 Left handed) and thirteen children (11.78 $\pm$ 0.44, 13 F, 2 Left handed) participated in this study. The protocol was approved by an Institutional Review Board and informed consents and assents were obtained from the children/their parents and from the adult subjects.

3.3.1 Experimental Setup

A 6-axis load cell (20E12, 100N, JR3,Inc., Woodland, CA) was mounted to an adjustable base. A 10 cm, custom hollow tube was created such that the base of it could be securely attached to the load cell, while the other end provided space to insert a fingertip (Fig. 3.1). An adjustable height platform was attached to four magnetic bases, such that it could support the forearm of the subjects. A dowel was attached to one end of the platform, to allow one to wrap their hand around it. A 16-bit data acquisition device (USB-6251, National Instruments, Austin, TX) was utilized to collect data from the load-cell and from a EMG system (Bagnoli-16, Delsys®, Boston, MA) (Fig. 3.1) using a custom written Matlab® program (MathWorks, Natick, MA). The data were acquired at 4000 Hz with a bandwidth of 20-2000Hz for the EMG signals.

Two single-axis miniature load cells (ELB4-10, Measurement Specialties, Hampton, VA) were mounted at the endcaps of a slender linear spring(Fig. 2.2). The load cells were connected to a signal-conditioning box, an USB-DAQ (USB-1408FS, Measurement Computing, Norton, MA) sampled the data at 400 Hz using a custom written Matlab® program (MathWorks, Natick, MA) and a 3 point deadweight calibration procedure was used for conversion from voltage to force.

3.3.2 Experimental Protocol

The subjects were seated with their dominant arm supported by the platform in around 20° shoulder abduction, 90° elbow flexion, wrist in mid prone, index finger in a few degrees of flexion and 0° of metacarophalengeal abduction, the remaining fingers were wrapped around a padded dowel (Fig 3.1). Dominance was determined by using a combination of the Edinburgh Handedness test, verbal questions of hand use for writing and daily activities to both the child subjects and parents. The single differential EMG electrode was placed on the first dorsal interosseous (FDI) diagonally to run along the length of the muscle fibers, ensuring that the skin was appropriately cleaned and did not have any lotions. The EMG signals were tested to ensure minimal baseline noise as well as appropriate gain to avoid clipping. The subjects were provided with a visual feedback of the vertical force and asked to apply forces vertically with their index finger such that they were in the target zone of 2N $\pm$ 0.5 and maintain it as steady as possible for 20-25

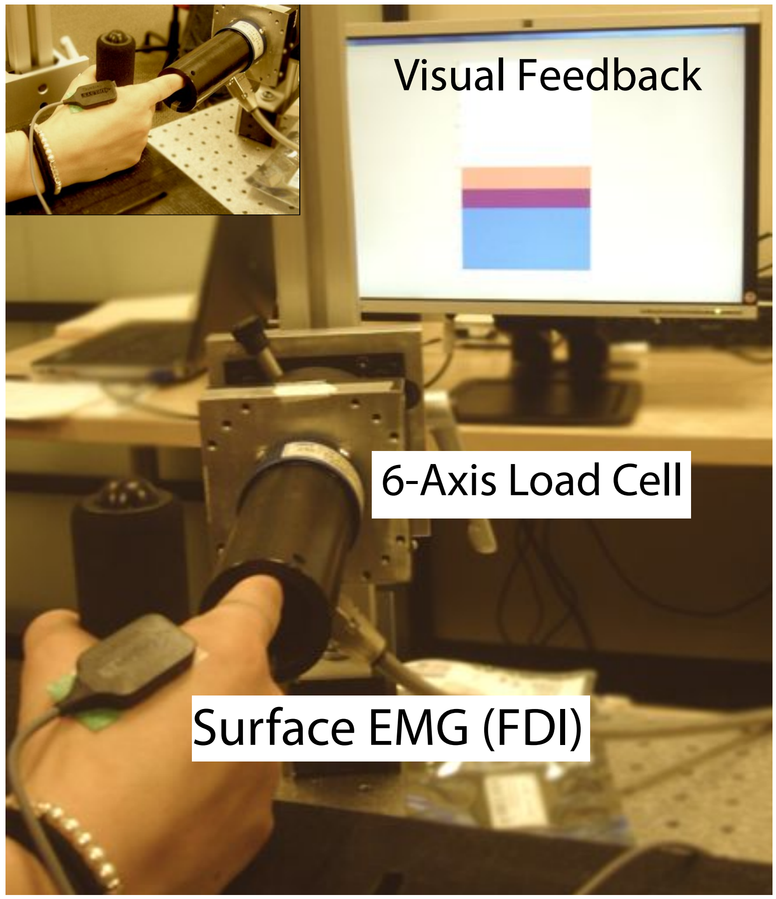

Figure 3.1: Experimental setup for EMG weighted average showing the surface EMG on the First Dorsal Interosseous, the 6-axis load cell with a tube attachment and visual feedback around 2N of force.The subjects were asked to wrap their fingers around the padded dowel, apply an isometric force of around 2N upwards against the tube with their index finger; around the distal interphalangeal joint and maintain it as steady as possible for around 20 seconds.

seconds. The target used was a low sub maximal force, less than 5% of the maximum isometric voluntary contraction for all subjects.

To test the dexterous manipulation abilities, defined as the ability to control finger tip force direction the subjects were asked to compress and hold the instrumented spring device. This device was designed such that the force required for full compression was only 2-3 N but as the spring was compressed the instability increased requiring a higher control of finger tip force direction with higher compression, consequently making it impossible-to-compress fully. The dominant forearms were supported in mid prone, the subjects were asked to pick up and compress this device with their index and thumb with no help from the other fingers as much as possible so as to maintain the compression for at least 3 seconds. In addition the maximal tip-to-tip as well as key pinch force was measured on the dominant hand using a pinch meter(B and L Engineering, Santa Ana, CA). One of the children only participated in the EWA experiment and did not complete the dexterous manipulation and strength testing components of the protocol. Her data was included in the analysis of the EWA component of the experiment.

3.3.3 Data Reduction and Analysis

Custom written programs in MATLAB were used for reducing the EWA and dexterous manipulation data. The steady state periods from the unfiltered force data were graphically selected using the function *ginput* and the force and full wave rectified EMG data were cross correlated. The steady state periods were at least 20-25 seconds in duration for both the adults and children and the maximum lag used for cross correlation was 100ms. To facilitate the identification of the time-to-peak of the EWA waveform the *findpeaks* function was used on data smoothed with a moving window of 10 ms. All the data were visually inspected to ensure that no erroneous identification of time-to-peak were performed. For the dexterous manipulation the mean of the force level at which the fingers could compress and hold the spring device was computed for each of the hold attempts. A representative time series was created as an average of the force from the index and thumb load cells and the mean of the maximal three force in the hold phases were computed for each of the subjects.

The independent variable was age, while the dependent variables were time-to-peak, mean force for dexterous manipulation and maximal compression force for tip-to-tip and key pinch. One-way ANOVAs were performed to compare differences between the age groups in both mean time-to-peak and mean force of dexterous manipulation. In addition linear regression between EWA time-to-peak and dexterous manipulation abilities were conducted, as well as between pinch strengths and EWA time-to-peak.

3.4 Results

3.4.1 EWA in adults and children

Histograms of all the trials in all the subjects show a mean time-to-peak across all trials for adults is 51ms while that for children is 74ms (Fig 3.2). A one-way ANOVA shows highly significant differences ($p<0.0001$, $F=19.19$) between adults and children in time-to-peak (Fig 3.3, Right) with children having a median time of 74ms and adults of 49ms; the mean values were respectively 66.54 ($\pm$12.4) and 50.37 ($\pm$6.47) ignoring the outliers (n=3). Representative EWA waveforms are shown in (Fig 3.4) with different time-to-peaks shown across the two age groups.

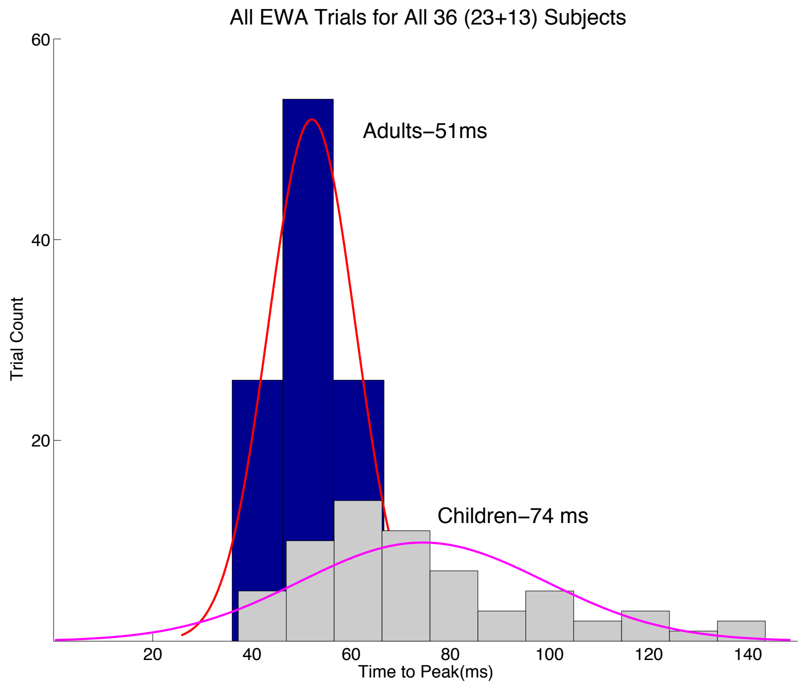

Figure 3.2: The Time to Peak from the EWA waveform for all 36 subjects for all trials. All the individual trials for all adults and children are illustrated along with the mean for both groups, with children having a longer time to peak.

3.4.2 Changes in dexterous manipulation abilities

Highly significant differences were observed on a one-way ANOVA between adults and children for small force dexterous manipulation abilities ($p<0.0001$, $F=79.71$) with adults having a mean value of 212.35 ($\pm$30.75) while the children have a mean value of 125.05 ($\pm$19.25)(Fig 3.3, Left).

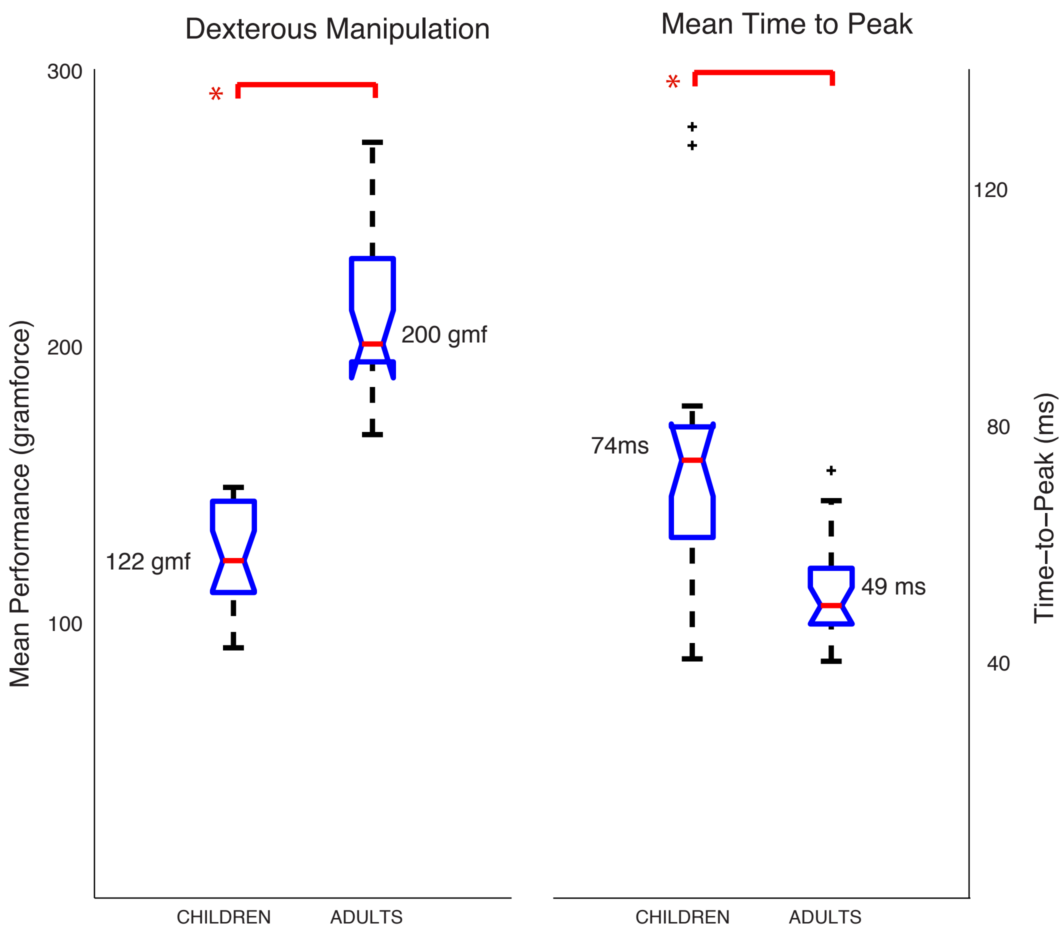

Figure 3.3: Change in dexterous manipulation (Left) and Time-to-Peak (Right) between young adults and children. Significant differences indicated with an asterisk, are based on a 95 % confidence interval around the median values for the age groups and show significant changes for both time-to-peak as well as dexterous manipulation abilities.

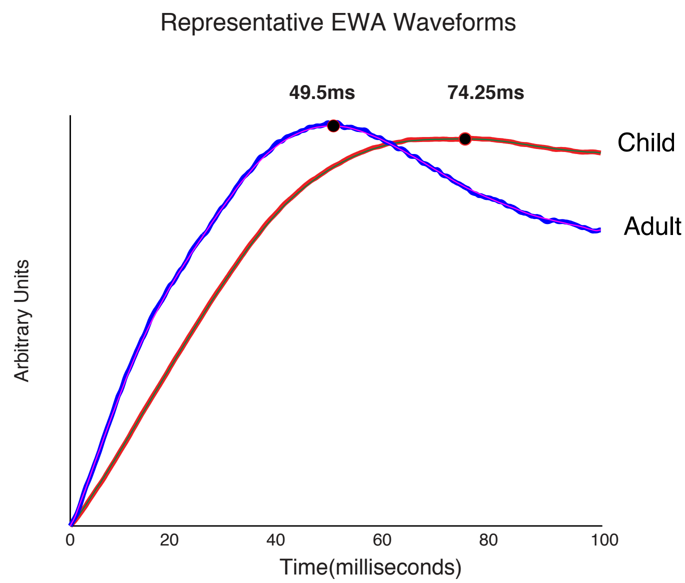

Figure 3.4: Representative examples of the EWA waveform, with identified time-to-peak, in young adults (blue) and children (red).

3.4.3 Relationship between time-to-peak and dexterous manipulation

Individual linear regressions for both ages show a non-significant association($p=0.18$, adults, $p=0.1$, children) between the time-to-peak and the mean hold force in dexterous manipulation (Fig 3.5).

3.4.4 Relationship between pinch strength and time-to-peak

The time-to-peak does not appear to be predictive of pinch strengths; the linear regression for time-to-peak and pinch strengths show a non-significant regression line for both adults and children for key as well as tip-to-tip pinch(Fig 3.6).

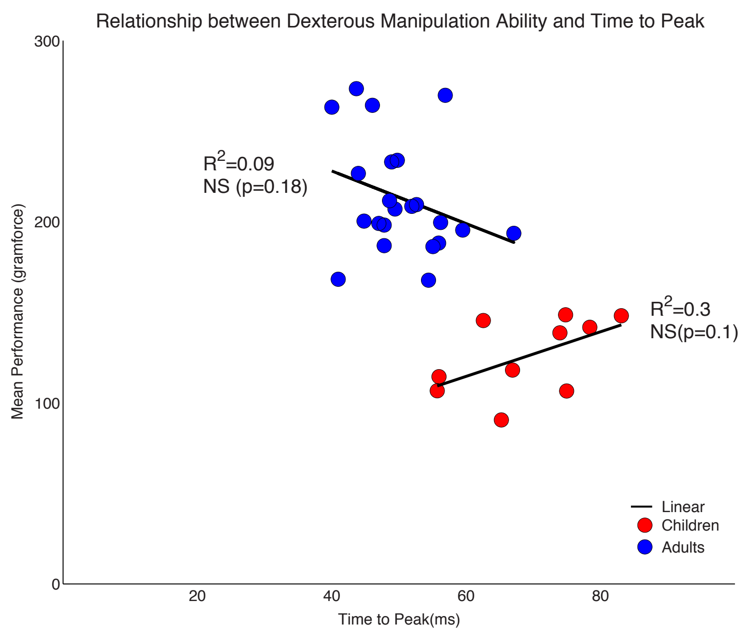

Figure 3.5: Relationship between Time-to-Peak and dexterous manipulation capabilities in young adults (Top) and children (Bottom). The regression lines for each of the age groups were non-significantly different from zero, indicating no association between these two variables within each age groups.

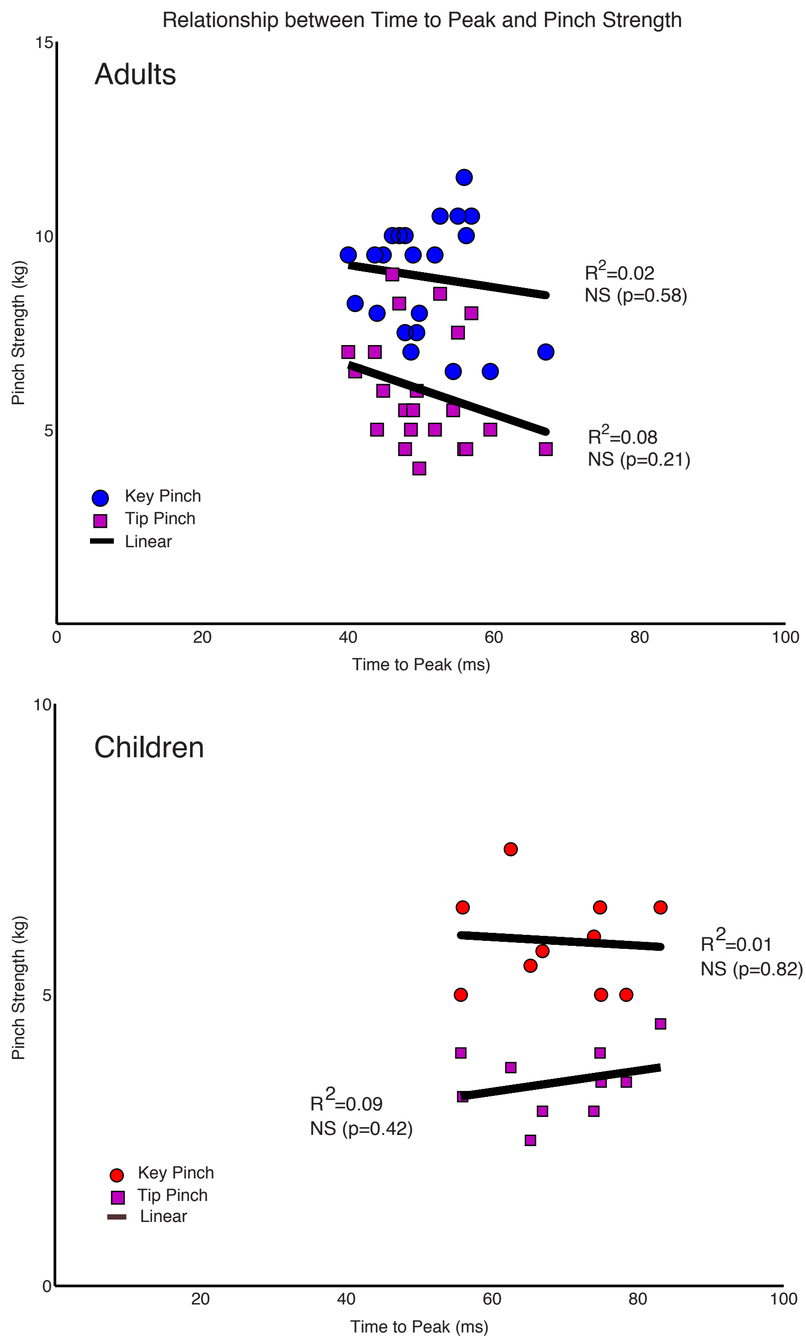

Figure 3.6: Relationship between time-to-peak and pinch strength (Tip-to-Tip and Key Pinch) in adults(Top) and children(Bottom). The regression lines for both the key pinch and tip-to-tip pinch are non-significantly different from zero, which is indicative of no association between maximal strength and mean time-to-peak.

3.5 Discussion

Children show significant increase in their time-to-peak, which for the first time demonstrates that there are peripheral aspects of small force muscle twitch in hand muscles which are different from adults. This in part could explain the observed improvements in dexterous manipulation capabilities observed past the age of 10. The values we observed in our adults (50.37 $\pm$ 6.47ms) is similar to what has been reported before with both the EWA (51.5 $\pm$11.5ms) (Kutch et al. 2010) and the STA (55 $\pm$12ms) (Milner-Brown, Stein & Yemm 1973*b*), but importantly included a large number of young adults (n=22). The relationship between EWA time-to-peak and muscle strength appears to not be associated with each other. In addition, we observe differences in low force dexterous manipulation capabilities between children, who are older than 10 and adults, similar to what we have reported before (Dayanidhi et al. 2011). While the time-to-peak decreases with development and increases are seen in the mean hold force, i.e. a measure of dexterous manipulation the discontinuity in our data prevents us from performing a regression analysis across age.

The time-to-peak has been observed to the same in the Triceps Surae in children, 11-14 years of age and adults in both sexes (Davies, White & Young 1983), while contrary to our observation suggests that there do not appear to be a gender based difference in the physiological properties of the muscle twitch. The contraction time of the dorsiflexors has been shown to have significant increases in value in late adolescence, but this again is not seen for the plantarflexors (Belanger & McComas 1989). Twitch contraction times in the extensor hallucis brevis has been reported to be similar in children from a young age, although there is a consistent increase in muscle twitch tension until adolescent years (McComas, Sica & Petito 1973). However, in other mammals in developmental studies it has been reported that there is a decrease in the time to peak from birth till adolescent years and then similar till adulthood (Close 1964). All of the human studies appear to be done only in lower extremity muscles and given the adult like walking pattern by the age of 5 (Sutherland 1997), it is unclear whether one would expect these results in case of the hand muscles which have a higher number of monosynpatic corticospinal connections (Rathelot & Strick 2006) as well as a prolonged period of improvement (Armand et al. 1997).

In children under low force($<$ 5 % MVC) visual feedback conditions no differences have been seen in isometric force output across ages, with improvements seen throughout childhood with sensorimotor organization of force at higher force levels (Deutsch & Newell 2001). Increased time-to-peak leading to differences in twitch properties have been attributed to improved Ca^{++} uptake by the sarcotubules (Brody 1976) in adulthood. The difference in time-to-peak could potentially also be explained on the basis of changes in the structure of muscle fibers and a shift of percentage of slow and fast-twitch muscle fibers changing during adolescent years. In infants the time-to-peak in the soles muscle based on stimulation shows an increase from 75 ms to 110 ms at around a year (Elder & Kakulas 1993), when they reach adult like values. Concomitantly at this time there is a change in percentage of type I muscle fibers, which also reach adult like percentages, i.e. 79 % around the age of 18 months. However in the same study the authors also reported on data obtained by autopsy on 20 individuals from newborn to 28 years. The percentage of type I fibers in the vastus laterals and gastrocnemius was significantly higher in the children between 3-16 years of age, however the sample sizes were small and they did not report on contraction times of those muscles. It is speculated that there is a period of change of fiber type distribution seen not just in infancy but also in the adolescent years. However it does not appear that there are differences in fiber type distribution in childhood compared to adults, at least for the vastus lateralis (Bell, Macdougall, Billeter & Howald 1980, Glenmark, Hedberg, Kaijser & Jansson 1994). Currently the research on changes in fiber type proportions during later development, if any are very sparse, unclear and inconclusive (Kraemer, Fry, Frykman, Conroy & Hoffman 1989, Martin, Dore, Twisk, Van praagh, Hautier & Bedu 2004).

It does not appear that there is any clear relationship between contraction times and fiber type. Long contraction times have been observed in human muscles with large proportion of fibers rich in mitochondria; Soleus around 74 ms while Tibialis Anterior was around 58 ms (Buchthal & Schmalbruch 1970) as well as in cat muscles (Burke & Tsairis 1974). However classification of motor units based on the basis of the physiological properties have not been successful with poor correlations seen in the first dorsal interosseous between contraction time and force (Milner-Brown et al. 1973*a*, Thomas, Bigland-Richie & Johansson 1991). Interestingly the finding by (Stephens & Usherwood 1977) have shown moderate correlations between contraction times and twitch tensions in the first dorsal interosseous. The relationship between contraction time/time-to-peak, twitch tension, and fiber types is not very clear given the many different techniques, muscles and contraction levels used.

3.6 Conclusions

Here we present for the first time that there are changes seen in the muscle twitch properties in submaximal contractions in hand muscles in children. These changes may help explain a part of the reason for improvements in dexterous manipulation capabilities in children during adolescent years. In addition here we show an application of the perviously developed noninvasive EWA method as a simple way to look at developmental changes in muscle twitch properties.

Chapter 4

Influence of Surface and Visual Conditions on Dexterous Manipulation

4.1 Abstract

Precision grip provides insights into corticospinal motor neuronal connections. Prior human studies of precision grip have focused primarily on isometric tasks using two fingers, which while useful in understanding basic two-finger force interactions, are limited for understanding manipulation. In our previous work we have demonstrated the significance of dynamically testing a system to the edge of instability to gain meaningful information about sensorimotor integration in the hand. In addition, we know from human and animal studies that precision grip takes years to develop. In this paper we extend our previous work on the dynamical control of one digit to the measurement of dynamic precision grip of instrumented unstable hand-held objects. We mounted compression load cells on the end-caps of a slender spring, which required 3-4 N of force for complete compression and was unstable under compression. The methodology was tested using three trials each for two conditions of the surface of the load cell: low friction (Teflon) and high friction (fine

sand paper, 120 grits) and two conditions of vision: vision allowed and vision occluded. The results suggest there is an increase in complexity in the dynamics of the precision grip with a decrease in friction, which may reflect higher sensorimotor integration demands and error correction for the low friction condition. In addition the parameters for low force dexterous manipulation might be different from what has been seen in static grasp studies. As suggested by a prior study of single digit manipulation, lower grip forces in response to lower friction for these unstable objects appears contrary to the concept of increased grip forces for higher safety margins for solid objects. Further studies are warranted to conclusively establish these differences between stable and unstable precision grip.

4.2 Introduction

Precision grip studies provide an insight into dexterous manipulation capabilities specifically using monosynaptic connections of the corticospinal tract (Muir & Lemon 1983, Kuypers 1960, Kuypers, Fleming & Farinholt 1960). In human studies with grip and lift studies it has been shown that people generate higher grip forces for the same weight in case of slippery/smoother surfaces(Johansson & Westling 1984, Edin et al. 1992, Forssberg et al. 1995, Westling & Johansson 1984). For example, if you were to lift an object which had condensation on it you would apply higher grip forces on it as a way to prevent it from slipping out of your fingers. This increase (10-40%) above the minimal required force to lift the object has been considered a safety margin to prevent slips or allows one to successfully do the task by activating the Fast Adapting Type-I (FA-1) receptors in the fingers. However this strategy of increased grip force will not work in case of dealing with a fragile or deformable object or worse a slippery fragile object.

The Strength-Dexterity paradigm, based on the propensity of slender springs to buckle under compression allows one to test the dynamic ability to regulate fingertip force direction and magnitude (Valero-Cuevas et al. 2003, Venkadesan et al. 2007). Our goal was to differentially test the influence of different sensory modalities of surface condition and vision on dexterous manipulation abilities. By utilizing the paradigm of manipulating at the edge of instability (Venkadesan et al. 2007) and confounding the sensorimotor system with changing sensory conditions we are testing the relative importance of the parameters required for dexterous manipulation.

4.3 Methods

Seven healthy young subjects (4 M/3 F, mean age 26 years) participated in this pilot study. Ethical approval was obtained from an institutional review board and all subjects consented to participate in this study.

4.3.1 Instrumentation

Two 6-axis load cells (ATI Instrumentation, Apex, NC) and a slender compression spring that required 4-5 N for full compression were used. The spring was chosen such that it could not be compressed fully but required low force for full compression. As shown by (Venkadesan et al. 2007) with compression the instability of the system increased requiring a greater amount of control of fingertip force direction in order to succeed at partially compressing and holding the spring. The load cells were mounted on to the end caps of the spring with double sided tape, the weight was around 20 grams and the length of the device was around 2.7 inches (6.75 cms). A custom written MATLAB © (Mathworks, Natick, MA) program was used to acquire data at 400 Hz.

4.3.2 Experimental Procedure

The subjects were seated with their dominant hand forearm resting on the table. A 2x2 factorial design [Friction(High/Low); Vision(Allowed/Occluded)] was used, with block randomized trials collected for each subject. Sandpaper of 120 grits was used for the High Friction condition while Teflon was used for the Low Friction condition. For the Vision condition the subjects were either able to see their hands or wore glasses masked with black tape to proven them from seeing anything. They were asked to pick up the spring device only with their Thumb-Index fingers and compress it as much as they could while ensuring that the device would not slip or buckle and to hold it while applying that force for at least 5 seconds (Fig. 4.1). The experimenter encouraged the subjects to compress as much as they could on the impossible-to-compress spring to try to get them to compress and hold close to the edge of instability. Three trials in 4 conditions [High Friction/Low Friction; Vision/Vision Occluded] were collected for each subject.

4.3.3 Data Reduction

The mean for each of the hold forces for each condition and for each finger were computed using a custom MATLAB program. The trials with the maximal hold force for each of the conditions were chosen to be representative for each subject. Two-way ANOVAs(Vision vs. Surface conditions) was used to compare the differences in grip force for the Thumb and Index fingers.

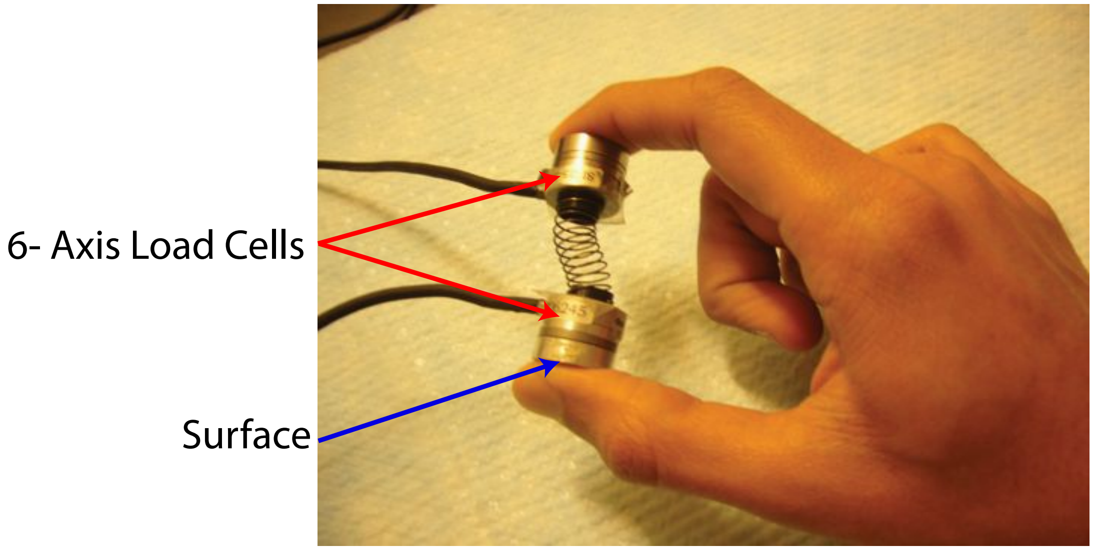

Figure 4.1: The experimental setup showing the two 6-axis load cells being grasped using a precision grip. The surface of both the load cells were either a rough surface or a smooth surface.

4.4 Results

4.4.1 Relationship between finger forces and surface and vision conditions

The mean forces of the thumb were 3.97($\pm$0.47) N for low friction and 4.15 ($\pm$1.05) N for high friction, in the vision condition and were 4.11($\pm$0.78) N for low friction and 3.88 ($\pm$0.82) N for high friction. The index finger forces were 3.95($\pm$0.48) N and 4.03 ($\pm$0.9) N for the low and high friction respectively with vision. With vision occluded the forces were 4.09($\pm$ 0.8) N and 3.78 ($\pm$0.9) N for the low and high friction.None of the differences were detected as significant (Table 4.1, 4.2). The range for all the surface

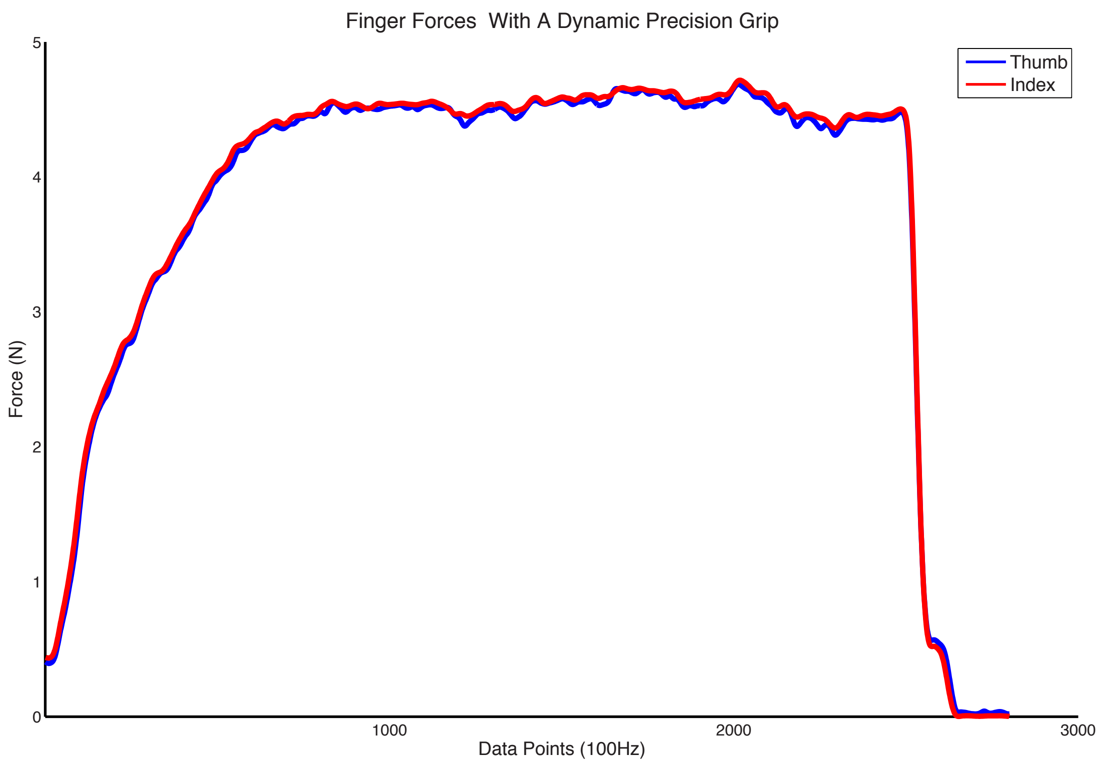

Figure 4.2: Time series of normal force from the thumb (blue) and index (red) finger load cells. The subjects were asked to compress the spring device maximally while ensuring it will not buckle or slip and maintain for at least 5 seconds.

and vision conditions for both Thumb and Index fingers are shown in Table 4.3,4.4. The variance seen was highest under the high friction and vision condition while it was the lowest for low friction and vision (Fig. 4.3).

Thumb Force	**High Friction**	**Low Friction**
Vision (mean ± sd)	4.16 ± 1.05	3.97 ± 0.47
No Vision (mean ± sd)	3.88 ± 0.80	4.11 ± 0.78

Table 4.1: Maximal hold forces for the Thumb under the high and low friction and vision and no vision conditions.

Index Force	**High Friction**	**Low Friction**
Vision (mean ± sd)	4.03 ± 0.93	3.95 ± 0.48
No Vision (mean ± sd)	3.78 ± 0.82	4.11 ± 0.80

Table 4.2: Maximal hold forces for the Index finger under the high and low friction and vision and no vision conditions.

Thumb Range (N)	**High Friction**	**Low Friction**
Vision	3.28	1.45
No Vision	2	2.14

Table 4.3: Range for maximal hold forces for the Thumb finger under the high and low friction and vision and no vision conditions.

4.5 Discussion and Conclusions

During low force dexterous manipulation under different conditions of vision and surfaces no significant differences were observed in between any of the conditions. The results

Index Range	High Friction	Low Friction
Vision	2.85	1.53
No Vision	2.08	2.22

Table 4.4: Range for maximal hold forces for the Index finger under the high and low friction and vision and no vision conditions.

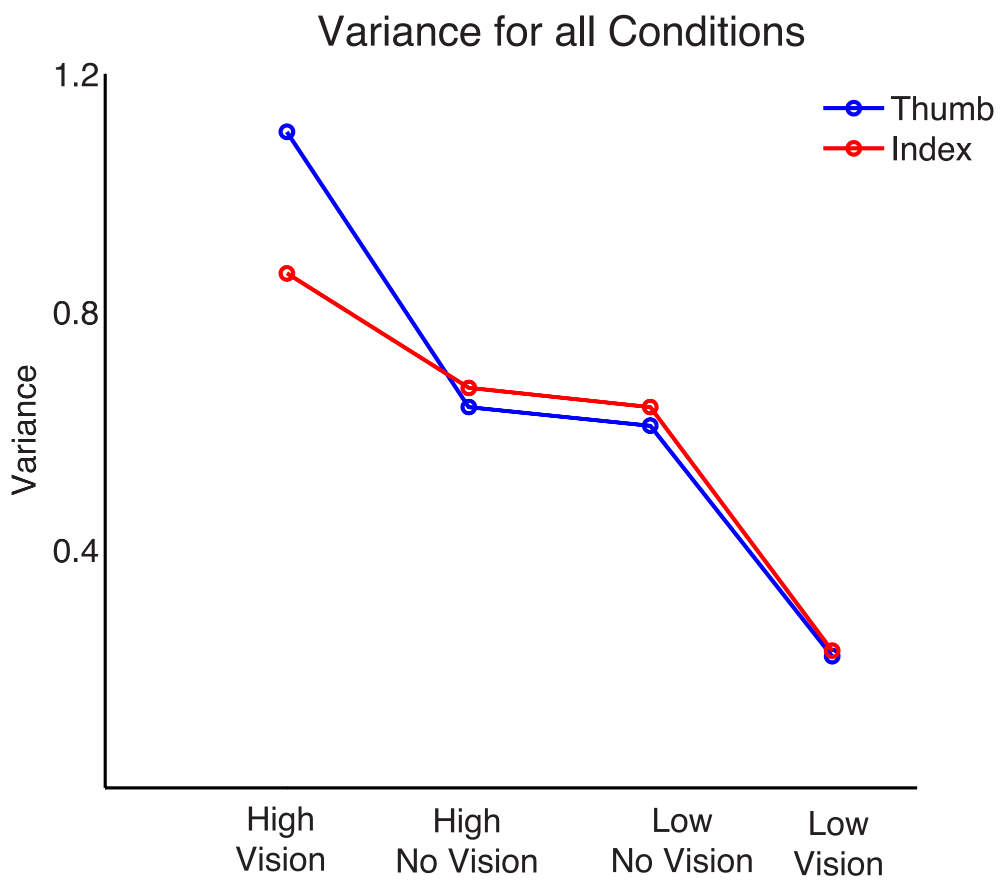

Figure 4.3: Variance across subjects in thumb (blue) and index (red) forces for low and high friction surface condition for all subjects under vision and no vision condition. Note the large change in variance from the High friction- Vision condition to the Low friction-Vision condition.

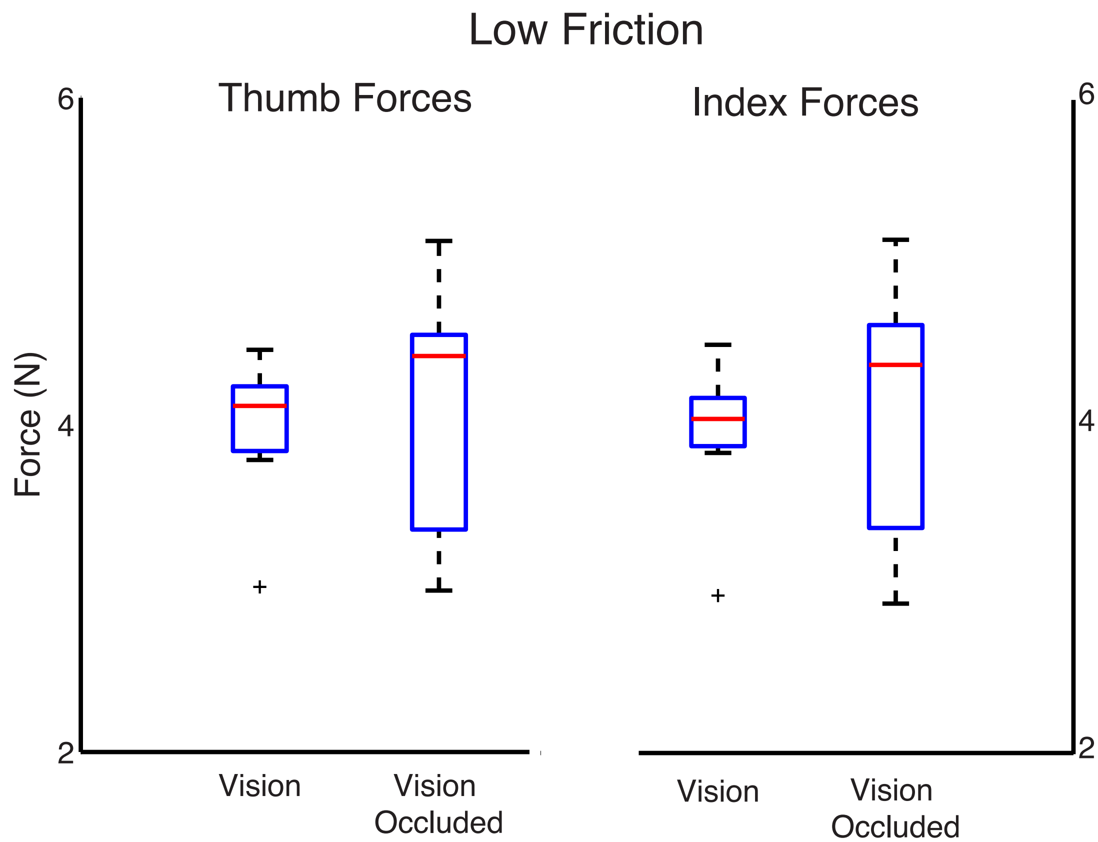

Figure 4.4: Thumb and Index finger forces for low friction surface condition for all subjects under vision and no vision condition. Note that one of the subjects was identified as an outlier in the vision condition for both the thumb and index fingers.

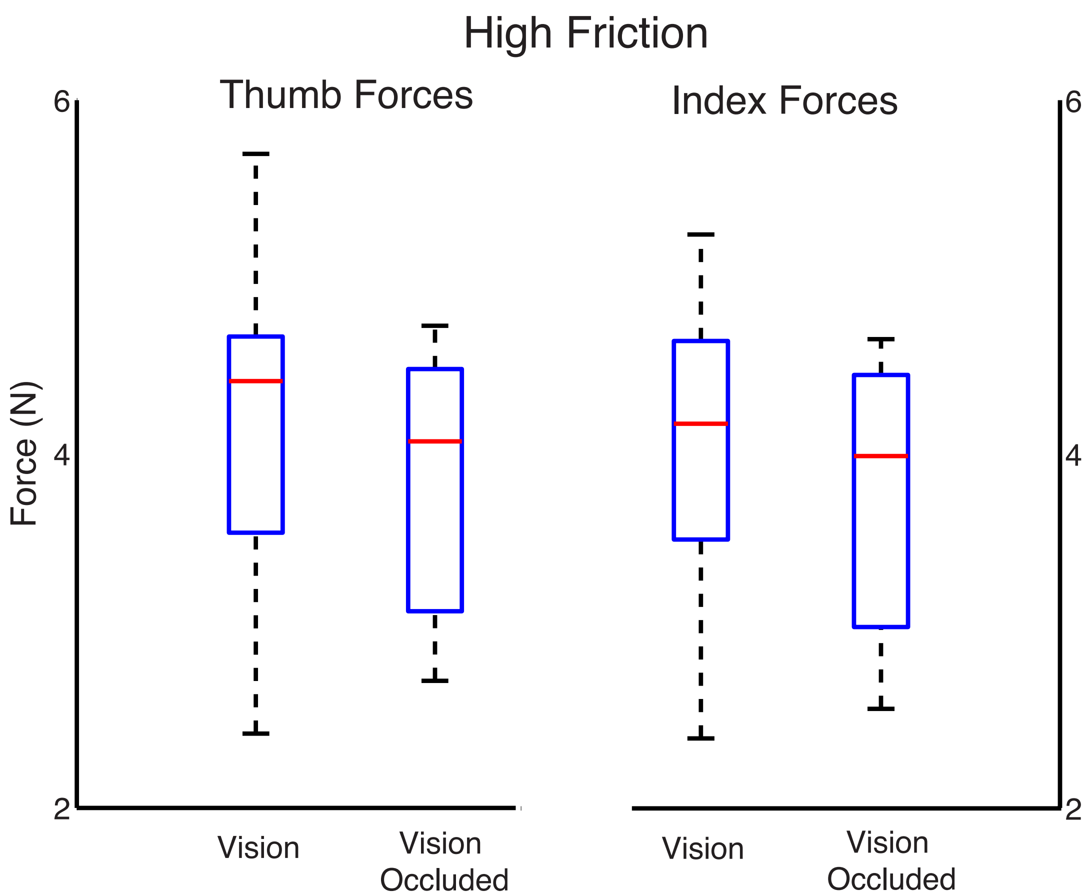

Figure 4.5: Thumb and Index finger forces for high friction surface condition for all subjects under vision and no vision condition.

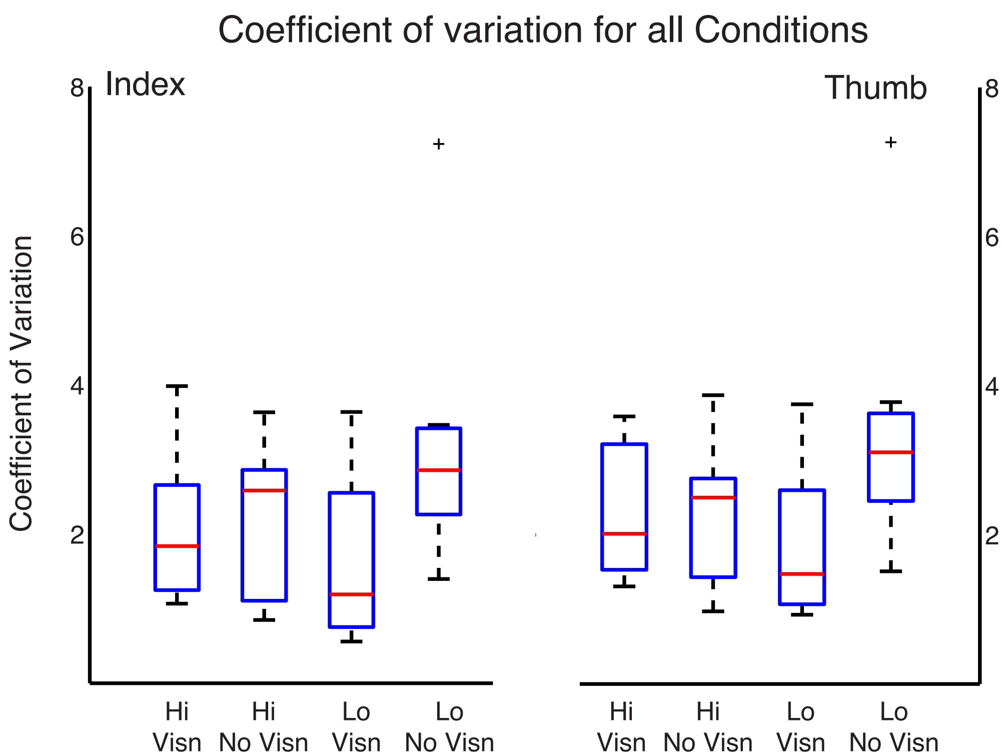

Figure 4.6: The coefficient of variation (Coev) for the thumb and index finger across low and high friction surface condition and under vision and no vision condition.

for the vision were similar to what has been reported before in dynamic manipulation (Venkadesan et al. 2007) that the role of vision becomes important only in the absence of tactile sensibility. The lack of differences in case of handling objects with low friction versus those with high friction are in contrast to what has been reported previously with higher grip forces seen in case of slippery surfaces (Johansson & Westling 1984, Edin et al. 1992, Forssberg et al. 1995, Westling & Johansson 1984). While the role of safety margin in anticipatory control with static objects is well known (Cole, Rotella & Harper 1999, Johansson & Flanagan 2009) it is not clear if the same parameters are used for dexterous manipulation. One factor which is very importantly different from the static grip and lift tasks was the weight of the object, the weight used in many of those studies is 100 grams or greater (Johansson & Flanagan 2009) while our device was less than 20 grams in weight. This suggests that for low force dexterous manipulation weight might not be an important parameter for internal models (Wolpert, Diedrichsen & Flanagan 2011) of manipulation given that many of the objects being manipulated, such as keys weigh less than 20 grams and are definitely lighter than 100 grams.

The lowest variance is seen across subjects for the Low Friction-Vision condition (Fig. 4.3) and highest for High Friction- Vision condition. The maximal hold forces for the thumb ranged from 3.28 to 1.45 N (Table 4.3) while that for the index was 2.85 to 1.53 N (Table 4.4). This can be seen in the whiskers of box plots for Low Friction (Fig. 4.4) versus that for High Friction (Fig. 4.5). These results could be interpreted to mean that when there is a high amount of safety, i.e. there is no requirement for the system to perform optimally. On the other hand under conditions of Low Friction-Vision one of the sensory modalities is challenged leading to a convergence on an optimal performance across subjects.

The most interesting result we were able to observe was that the metric of performance in our experiment was not the mean grip force a person could generate while holding the spring maximally compressed (i.e. compressed partially but to the best of their abilities) rather was the Coefficient of Variation (Coev). The Coev for the most difficult of the conditions, Low Friction-No Vision was the highest implying that this was the most challenging of the 4 conditions for the subjects to perform. While this was not significant (p=0.10) it is still an interesting finding that illustrates that this seemingly simple task can be challenging to the sensorimotor system. In our healthy young adults they were perhaps able to modify their motor unit recruitment, reflected by their decrease in steadiness (Jesunathadas, Marmon, Gibb & Enoka 2010) under the most testing of the conditions which shows some adaptability as is expected. However this might not hold true in clinical populations and this can be modified to create a challenging task to test for differential contribution of sensory modalities in different clinical conditions.

This study showed some promising results, which while not significant reveal two important things; the most challenging of the condition, i.e. low friction and no vision changes the task requirement and solely challenging the tactile system seemed to narrow the task variance. Our pilot project requires to be expanded to see if there are significant differences under the different friction and vision conditions and particularly if Coefficient of Variation would be a good metric to evaluate the change. The importance of this work would be to see if the parameters for static manipulation tasks such as surface conditions, weight remain the same in case of low force dexterous manipulation.

4.6 Acknowledgements

We are thankful to Kornelius Ràcz for his technical assistance with data acquisition.

Chapter 5

Change in Dexterous Manipulation with Aging

5.1 Abstract

The control of fingertip force direction appears to change with aging and is presumed to cause impairments in manipulation abilities. By using a task which requires one to control the fingertip force vector near normal in order to succeed in the task and by testing people from the young through the old age (range 18-89 years) we were able to systematically study the effect of aging on it. We extend our previous work to show a simple, instrumented hand held device that requires low force but a high control of finger tip force direction can be used without any ceiling effects to effectively show changes across the whole of adulthood. Importantly the decline in the ability to overcome instabilities with improved control of force direction appears to decline starting in the middle ages and is dissociated from the changes in strength.

5.2 Introduction

Dramatic decline in strength is seen in elderly people (Lexell, Henriksson-Larsén, Winblad & Sjöström 1983) and while balance and falls are a major health concern in older age (Close, Ellis, Hooper, Glucksman, Jackson & Swift 1999) appropriate daily interactions require fine motor abilities. With aging a decline in dexterity has been demonstrated on pick and place tasks, as well as static tasks (Cole et al. 1999, Desrosiers, Hbert, Bravo & Rochette 1999, Parikh & Cole 2012, Ranganathan, Siemionow, Sahgal & Yue 2001) with a multitude of changes after the age of 65 (Carmeli, Patish & Coleman 2003). Importantly, older people appear to have an incorrect directional bias and when asked to generate normal forces are unable to control the direction of the fingertip force vector to be perfectly normal to the surface during isometric tasks (Cole 2006). Consequently this could lead to inappropriate external moment generation (Parikh & Cole 2012) leading to functional difficulties handling small objects. A perfect experiment to test if indeed there is a directional bias in fingertip force direction with aging requires that the subjects be constrained to have to produce a perfectly normal force direction in order to succeed at the task. The Strength-Dexterity paradigm, based on the propensity of slender springs to buckle under compression defines dexterity as the dynamic ability to regulate fingertip force direction (Valero-Cuevas et al. 2003) and provides a clear scientific framework in which to study if aging causes a directional bias in fingertip force.

During the transition from early adulthood to middle age there appears to be changes in precision of fingertip force (Cole et al. 1999, Lindberg, Ody, Feydy & Maier 2009) especially at low forces but not in maximal force generation (Lindberg et al. 2009). However this decrement has not been observed consistently (Lowe 2001) and currently it is not clear if there is a change in fingertip force direction during a dynamic task and if the directional bias observed in the elderly has an earlier onset. Given that with aging there is a loss of alpha motor neurons, reinnervation leading to an increased number of muscle fibers per motor unit (Lexell et al. 1983, Brown, Strong & Snow 1988) and that there is a high percentage of intrinsic hand muscle motor units recruited for low forces (Milner-Brown et al. 1973*b*, Fuglevand 2011), leading to loss of refinement of recruitment we hypothesize that past the age of 65 adults will be worse in their low force dexterous manipulation abilities, specifically their ability to control their fingertip force direction, but these would start from the middle age and these will be independent of changes in strength. The goal of this study was to evaluate how the ability of individuals to control their fingertip force direction during low force manipulation changes with age and to explore its association with strength.

5.3 Methods

32 young adults (18-34 years) and 66 adults (45-89 years) participated in this study. They were divided into three age distributions with around 33 subjects in each group; young, 18-34 (28.38 $\pm$ 3.69), middle aged, 45-65 (57.06 $\pm$ 6.58) and older, 66-89 (75.6 $\pm$ 7.15). Ethical approval was obtained from an institutional review board and all subjects consented to participate in this study.

5.3.1 Instrumentation for Dexterity Instrument

A linear spring with stiffness, k=0.49 lb/inch that requires low force for complete compression were used (Table 2.1)(# 4268, Century Springs Corp., Los Angeles, CA) . This was the longest spring, part of the spring setup used in children in a complementary study. The spring was chosen to provide higher resolution in dexterity while maintaining a low strength requirement (Fig. 5.1). In addition the following criteria were used: less 4 N of force (Ehrsson et al. 2001) and length between 2-4 cms.

Two compression load cells (ELB4-10, Measurement Specialties, Hampton, VA) were mounted at the spring endcaps (Fig. 2.2). The load cells were connected to a signal-conditioning box, an USB-DAQ (Measurement Computing, Norton, MA) sampled the data at 400 Hz using a custom written MATLAB program (Natick, MA) and a deadweight calibration procedure was used for conversion from voltage to force.

5.3.2 Experimental Procedure

The aim of the task was to maintain a sustained compression, with the index finger and the thumb of their dominant hand, for at least three seconds at the highest individual level of control of force magnitude and force directions. After a brief familiarization with the spring and the task the subjects were asked to compress the spring as close as possible to the point beyond which the device will slip from their hand and maintain that compression at a steady level for at least three seconds (Fig. 5.1). The subjects were encouraged to try to push their limits to ensure they were being tested to their true abilities. At least three successful compression holds were collected per subject.

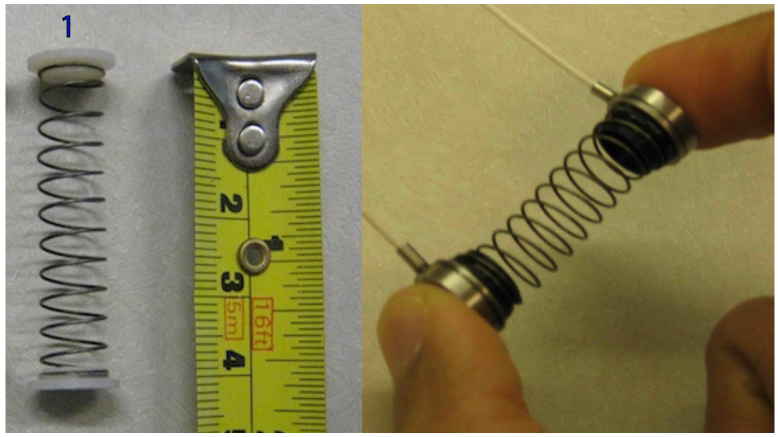

Figure 5.1: Strength-Dexterity setup demonstrating the longest spring and the hardware for force data capture. The spring had a stiffness, k=0.86 N/cm, the length of the spring was 3.96 cm, while the maximum force required for compression of the spring was around 3 N of force. Compression load cells were mounted on custom ABS plastic endcaps with double-sided tape. The spring was chosen such that while the force required to compress it was minimal, with higher compression the instabilities increased and the subject was not able to compress it fully, i.e. it was a impossible-to-compress spring. The figure of the right shows an example compression and hold.

Pinch strength with the index finger and the thumb of the dominant hand using a tip-to-tip pinch was measured using pinch gauge (B&L Engineering, Tustin, CA, USA). The subjects were asked to compress the pinch meter with maximum force for a couple of seconds and the maximal value of two attempts was used.

5.3.3 Data Reduction

A custom written MATLAB © (Mathworks, Natick, MA) program was used to visually identify (ginput) the sustained compression phases based on the force and force rate. To facilitate this in the presence of high frequency dynamic changes in the force, we used a loess smoother with a span of 10% before the force rate was computed. We defined a sustained compression phase when the rate was bounded within 1 standard deviation of the mean force rate. The start was identified when the rate was close to zero and the end when the rate went out of bounds and the force dropped towards baseline. The sustained compression phase data were downsampled to 100 Hz, low pass filtered at 25 Hz while maintaining phase (Butterworth, 2nd order, filtfilt). A time series was computed as the average of the two finger force time series to create a representative force. A mean of the the highest three hold phases was computed for each subject.

In order to characterize the dynamics of how children control the dexterity device during the sustained compression we examined the data in the state space i.e. ($\ddot{F}$-$\dot{F}$-F). We calculated the sum of Euclidean distances (norm) of the trajectories through the time series of the maximal hold phase per subject normalized to the time held.

The independent variables were age distributions (18-34, 45-65, 66-89), while the dependent variables were mean hold phase force, maximum pinch strength and state space Euclidean norms/second.

5.4 Results

5.4.1 Changes in dexterous manipulation abilities with aging

Significant differences ($p<0.0001$, $F=17.99$) were observed on a one-way ANOVA across the three age groups (18-34, 45-65, 66-89)(Fig. 5.2, Fig. 5.3). Scheffe's test for multiple comparisons was used post-hoc to test for pair wise significance and demonstrated significant differences between all three groups. There was a reduction in the mean hold phase force across the three age groups [mean(±SEM)]; 213.79(± 6.8), 185.73(±6.6), and

156.15± 6.8, for the 18-34, 45-65 and 66-89 respectively. Prior to statistical analysis the groups were tested for normality using the Kolmogorov-Smirnov test.

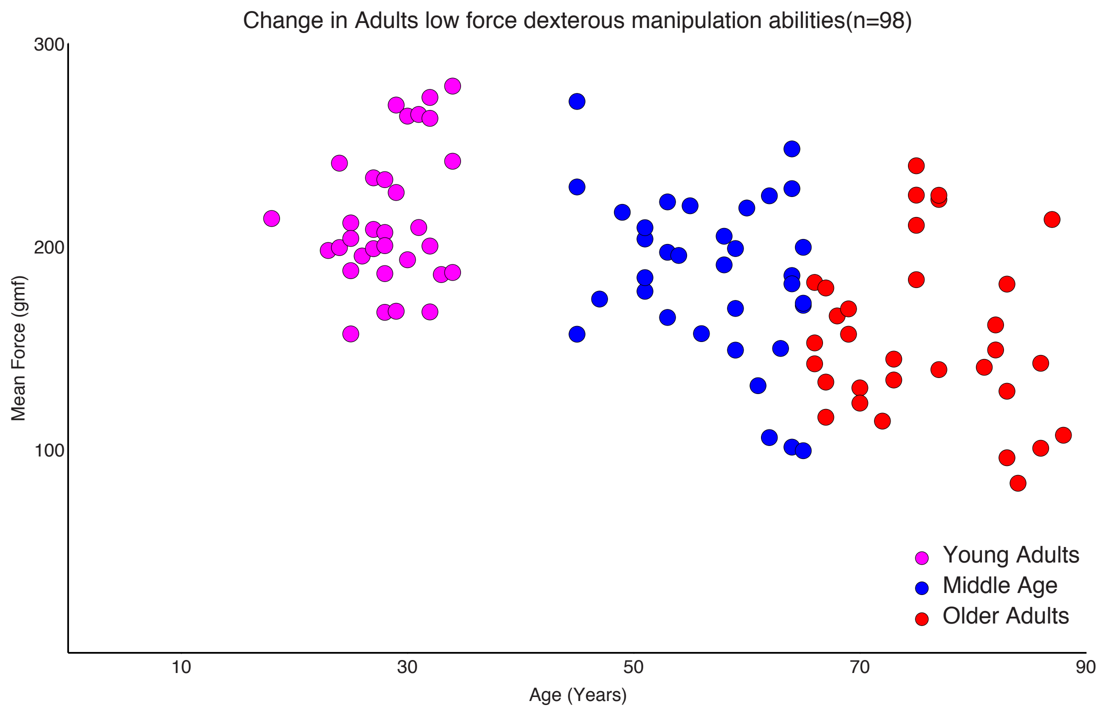

Figure 5.2: The mean hold force for the 98 subjects from 18-89 years is shown here.There is a decline in low force dexterous manipulation capabilities between young adults (magenta/left) and older adults (red/right).

5.4.2 Relationship between dexterous manipulation and pinch strength

There does not appear to be any association between maximal pinch strength and dexterous manipulation capabilities (Fig. 5.4). The regression line between maximal hold force and maximal tip-to-tip pinch strength is not significantly different from the null hypothesis that the slope of the line is equal to zero (p=0.07, R^2 =0.05). In other words, pinch strength is not predictive of low force dexterous manipulation capabilities. Two

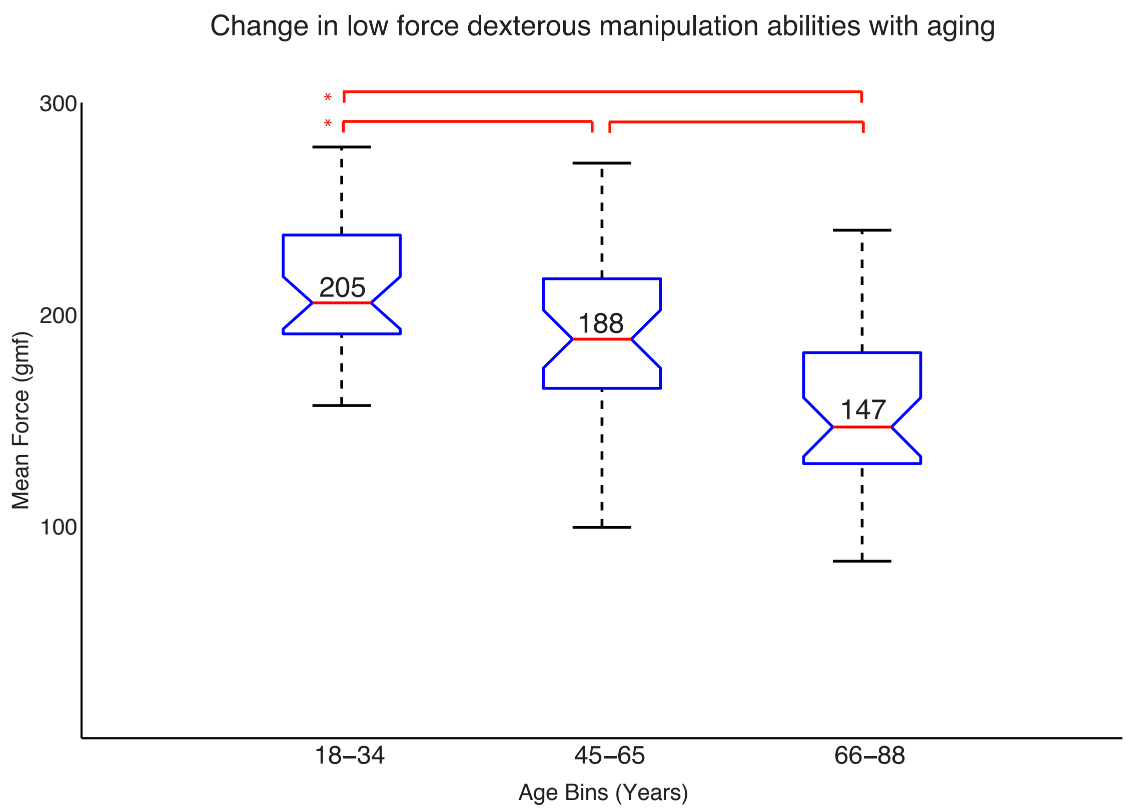

Figure 5.3: There is a significant decline in low force dexterous manipulation capabilities between young adults (left) and older adults (right), between middle age group (middle) and older adults (right), and also between young and middle age adults. Significant differences indicated with an asterisk, are based on a one-way ANOVA with post hoc multiple comparisons.

subjects were detected to be outliers in their strength (Fig. 5.4, inset) and were not included for the analysis. Including them while making the regression line significantly different from a zero slope, still maintains the main result that only a small percentage of variance in dexterous manipulation could be explained by changes in strength.

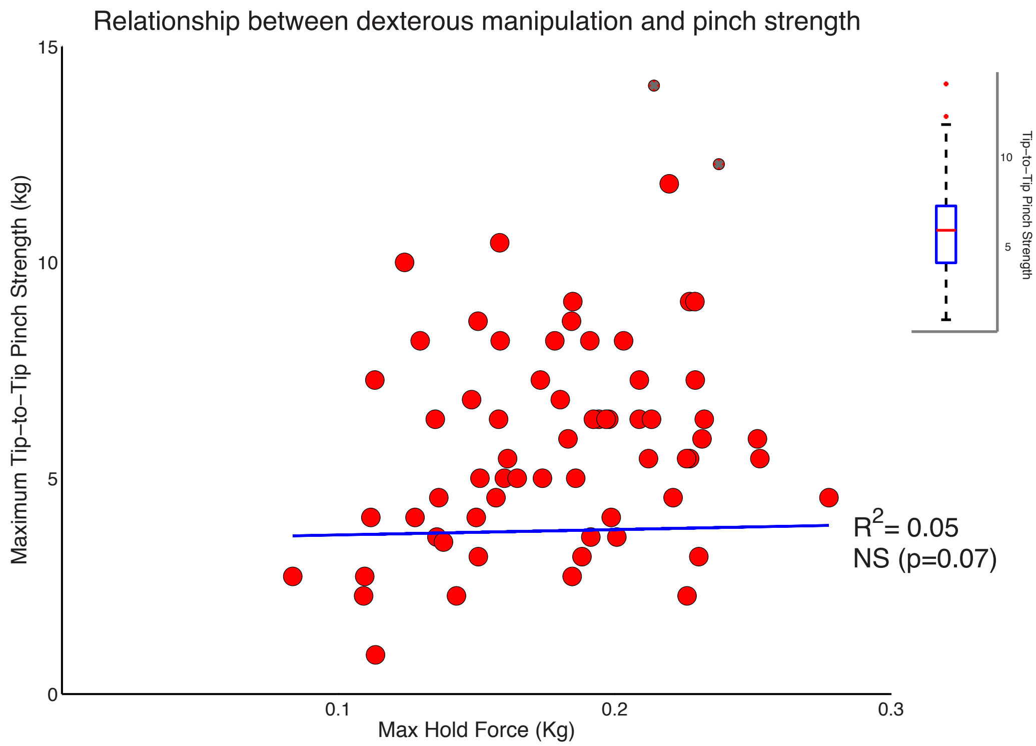

Figure 5.4: Regression between maximum tip-to-tip pinch strength and maximal hold phase. Pinch strength does not appear to be predictive of ability in dexterous manipulation with only 5% of the variance being explained by strength. Note that two subjects were detected to be outliers for strength (gray), the boxplot in the inset shows the data for the tip-to-tip pinch strength and the two outliers.

5.4.3 Change in dynamics of control with aging

There are significant differences in the dynamics of control, measured by the Euclidean distance/second seen on a one-way ANOVA ($p<0.001$, $F=7.99$). Post-hoc multiple comparison test (Scheffe's) revealed the differences were only present between the younger (18-34, 23.93±3.5) and middle (45-65, 34.88±3.4) age group as well as between the younger (18-34, 23.93±3.5) and the older (66-89, 40.46±3.5) age group (Fig. 5.5) but not between the middle and older age groups. Prior to statistical analysis the groups were tested for normality using the Kolmogorov-Smirnov test and the outliers as seen in Fig. 5.5 were removed.

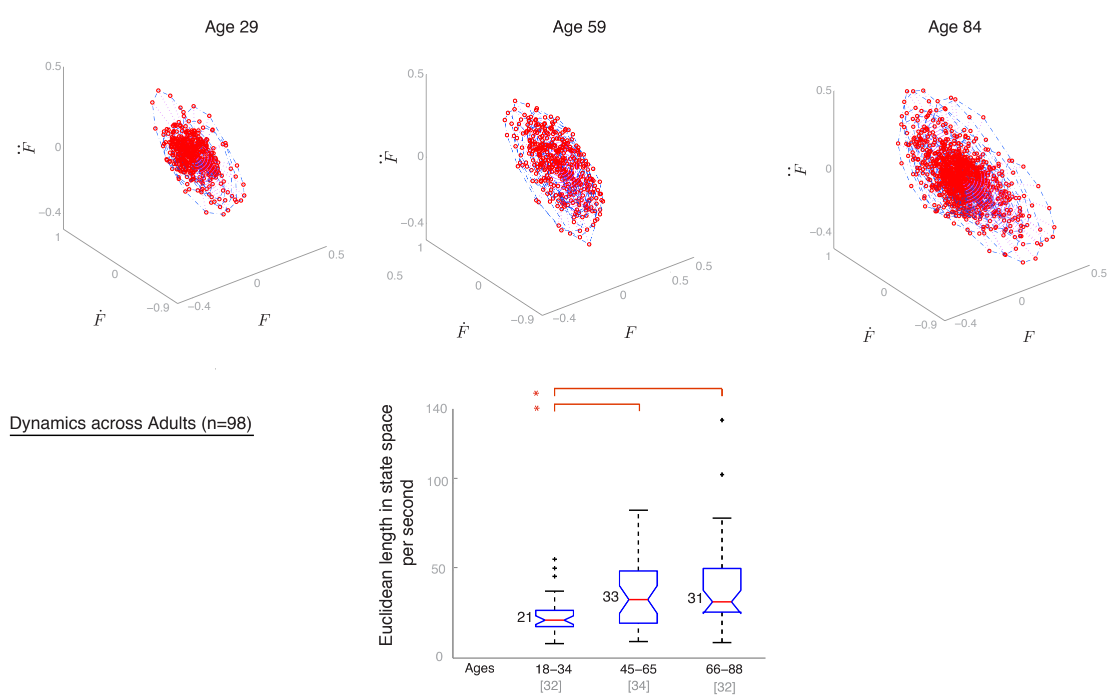

Figure 5.5: Changing dynamics of control quantified by Euclidean length in the state space. Representative adults for each age range show some changes with aging (Top). Mean values are significantly different, indicated by the asterisks, in the young adults (18-34 years) compared to the older adults in both groups (45-65 & 66-89) (Bottom).

5.5 Discussion

With aging there is a consistent decline in the ability to control finger tip force direction during low force dexterous manipulation, with higher decline seen after the age of 65. In addition, there are some early changes in the ability to stabilize an unstable object with differences seen even in the middle aged group, specifically how they are able to maintain stability in the state space. Finally we were able to show that the dexterous manipulation capabilities were not related to pinch strength and suggesting while loss in strength is a dramatic change in old age, change in fine motor abilities are not explained by the loss of strength. Importantly, even for such low forces we are able to show significant changes across adulthood without saturation effects.

Our results support the landmark study by (Cole 2006) which showed that there is a directional bias in older people in addition to supporting the early changes in precision from middle age (Lindberg et al. 2009). The two limitations of the (Cole 2006) study were only inclusion of people past the age of 75 and importantly not requiring a task constraint that the force vector direction be constrained to be normal to the surface against which force is being applied. In our setup by design the subjects were required to maintain relatively normal fingertip forces in order to succeed at the task. The metric of performance, the compression force reflects the ability to dynamically control the fingertip force direction with higher forces requiring higher amounts of control of fingertip force direction. Additionally here we include people from 45-89 and show that this ability to dynamically regulate fingertip force direction declines significantly much earlier than 75 years of age.

There are a number of changes in the muscular system which can account for the observed changes. There is minimal change in proportion of type 1 fiber % seen beyond the age of 60, but strength loss is more related to marked reduction in number of fibers and reduction in fiber size of type 2 fibers with an almost 25 % reduction in relative area occupied by type 2 fibers (Lexell et al. 1983, Lexell, Taylor & Sjöström 1988, Lexell & Downham 1992). Tip-to-tip pinch strength has been observed to be relatively stable till around 60 years of age, after which there is a gradual decline (Mathiowetz et al. 1985), this again reinforces the observation that the early change in dexterous manipulation capabilities observed in our study are probably not related to strength. Our results of poor predictive abilities of strength observed across the adult ages of 18-89 has also been observed in studies in development in children (Dayanidhi et al. 2011) as well as in adults using one finger manipulation (Venkadesan et al. 2007).

Even low force activation of around 2 N, such as that used for manipulation can recruit around 50% of the motor units of the first dorsal interosseous (Milner-Brown et al. 1973*b*), which has been suggested to be an added level of control (Fuglevand 2011). The muscle twitch time to peak using spike-triggered average force of the first dorsal interosseous (FDI) in the elderly people has been reported to be similar to that observed in young adults (Galganski, Fuglevand & Enoka 1993). With aging there is a loss of alpha motor neurons and consequent reinnervation leading to a increased number of muscle fibers per motor unit (Lexell et al. 1983, Brown et al. 1988). Steadiness in maintaining force even at low values has been observed to be worse in older adults (Enoka, Christou, Hunter, Kornatz, Semmler, Taylor & Tracy 2003, Galganski et al. 1993, Jesunathadas et al. 2010) and partly contributes to changes in functional pick and place tests such as purdue pegboard test (Marmon, Pascoe, Schwartz & Enoka 2011, Marmon, Gould & Enoka 2011). The reduction in steadiness could potentially be a reason for decline in the mean hold force seen in the older people.

From early adulthood there is some degenerative changes in the brain volume, mainly in cortical areas of the sensorimotor system (Pieperhoff et al. 2008), and it appears in particular to have an impact on the diffuse cortical circuits which have been shown to be associated with precision grasp behavior (Bonnard et al. 2007, Ehrsson et al. 2001, Holmström et al. 2011, Mosier et al. 2011). This change at a cortical level might explain some of the changes seen in our study in middle aged adults, in particular the ability to maintain the dexterous manipulation device stably in the state space might reflect this decrement in control of the precision dynamics. In addition slowing of central and peripheral (motor and sensory) conduction velocities have been observed in people older than 60 years of age (Dorfman & Bosley 1979), but the significance of this in the context of dexterous manipulation is not known. Finally while tactile impairments are seen with aging just degradation of tactile sensibility does not appear to be able to explain differences in manipulation abilities (Cole, Rotella & Harper 1998) but obviously tactile sensibility and vision do play a role (Johansson & Flanagan 2009) with vision compensating to some extent for lack of tactile sensibility (Venkadesan et al. 2007). With aging in the elderly there appears to be a complex interaction between cortical, spinal and motor unit changes as well as peripheral changes in tactile sensibility and muscle strength all of which have an impact on their ability to control their fingertip force direction and perform dexterous manipulation tasks.

5.6 Conclusion

Control of finger tip force direction show deterioration with age, even at low forces (< 3 N). Here we present a proof of principle in ninety eight healthy adults from 18-89 years of age and demonstrate the capacity of a simple device to capture the changing capabilities in low force dexterous manipulation with aging. Importantly, we are able to show there are significant changes in this capabilities from the middle age onwards. In addition, we are able to show that the pinch strength is not predictive of dexterous manipulation abilities.

Acknowledgments

We acknowledge the assistance of Kathleen Shanfield, Allison Chu, Juan Garibay, Wenhsin Hu, Emily Lawrence, Na-hyeon Ko, Isak Hägg, Novalie Lilja and Phil Requejo with data collection and recruitment, Nora Nelson and Jon Weisz with technical assistance. NSF EFRI 0836042, NIDRR RERC 84-133E2008-8 to FVC.

Chapter 6

Dynamical Analysis to Quantify Changes in Low Force Dexterous Manipulation across the Lifespan

6.1 Abstract

In order to understand the changes in low force dexterous manipulation capabilities across the lifespan we combine the data from 3 of the previous studies to look at the changes in 240 individuals (142 children, 32 young adults, 66 older adults) ranging from 4-89 years of age. There are improvements in dexterity seen throughout the childhood and adolescent years and appears to peak only in early adulthood. There are changes in the ability to dynamically regulate and maintain the fingertip forces during dexterous manipulation, most of which are seen in early childhood but there are some late adolescent changes as well. During adulthood there is a gradual decline in both the dynamic abilities to overcome and postpone instabilities and in the stability with which this is achieved. The use of simple dynamical state space plots and nonlinear analysis help reveal a rich dynamical source of change in dexterous manipulation across the lifespan.

6.2 Introduction

Conceptually the analysis of dynamic behaviors can yield a wealth of information on the development of control. (Newell, Liu & Mayer-Kress 2001) among others have proposed how dynamical systems analysis can provide a framework to explore the stability of a developing system as well as the role of bifurcations in changing dynamics over large timescales can help explain different patterns of skill acquisition. A conceptual schematic of relationship between age and stability is shown in Fig. 6.1, where over the course of years the stability of particular behaviors is reinforced and is more robust to perturbations.

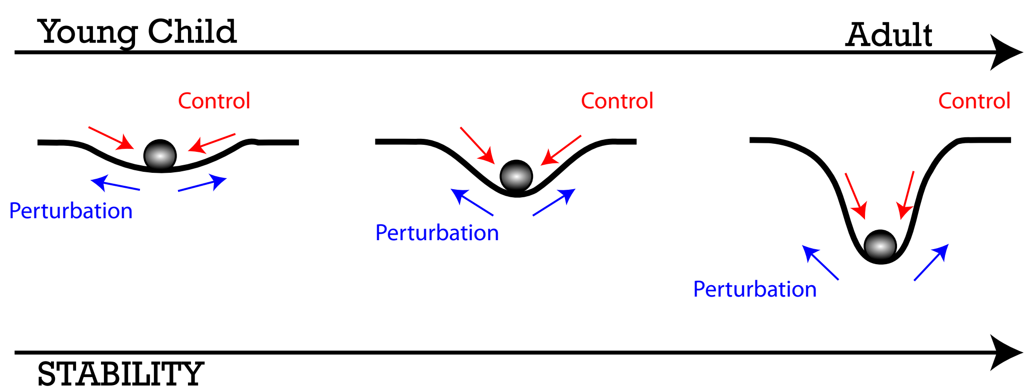

Figure 6.1: Conceptual schematic of development of stability through changing attractor landscape. The perturbation is trying to change the current state of the system while the control is trying to overcome the perturbation and maintain the current state of the system. The spring device in our case is considered to be a perturbation challenging the control while the children/subjects are trying to stably maintain a hold force. Stable behaviors are more robust to perturbations.

In this study the spring is considered to be a perturbation challenging the control while the children are trying to stably maintain a hold force. Since the use precision grip and dexterity is a behavior that evolves through a complex interaction of neuromaturation as well experience dependent processes, it is expected to reflect stability with improvements in dexterous manipulation. In particular, it is important to also consider the need for challenging the developing system in children with cerebral palsy effectively so as to promote the appropriate development of functionally meaningful stable behaviors. The real problem is to identify both the appropriate challenge level for skill acquisition (Plautz, Milliken & Nudo 2000) as well the specific behavior to train in rehabilitation.

The dynamics of the processes involved in overcoming instabilities can reveal the underlying change in stability. Anomalous diffusion laws relate mean square displacement and time intervals,

$$< \Delta x^2 > \propto \Delta t^{2H}$$

This can be expressed as,

$$< (x_t - x_{t_0})^2 > \propto (t - t_0)^{2H},$$

where H is the Hurst Exponent, $0 \leq \mathrm{H} \leq 1$. A value of 0.5 would be a random walk, which suggests the time series has no autocorrelation or memory processes in it, while a value between 0-0.5 is negatively correlated (i.e. diffusion is suppressed, anti-persistence), whereas a value between 0.5-1 suggests positive correlation (i.e. diffusion is enhanced, persistence) (Kantz & Schreiber 2004). Diffusion analyses have been used in biomechanics to look at postural adjustments during quiet standing such as the random walk analysis (Collins & De Luca 1993, Collins & De Luca 1994, Collins & De Luca 1995). Rather than the use of the simple Hurst exponent it has been shown that the use of the Detrended Fluctuation Analysis (DFA) to calculate it is superior to the computation as described above (Kantz & Schreiber 2004, Peng, Havlin, Stanley & Goldberger 1995), especially in the presence of nonstationarities and biological noise. The goal of this study was to summarize the changes in low force dexterous manipulation capabilities during development through adolescence as well as aging in the middle and later years. In particular we wanted to characterize the changes seen in the state space of the task and utilize nonlinear methods of diffusion analysis to understand the changes.

6.3 Methods

240 subjects (130 children, 4-16 yrs of age, 32 young adults, 18-34 years of age, 66 older adults, 45-89 years of age) participated in this study (see Chapters 2, 3 and 5). They represented the entire lifespan from 4-89 years of age (Table 6.1).

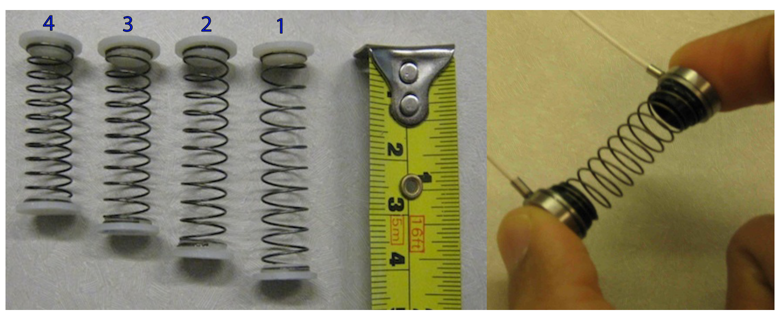

Figure 6.2: Strength-Dexterity Setup demonstrating the four springs and the hardware for force data capture. The springs were custom made such that the spring stiffness was maintained the same (k=0.86 N/cm) across all the four springs. The lengths of the springs varied from 2.90- 3.96 cm, while the maximum force required for compression of the springs ranged from 2-3 N of force. Compression load cells were mounted on custom ABS plastic endcaps with double-sided tape. The springs were presented in a sequential order from the shortest, i.e. spring 4 and the test spring was chosen such that it was the first spring the subject was not able to compress fully, i.e. the minimally-impossible-to-compress spring. The figure on the right shows an example compression and hold.

Age by decade (years)	Number of Subjects
0-10	66
11-20	78
21-30	22
31-40	10
41-50	5
51-60	16
61-70	24
71-80	10
81-90	11

Table 6.1: Table showing the subjects enrolled in all the studies by decades.

6.3.1 Experimental Setup

Briefly, low force dexterous manipulation capabilities were tested by using a slender spring(s) with two compression load cells attached to the end caps (Fig 6.2). The subjects were tested on their minimally impossible-to-compress spring, i.e. when the springs are presented in the order of lengths the first spring which the subjects are unable to compress fully. All the subjects were able to compress spring 4, the shortest spring and except for 3 children all the child subject used spring 2 or 1 as their test spring. All adult subjects used spring 1 as their test spring. The subjects were asked to compress the test spring as much as they could and maintain it for at least 3 seconds without letting the spring buckle or slip. For details of the experiment see Chapter 2, 3, 5.

6.3.2 Data Reduction

The maximal hold phase for each of the subjects was converted to the dexterity score as described in Chapter 2. Eureqa (Schmidt & Lipson 2009) was used to find the optimal form of the regression function. Additionally the Euclidean length in the state space

($\ddot{F}$-$\dot{F}$-F) was calculated and normalized to time, similar to described in Chapter 2 and Chapter 5. Detrended fluctuation analysis (DFA) was chosen as the nonlinear analysis to evaluate any correlative memory and diffusion processes in the 100-1000ms time window in the maximal hold forces.

6.4 Results and Discussion

6.4.1 Lifespan changes in the Dexterity Score

Dramatic improvements in low force dexterous manipulation capabilities are seen in children throughout the childhood and adolescent years, appearing to improve till early adulthood (Fig. 6.3). This appears to match the changes in the corticospinal tract (CST) in the developmental years changing well into early adulthood (Lebel et al. 2008, Lebel & Beaulieu 2011, Paus et al. 1999). On the other side of the peak there is a gradual decline from the middle ages and presumably this is accentuated with any other illnesses or confounds in the later years.

The whole change across the lifespan appears to be best approximated by an exponential form with increase till early adulthood and gradual consequent decline (Fig. 6.3) with the RMSE and R^2 4.63 and 0.73 respectively. The exponential fit was cross -validated using Eureqa and seems to match up well. This form of the equation was based only on part of the data which was used as a training dataset and was validated on the remaining points (Fig. 6.4, top). In addition this form of equation was chosen based on a Pareto front of error and complexity of expressions (Fig. 6.4, bottom) ensuring low error and low complexity such that the sparse data set was not over fitted. This unique method for finding the form of equation for biological data appears to be superior to the traditional approaches, such as polynomial fitting (Kurse, Lipson & Valero-Cuevas 2012, Schmidt & Lipson 2009).

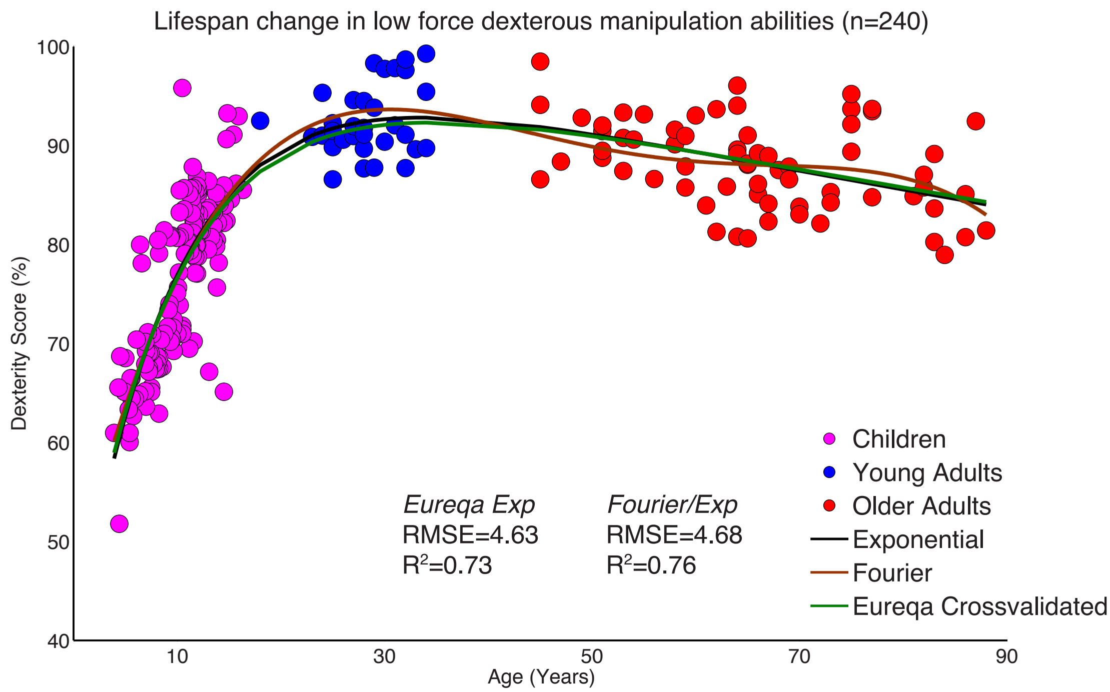

Figure 6.3: Lifespan change in low force dexterous manipulation capabilities from 4-89 years of age. This includes 240 subjects;142 children (magenta), 32 young adults (blue) and 66 older adults (red). The exponential regression appears to represent the data well. This was cross validated with the use of symbolic regression (Eureqa), which used part of the data for training and validated it based on the remaining points.

6.4.2 Lifespan changes in dynamics of control

Children in the years before 6 appear to have greater problems with maintaining their fingertip force direction and magnitude stably and occupy a large area in the state space (Fig. 6.5). With development this improves and children have improved stability in

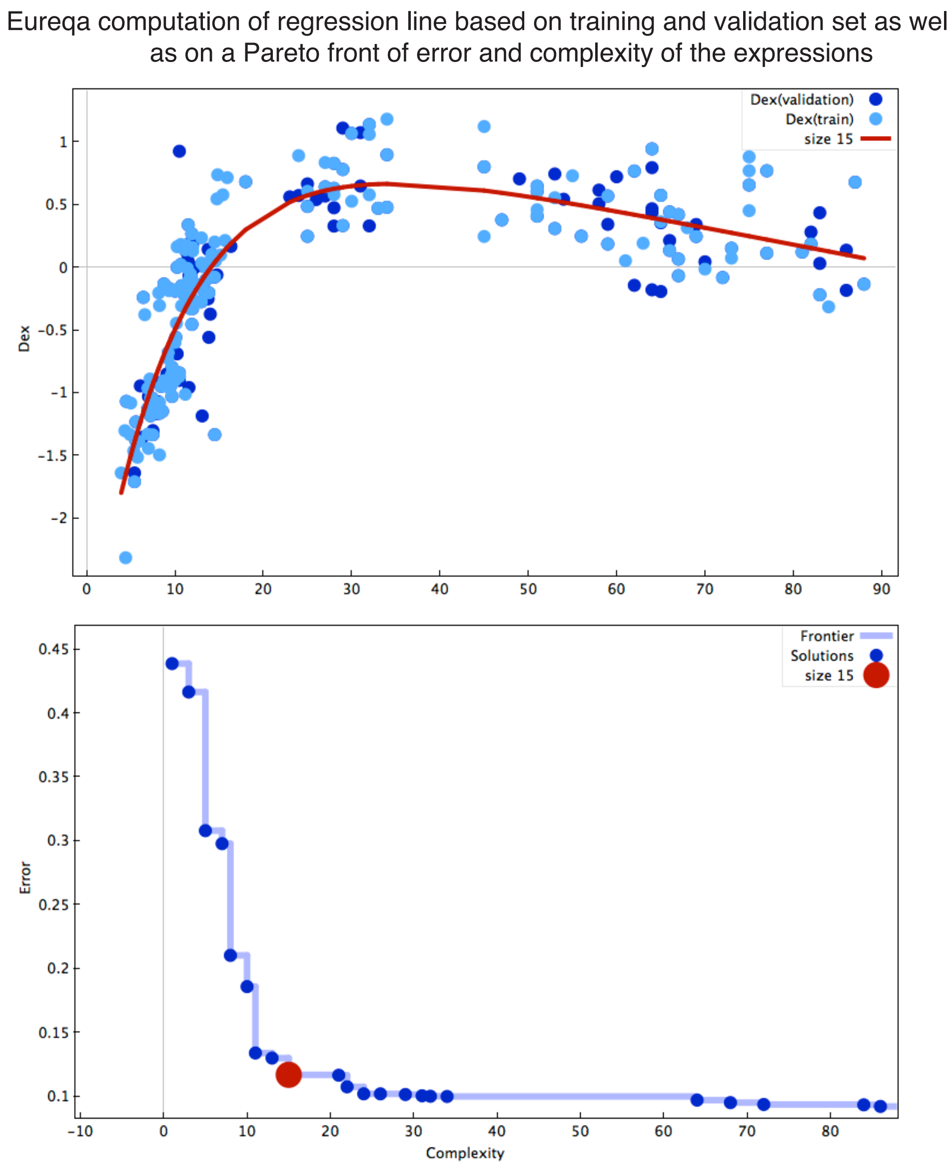

Figure 6.4: Regression using training (cyan) and validation (blue) data sets (Top) and computation of a Pareto front of error and complexity of expressions (Bottom). The solution which had a combination of low error and low complexity and did not over fit the data was chosen as the solution.

overcoming the gentle perturbations of the spring device with the adolescents and the young adults having similar Euclidean lengths per second. Both middle aged adults and older adults appear to have worse stability than the younger adults and adolescents in overcoming the instabilities (Fig. 6.5).

This lifespan change in dynamics of control with improvements in the ability to overcome instabilities and perturbations and then a gradual decline appears to match our conceptualized schematic of the changing attractor landscape during the lifespan. The control against perturbations and instabilities appears worse in the early childhood years and begins to deteriorate starting in the middle ages. The important point here is also that in the late adolescent years and early adulthood the forces which the people are higher leading to higher amounts of perturbations they are able to overcome while maintaining their fingertip forces stably.

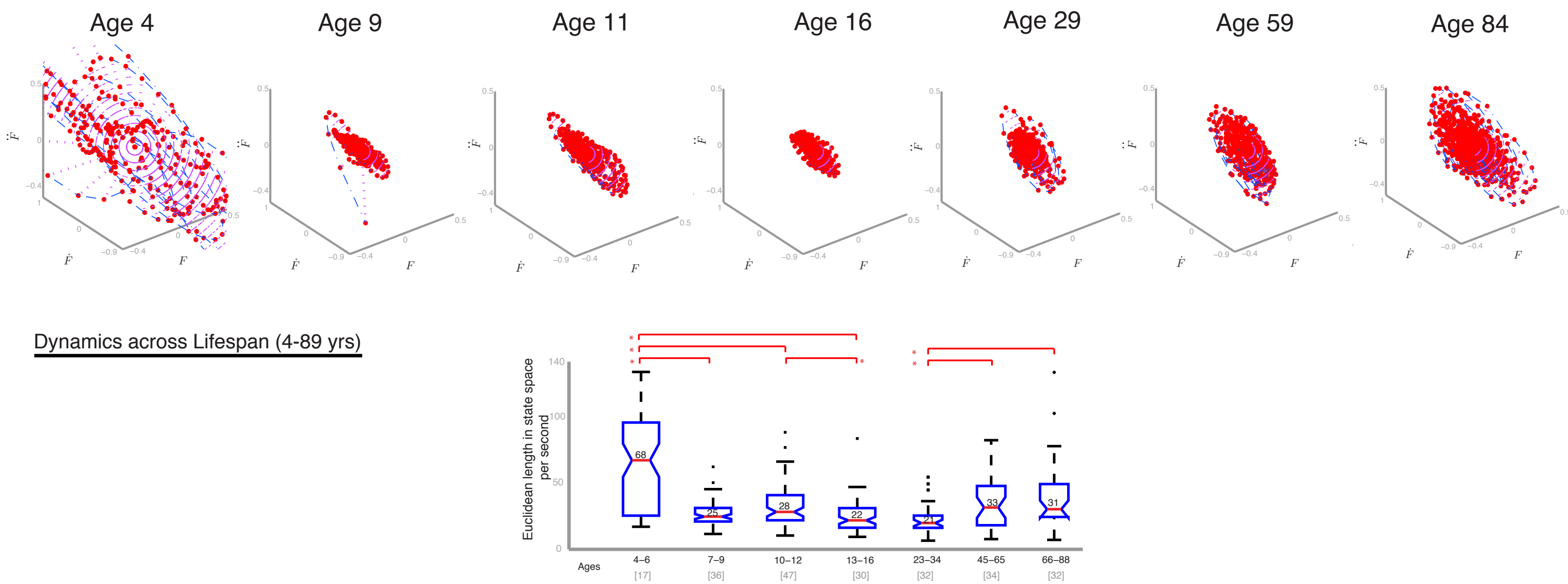

Figure 6.5: Changing dynamics of control across the lifespan quantified by Euclidean length in the state space. Representative subjects for each age range show changes throughout the lifespan (Top). Median values are significantly different, indicated by the asterisks in both developmental years and with aging (Bottom).

6.4.3 Detrended Fluctuation Analysis

The Detrended Fluctuation Analysis (DFA) results in children primarily indicate that the youngest and oldest children are significantly different from each other (Fig. 6.6, $F=8.26$, $p<0.005$). All the children younger than 6 had Hurst exponent values greater than 0.5, indicating they had a positive correlation processes or demonstrated persistence. The young adults had values for their Hurst exponent which are great than 0.5, which were significantly different from both the middle aged adults and older adults (Fig. 6.7 , $F=7.53$, $p<.001$).

These results can be understood only in the context of the associated changes in the lifespan, in particular with the improvement in the dexterity score during development and the decline in aging. During development the high Hurst exponent values and in particular the fact that all the children below the age of 6 had high values indicate they their diffusion was enhanced , i.e. the system was persistent. This is possibly due to delays in the sensorimotor pathways in this age (Fietzek et al. 2000). In the case of the young adults who performed the best among all in the lifespan, the high Hurst exponent values probably indicate the lack of constant feedback control, with the controller stepping in when needed. In the case of the older people who were performing poorly the higher Hurst exponent values probably indicate that the strategy they use depends on negative feedback control, i.e. they are constantly correcting presumably to be able to succeed at the task.

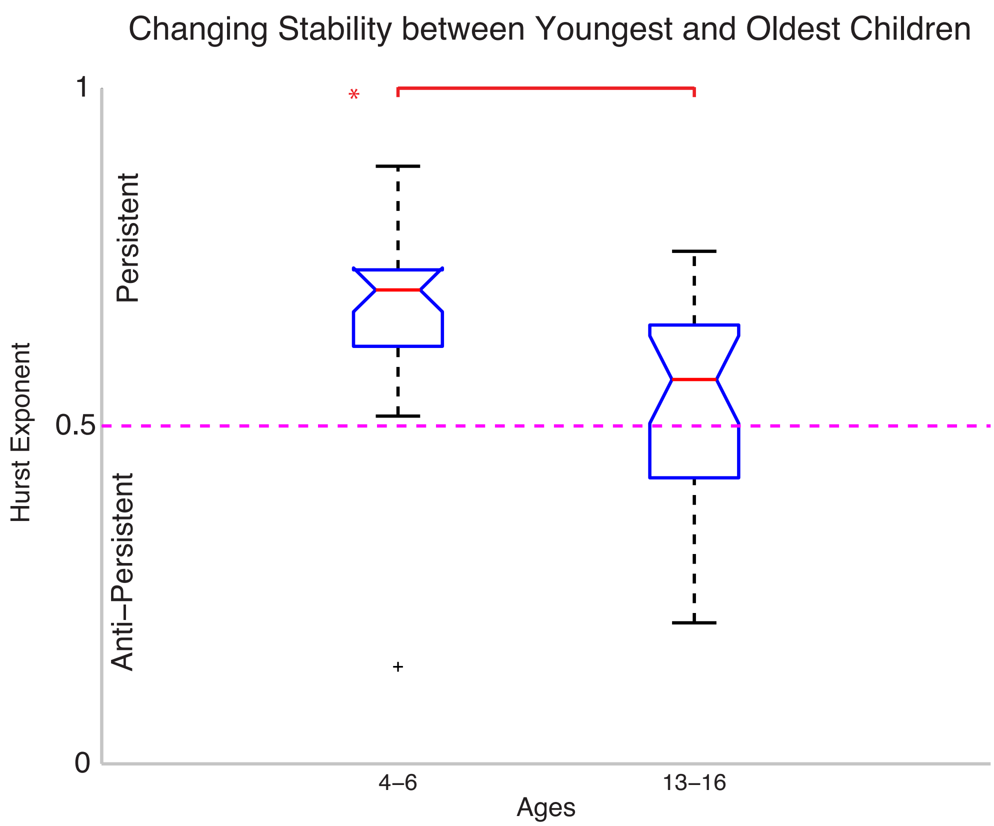

Figure 6.6: Differences in Hurst Exponent values between youngest (4-6 years of age, left) and oldest (13-16 years of age, right) children. Values higher than 0.5 indicate positive correlations are induced i.e. diffusion is enhanced while values less than 0.5 indicates diffusion is suppressed. Hurst exponent values of 0.5 indicate Brownian motion or a random walk, where all time steps are uncorrelated. Significance values are based on a one-way ANOVA ($p<0.005$).

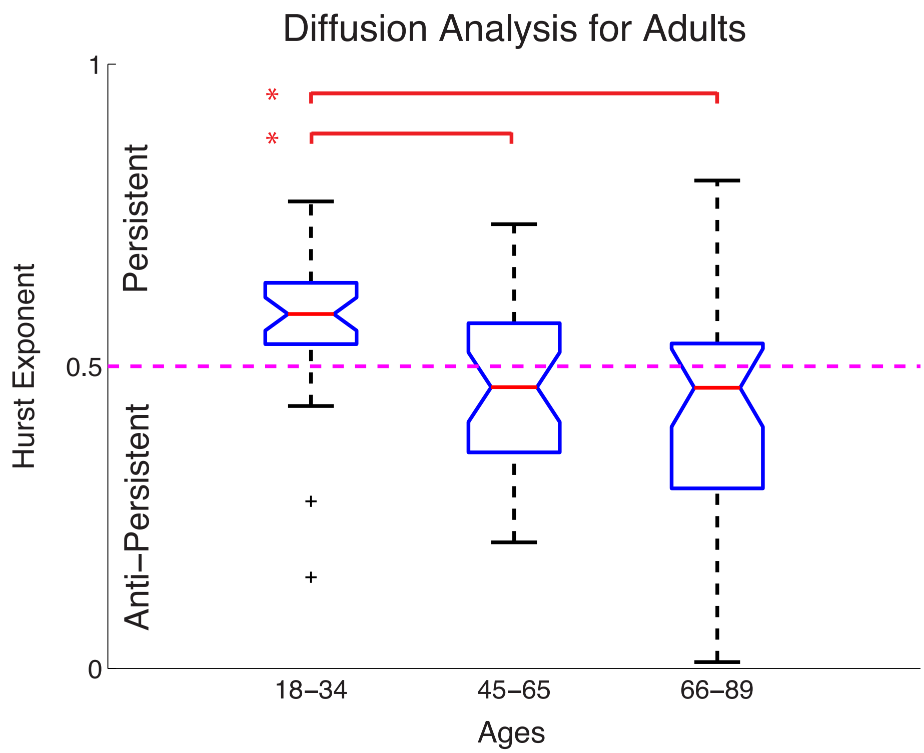

Figure 6.7: Differences in Hurst Exponent values between young adults (18-34 years of age, left), middle aged (45-65 years of age, middle) and older adults (66-89 years of age, right). Values higher than 0.5 indicate positive correlations are induced i.e. diffusion is enhanced while values less than 0.5 indicates diffusion is suppressed. Hurst exponent values of 0.5 indicate Brownian motion or a random walk, where all time steps are uncorrelated. Significance values are based on a one-way ANOVA (p<0.005).

6.5 Conclusions

For low force dexterous manipulation large improvements and gradual declines are seen across the lifespan in the ability to overcome and postpone instabilities as well as in the control of fingertip force direction.

6.6 Acknowledgments

We thank Kornelius Ràcz for his input and assistance with the time series analysis methods focusing on the DFA.

Chapter 7

Conclusions and Future Work

In spite of the low force (< 3N) required for the task developed for the study we are able to show substantial changes in dexterous manipulation capabilities in healthy humans across development and in aging. Importantly, we are able to show there is development of dexterity well into the adolescent years, much longer than previously understood. This appears to be relatively independent of strength and hand anthropometrics. Children in early adolescent years appear to have slower hand muscle twitch time-to-peak than young adults, demonstrated for the first time with noninvasive method of the EMG weighted average (EWA). In the case of the adults, the surprising finding was that adults seem to start to decline in their capabilities even at this low force from the middle age. Additionally we use some simple linear and nonlinear methods to show the change in the ability to control dexterous manipulation.

Our current work provides the foundation across the lifespan which needs to be elaborated and built upon. Much work is needed in the clinical domain, in particular in children with cerebral palsy in order to understand and promote the development of dexterity. The rehabilitation window, so to speak, appears to be wider than previously thought in children and both the timelines as well as the appropriate challenge levels for this needs to be elucidated. The hope for the future is that this work leads to innovative and novel methods of appropriate training at specific challenge levels for improvements in dexterity in clinical populations as well as in healthy aging.

Bibliography

Armand, J. (1982), *The Origin, Course and Terminations of Corticospinal Fibers in Various Mammals*, Vol. 57, Elsevier, pp. 329–360.

Armand, J., Edgley, S. A., Lemon, R. N. & Olivier, E. (1994), 'Protracted postnatal development of corticospinal projections from the primary motor cortex to hand motoneurones in the macaque monkey', *Exp Brain Res* **101**(1), 178–82.

Armand, J., Olivier, E., Edgley, S. A. & Lemon, R. N. (1997), 'Postnatal development of corticospinal projections from motor cortex to the cervical enlargement in the macaque monkey', *J. Neurosci.* **17**(1), 251–266.

Belanger, A. & McComas, A. (1989), 'Contractile properties of human skeletal muscle in childhood and adolescence', *European Journal of Applied Physiology and Occupational Physiology* **58**(6), 563–567.

Bell, R. D., Macdougall, J. D., Billeter, R. & Howald, H. (1980), 'Muscle-fiber types and morphometric analysis of skeletal-muscle in 6-year-old children', *Med Sci Sports Exerc* **12**(1), 28–31.

Bengtsson, S. L., Nagy, Z., Skare, S., Forsman, L., Forssberg, H. & Ullen, F. (2005), 'Extensive piano practicing has regionally specific effects on white matter development', *Nat Neurosci* **8**(9), 1148–1150.

Bernhard, C. & Bohm, M. (1954), 'Cortical representation and functional significance of the corticomotoneuronal system', *Archives of Neurology and Psychiatry* .

Bleyenheuft, Y., Wilmotte, P. & Thonnard, J.-L. (2010), 'Relationship between tactile spatial resolution and digital dexterity during childhood', *Somatosensory & Motor Research* **27**(1), 9–14.

Bohannon, R. W. & Smith, M. B. (1987), 'Interrater reliability of a modified ashworth scale of muscle spasticity', *Phys Ther* **67**(2), 206–207.

Bonnard, M., Gallèa, C., De Graaf, J. B. & Pailhous, J. (2007), 'Corticospinal control of the thumb-index grip depends on precision of force control: a transcranial magnetic stimulation and functional magnetic resonance imagery study in humans', *European Journal of Neuroscience* **25**(3), 872–880.

Bonnier, B., Eliasson, A. C. & Krumlinde-Sundholm, L. (2006), 'Effects of constraint-induced movement therapy in adolescents with hemiplegic cerebral palsy: a day camp model', *Scand J Occup Ther* **13**(1), 13–22.

Brody, I. A. (1976), 'Regulation of isometric contraction in skeletal muscle', *Experimental Neurology* **50**(3), 673–683.

Brown, W. F., Strong, M. J. & Snow, R. (1988), 'Methods for estimating numbers of motor units in biceps-brachialis muscles and losses of motor units with aging', *Muscle Nerve* **11**(5), 423–32.

Buchthal, F. & Schmalbruch, H. (1970), 'Contraction times and fibre types in intact human muscle', *Acta Physiologica Scandinavica* **79**(4), 435–452.

Burke, D. (2001), 'Clinical relevance of the putative c-3–4 propriospinal system in humans', *Muscle & Nerve* **24**(11), 1437–1439.

Burke, R. E. & Tsairis, P. (1974), 'The correlation of physiological properties with histochemical characteristics in single muscle units', *Annals of the New York Academy of Sciences* **228**(1), 145–158.

Carmeli, E., Patish, H. & Coleman, R. (2003), 'The aging hand', *J Gerontol A Biol Sci Med Sci* **58**(2), M146–152.

Carr, L. J., Harrison, L. M., Evans, A. L. & Stephens, J. A. (1993), 'Patterns of central motor reorganization in hemiplegic cerebral palsy', *Brain* **116**(5), 1223–1247.

Close, J., Ellis, M., Hooper, R., Glucksman, E., Jackson, S. & Swift, C. (1999), 'Prevention of falls in the elderly trial (profet): a randomised controlled trial', *The Lancet* **353**(9147), 93–97.

Close, R. (1964), 'Dynamic properties of fast and slow skeletal muscles of the rat during development', *The Journal of Physiology* **173**(1), 74–95.

Cole, K. J. (2006), 'Age-related directional bias of fingertip force', *Exp Brain Res* **175**(2), 285–91.

Cole, K. J., Rotella, D. L. & Harper, J. G. (1998), 'Tactile impairments cannot explain the effect of age on a grasp and lift task', *Experimental Brain Research* **121**(3), 263–269.

Cole, K. J., Rotella, D. L. & Harper, J. G. (1999), 'Mechanisms for age-related changes of fingertip forces during precision gripping and lifting in adults', *The Journal of Neuroscience* **19**(8), 3238–3247.

Collins, J. J. & De Luca, C. J. (1993), 'Open-loop and closed-loop control of posture: a random-walk analysis of center-of-pressure trajectories', *Exp Brain Res* **95**(2), 308–18.

Collins, J. J. & De Luca, C. J. (1994), 'Random walking during quiet standing', *Phys Rev Lett* **73**(5), 764–767.

Collins, J. J. & De Luca, C. J. (1995), 'Upright, correlated random walks: A statistical-biomechanics approach to the human postural control system', *Chaos* **5**(1), 57–63.

Courtine, G., Bunge, M. B., Fawcett, J. W., Grossman, R. G., Kaas, J. H., Lemon, R., Maier, I., Martin, J., Nudo, R. J., Ramon-Cueto, A., Rouiller, E. M., Schnell, L., Wannier, T., Schwab, M. E. & Edgerton, V. R. (2007), 'Can experiments in nonhuman primates expedite the translation of treatments for spinal cord injury in humans?', *Nat Med* **13**(5), 561–566.

Davare, M., Andres, M., Cosnard, G., Thonnard, J. L. & Olivier, E. (2006), 'Dissociating the role of ventral and dorsal premotor cortex in precision grasping', *J Neurosci* **26**(8), 2260–8.

Davids, J. R., Peace, L. C., Wagner, L. V., Gidewall, M. A., Blackhurst, D. W. & Roberson, W. M. (2006), 'Validation of the shriners hospital for children upper extremity evaluation (shuee) for children with hemiplegic cerebral palsy', *J Bone Joint Surg Am* **88**(2), 326–333.

Davies, C., White, M. & Young, K. (1983), 'Muscle function in children', *European Journal of Applied Physiology and Occupational Physiology* **52**(1), 111–114.

Davis Sears, E. & Chung, K. C. (2010), 'Validity and responsiveness of the jebsen-taylor hand function test', *The Journal of Hand Surgery* **35**(1), 30–37.

Dayanidhi, S., Hedberg, Å., Hägg, I., Lilja, N., Forssberg, H. & Valero-Cuevas, F. (2011), Dynamic control of fingertip forces: Development in childhood and decline with aging, *in* 'Proceedings of the 35th Annual Meeting of the American Society of Biomechanics'.

DeMatteo, C., Law, M., Russell, D., Pollock, N., Rosenbaum, P. & Walter, S. (1993), 'The reliability and validity of the quality of upper extremity skills test', *Physical & Occupational Therapy in Pediatrics* **13**(2), 1–18.

Desrosiers, J., Hbert, R., Bravo, G. & Rochette, A. (1999), 'Age-related changes in upper extremity performance of elderly people: a longitudinal study', *Experimental Gerontology* **34**(3), 393–405.

Deutsch, K. M. & Newell, K. M. (2001), 'Age differences in noise and variability of isometric force production', *J Exp Child Psychol* **80**(4), 392–408.

Deutsch, K. M. & Newell, K. M. (2002), 'Children's coordination of force output in a pinch grip task', *Dev Psychobiol* **41**(3), 253–64.

Dorfman, L. J. & Bosley, T. M. (1979), 'Age?related changes in peripheral and central nerve conduction in man', *Neurology* **29**(1), 38.

Dum, R. P. & Strick, P. L. (2002), 'Motor areas in the frontal lobe of the primate', *Physiology and Behavior* **77**(4-5), 677–682.

Dum, R. & Strick, P. (1991), 'The origin of corticospinal projections from the premotor areas in the frontal lobe', *The Journal of Neuroscience* **11**(3), 667–689.

Duque, J., Thonnard, J.-L., Vandermeeren, Y., Sebire, G., Cosnard, G. & Olivier, E. (2003), 'Correlation between impaired dexterity and corticospinal tract dysgenesis in congenital hemiplegia', *Brain* **126**(3), 732–747.

Edin, B. B., Westling, G. & Johansson, R. S. (1992), 'Independent control of human finger-tip forces at individual digits during precision lifting', *J Physiol* **450**, 547–64.

Ehrsson, H. H., Fagergren, A., Jonsson, T., Westling, G., Johansson, R. S. & Forssberg, H. (2000), 'Cortical activity in precision- versus power-grip tasks: an fmri study', *J Neurophysiol* **83**(1), 528–36.

Ehrsson, H. H., Fagergren, E. & Forssberg, H. (2001), 'Differential fronto-parietal activation depending on force used in a precision grip task: an fmri study', *J Neurophysiol* **85**(6), 2613–23.

Elder, G. C. & Kakulas, B. A. (1993), 'Histochemical and contractile property changes during human muscle development', *Muscle Nerve* **16**(11), 1246–53.

Eliasson, A. C., Forssberg, H., Hung, Y. C. & Gordon, A. M. (2006), 'Development of hand function and precision grip control in individuals with cerebral palsy: a 13-year follow-up study', *Pediatrics* **118**(4), e1226–36.

Eliasson, A. C., Forssberg, H., Ikuta, K., Apel, I., Westling, G. & Johansson, R. (1995), 'Development of human precision grip. v. anticipatory and triggered grip actions during sudden loading', *Exp Brain Res* **106**(3), 425–33.

Eliasson, A. C., Gordon, A. M. & Forssberg, H. (1991), 'Basic co-ordination of manipulative forces of children with cerebral palsy', *Dev Med Child Neurol* **33**(8), 661–70.

Eliasson, A. C., Gordon, A. M. & Forssberg, H. (1992), 'Impaired anticipatory control of isometric forces during grasping by children with cerebral palsy', *Dev Med Child Neurol* **34**(3), 216–25.

Eliasson, A. C., Gordon, A. M. & Forssberg, H. (1995), 'Tactile control of isometric fingertip forces during grasping in children with cerebral palsy', *Dev Med Child Neurol* **37**(1), 72–84.

Enoka, R. M., Christou, E. A., Hunter, S. K., Kornatz, K. W., Semmler, J. G., Taylor, A. M. & Tracy, B. L. (2003), 'Mechanisms that contribute to differences in motor performance between young and old adults', *Journal of Electromyography and Kinesiology* **13**(1), 1–12.

Eyre, J. A. (2007), 'Corticospinal tract development and its plasticity after perinatal injury', *Neurosci Biobehav Rev* **31**(8), 1136–49.

Eyre, J. A., Taylor, J. P., Villagra, F., Smith, M. & Miller, S. (2001), 'Evidence of activity-dependent withdrawal of corticospinal projections during human development', *Neurology* **57**(9), 1543–54.

Fietzek, U. M., Heinen, F., Berweck, S., Maute, S., Hufschmidt, A., Schulte-Monting, J., Lucking, C. H. & Korinthenberg, R. (2000), 'Development of the corticospinal system and hand motor function: central conduction times and motor performance tests', *Dev Med Child Neurol* **42**(4), 220–7.

Fleuren, J. F. M., Voerman, G. E., Erren-Wolters, C. V., Snoek, G. J., Rietman, J. S., Hermens, H. J. & Nene, A. V. (2010), 'Stop using the ashworth scale for the assessment of spasticity', *Journal of Neurology, Neurosurgery & Psychiatry* **81**(1), 46–52.

Forssberg, H., Eliasson, A. C., Kinoshita, H., Johansson, R. S. & Westling, G. (1991), 'Development of human precision grip. i: Basic coordination of force', *Exp Brain Res* **85**(2), 451–7.

Forssberg, H., Eliasson, A. C., Kinoshita, H., Westling, G. & Johansson, R. S. (1995), 'Development of human precision grip. iv. tactile adaptation of isometric finger forces to the frictional condition', *Exp Brain Res* **104**(2), 323–30.

Forssberg, H., Eliasson, A. C., Redon-Zouitenn, C., Mercuri, E. & Dubowitz, L. (1999), 'Impaired grip-lift synergy in children with unilateral brain lesions', *Brain* **122 (Pt 6)**, 1157–68.

Forssberg, H., Kinoshita, H., Eliasson, A. C., Johansson, R. S., Westling, G. & Gordon, A. M. (1992), 'Development of human precision grip. ii. anticipatory control of isometric forces targeted for object's weight', *Exp Brain Res* **90**(2), 393–8.

Friel, K. M. & Martin, J. H. (2007), 'Bilateral activity-dependent interactions in the developing corticospinal system', *J Neurosci* **27**(41), 11083–90.

Fugl-Meyer, A. R., Jaasko, L., Leyman, I., Olsson, S. & Steglind, S. (1975), 'The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance', *Scand J Rehabil Med* **7**(1), 13–31.

Fuglevand, A. J. (2011), 'Mechanical properties and neural control of human hand motor units', *The Journal of Physiology* **589**(23), 5595–5602.

Gajdosik, R. L. & Bohannon, R. W. (1987), 'Clinical measurement of range of motion. review of goniometry emphasizing reliability and validity', *Phys Ther* **67**(12), 1867–72.

Galganski, M. E., Fuglevand, A. J. & Enoka, R. M. (1993), 'Reduced control of motor output in a human hand muscle of elderly subjects during submaximal contractions', *Journal of Neurophysiology* **69**(6), 2108–2115.

Gallèa, C., de Graaf, J. B., Bonnard, M. & Pailhous, J. (2005), 'High level of dexterity: differential contributions of frontal and parietal areas', *Neuroreport* **16**(12), 1271–1274.

Gallus, J. & Mathiowetz, V. (2003), 'Test-retest reliability of the purdue pegboard for persons with multiple sclerosis', *Am J Occup Ther* **57**(1), 108–11.

Gilmore, R., Sakzewski, L. & Boyd, R. (2009), 'Upper limb activity measures for 5- to 16-year-old children with congenital hemiplegia: a systematic review', *Developmental Medicine & Child Neurology* **52**(1), 14–21.

Glenmark, B., Hedberg, G., Kaijser, L. & Jansson, E. (1994), 'Muscle strength from aldolescence to adulthood relationship to muscle fibre types', *European Journal of Applied Physiology and Occupational Physiology* **68**(1), 9–19.

Gordon, A. M., Forssberg, H., Johansson, R. S., Eliasson, A. C. & Westling, G. (1992), 'Development of human precision grip. iii. integration of visual size cues during the programming of isometric forces', *Exp Brain Res* **90**(2), 399–403.

Gordon, A. M., Schneider, J. A., Chinnan, A. & Charles, J. R. (2007), 'Efficacy of a hand-arm bimanual intensive therapy (habit) in children with hemiplegic cerebral palsy: a randomized control trial', *Dev Med Child Neurol* **49**(11), 830–8.

Greaves, S., Imms, C., Dodd, K. & Krumlinde-Sundholm, L. (2010), 'Assessing bimanual performance in young children with hemiplegic cerebral palsy: a systematic review', *Developmental Medicine & Child Neurology* **52**(5), 413–421.

Häger-Ross, C. & Rösblad, B. (2002), 'Norms for grip strength in children aged 4–16 years', *Acta Pædiatrica* **91**(6), 617–625.

Häger-Ross, C. & Schieber, M. H. (2000), 'Quantifying the independence of human finger movements: Comparisons of digits, hands, and movement frequencies', *J. Neurosci.* **20**(22), 8542–8550.

Heffner, R. S. & Masterton, R. B. (1983), 'The role of the corticospinal tract in the evolution of human digital dexterity', *Brain, Behavior and Evolution* **23**(3-4), 165–183.

Hirtz, D., Thurman, D. J., Gwinn-Hardy, K., Mohamed, M., Chaudhuri, A. R. & Zalutsky, R. (2007), 'How common are the "common" neurologic disorders?', *Neurology* **68**(5), 326–37.

Holmefur, M., Krumlinde-Sundholm, L. & Eliasson, A. C. (2007), 'Interrater and intrarater reliability of the assisting hand assessment', *Am J Occup Ther* **61**(1), 79–84.

Holmström, L., Lennartsson, F., Eliasson, A. C., Flodmark, O., Clark, C., Tedroff, K., Forssberg, H. & Vollmer, B. (2011), 'Diffusion mri in corticofugal fibers correlates with hand function in unilateral cerebral palsy', *Neurology* **77**(8), 775–83.

Holmström, L., Vollmer, B., Tedroff, K., Islam, M., Persson, J. K., Kits, A., Forssberg, H. & Eliasson, A. C. (2010), 'Hand function in relation to brain lesions and corticomotor-projection pattern in children with unilateral cerebral palsy', *Dev Med Child Neurol* **52**(2), 145–52.

House, J. H., Gwathmey, F. W. & Fidler, M. O. (1981), 'A dynamic approach to the thumb-in palm deformity in cerebral palsy', *J Bone Joint Surg Am* **63**(2), 216–25.

Jebsen, R. H., Taylor, N., Trieschmann, R. B., Trotter, M. J. & Howard, L. A. (1969), 'An objective and standardized test of hand function', *Arch Phys Med Rehabil* **50**(6), 311–9.

Jesunathadas, M., Marmon, A. R., Gibb, J. M. & Enoka, R. M. (2010), 'Recruitment and derecruitment characteristics of motor units in a hand muscle of young and old adults', *Journal of Applied Physiology* **108**(6), 1659–1667.

Jette, A. M. (2006), 'Toward a common language for function, disability, and health', *PHYS THER* **86**(5), 726–734.

Johansson, R. S. & Flanagan, J. R. (2009), 'Coding and use of tactile signals from the fingertips in object manipulation tasks', *Nat Rev Neurosci* **10**(5), 345–59.

Johansson, R. S. & Westling, G. (1984), 'Roles of glabrous skin receptors and sensorimotor memory in automatic control of precision grip when lifting rougher or more slippery objects', *Exp Brain Res* **56**(3), 550–64.

Johansson, R. S. & Westling, G. (1988), 'Coordinated isometric muscle commands adequately and erroneously programmed for the weight during lifting task with precision grip', *Experimental Brain Research* **71**(1), 59–71.

Johnson, L. M., Randall, M. J., Reddihough, D. S., Oke, L. E., Byrt, T. A. & Bach, T. M. (1994), 'Development of a clinical assessment of quality of movement for unilateral upper-limb function', *Dev Med Child Neurol* **36**(11), 965–73.

Kantz, H. & Schreiber, T. (2004), *Nonlinear Time Series Analysis*, Cambridge.

Kellor, M., Frost, J., Silberberg, N., Iversen, I. & Cummings, R. (1971), 'Hand strength and dexterity', *Am J Occup Ther* **25**(2), 77–83.

Kraemer, W. J., Fry, A. C., Frykman, P. N., Conroy, B. & Hoffman, J. (1989), 'Resistance training and youth', *Pediatric Exercise Science* **1**(4), 336–350.

Krumlinde-Sundholm, L., Holmefur, M., Kottorp, A. & Eliasson, A. C. (2007), 'The assisting hand assessment: current evidence of validity, reliability, and responsiveness to change', *Dev Med Child Neurol* **49**(4), 259–64.

Kuhtz-Buschbeck, J. P., Ehrsson, H. H. & Forssberg, H. (2001), 'Human brain activity in the control of fine static precision grip forces: an fmri study', *Eur J Neurosci* **14**(2), 382–90.

Kuhtz-Buschbeck, J. P., Sundholm, L. K., Eliasson, A. C. & Forssberg, H. (2000), 'Quantitative assessment of mirror movements in children and adolescents with hemiplegic cerebral palsy', *Dev Med Child Neurol* **42**(11), 728–36.

Kurse, M. U., Lipson, H. & Valero-Cuevas, F. J. (2012), 'Extrapolatable analytical functions for tendon excursions and moment arms from sparse datasets', *IEEE Trans Biomed Eng* **59**(6), 1572–82.

Kutch, J. J., Kuo, A. D. & Rymer, W. Z. (2010), 'Extraction of individual muscle mechanical action from endpoint force', *Journal of Neurophysiology* **103**(6), 3535–3546.

Kuypers, H. G. (1960), 'Central cortical projections to motor and somato-sensory cell groups. an experimental study in the rhesus monkey', *Brain* **83**, 161–84.

Kuypers, H. G. (1962), 'Corticospinal connections: postnatal development in the rhesus monkey', *Science* **138**, 678–80.

Kuypers, H. G., Fleming, W. R. & Farinholt, J. W. (1960), 'Descending projections to spinal motor and sensory cell groups in the monkey: cortex versus subcortex', *Science* **132**, 38–40.

Kuypers, H. G. J. M. (1964), *The Descending Pathways to the Spinal Cord, their Anatomy and Function*, Vol. Volume 11, Elsevier, pp. 178–202. doi: DOI: 10.1016/S0079-6123(08)64048-0.

Lawrence, D. G. & Kuypers, H. G. (1968a), 'The functional organization of the motor system in the monkey. i. the effects of bilateral pyramidal lesions', *Brain* **91**(1), 1–14.

Lawrence, D. G. & Kuypers, H. G. (1968b), 'The functional organization of the motor system in the monkey. ii. the effects of lesions of the descending brain-stem pathways', *Brain* **91**(1), 15–36.

Lebel, C. & Beaulieu, C. (2011), 'Longitudinal development of human brain wiring continues from childhood into adulthood', *The Journal of Neuroscience* **31**(30), 10937–10947.

Lebel, C., Walker, L., Leemans, A., Phillips, L. & Beaulieu, C. (2008), 'Microstructural maturation of the human brain from childhood to adulthood', *Neuroimage* **40**(3), 1044–55.

Lemon, R. N. (1993), 'The g. l. brown prize lecture. cortical control of the primate hand', *Exp Physiol* **78**(3), 263–301.

Lemon, R. N. (1999), 'Neural control of dexterity: what has been achieved?', *Exp Brain Res* **128**(1-2), 6–12.

Lemon, R. N. (2008), 'Descending pathways in motor control', *Annu Rev Neurosci* **31**, 195–218.

Lemon, R. N. & Griffiths, J. (2005), 'Comparing the function of the corticospinal system in different species: organizational differences for motor specialization?', *Muscle Nerve* **32**(3), 261–79.

Lexell, J. & Downham, D. (1992), 'What is the effect of ageing on type 2 muscle fibres?', *Journal of the Neurological Sciences* **107**(2), 250–251.

Lexell, J., Henriksson-Larsén, K., Winblad, B. & Sjöström, M. (1983), 'Distribution of different fiber types in human skeletal muscles: Effects of aging studied in whole muscle cross sections', *Muscle & Nerve* **6**(8), 588–595.

Lexell, J., Taylor, C. C. & Sjöström, M. (1988), 'What is the cause of the ageing atrophy?: Total number, size and proportion of different fiber types studied in whole vastus lateralis muscle from 15- to 83-year-old men', *Journal of the Neurological Sciences* **84**(2–3), 275–294.

Lindberg, P., Ody, C., Feydy, A. & Maier, M. (2009), 'Precision in isometric precision grip force is reduced in middle-aged adults', *Experimental Brain Research* **193**(2), 213–224.

Lowe, B. D. (2001), 'Precision grip force control of older and younger adults, revisited', *Journal of Occupational Rehabilitation* **11**(4), 267–279.

Marmon, A. R., Gould, J. R. & Enoka, R. M. (2011), 'Practicing a functional task improves steadiness with hand muscles in older adults', *Medicine & Science in Sports & Exercise* **43**(8), 1531–1537 10.1249/MSS.0b013e3182100439.

Marmon, A. R., Pascoe, M. A., Schwartz, R. S. & Enoka, R. M. (2011), 'Associations among strength, steadiness, and hand function across the adult life span', *Medicine & Science in Sports & Exercise* **43**(4), 560–567 10.1249/MSS.0b013e3181f3f3ab.

Martin, J. H. (2005), 'The corticospinal system: from development to motor control', *Neuroscientist* **11**(2), 161–73.

Martin, J. H., Donarummo, L. & Hacking, A. (2000), 'Impairments in prehension produced by early postnatal sensory motor cortex activity blockade', *J Neurophysiol* **83**(2), 895–906.

Martin, J. H., Friel, K. M., Salimi, I. & Chakrabarty, S. (2007), 'Activity- and use-dependent plasticity of the developing corticospinal system', *Neurosci Biobehav Rev* **31**(8), 1125–35.

Martin, J. H. & Lee, S. J. (1999), 'Activity-dependent competition between developing corticospinal terminations', *Neuroreport* **10**(11), 2277–82.

Martin, R. J. F., Dore, E., Twisk, J., Van praagh, E., Hautier, C. A. & Bedu, M. (2004), 'Longitudinal changes of maximal short-term peak power in girls and boys during growth', *Medicine & Science in Sports & Exercise* **36**(3), 498–503.

Matano, S. & Hirasaki, E. (1997), 'Volumetric comparisons in the cerebellar complex of anthropoids, with special reference to locomotor types', *Am J Phys Anthropol* **103**(2), 173–83.

Mathiowetz, V., Volland, G., Kashman, N. & Weber, K. (1985), 'Adult norms for the box and block test of manual dexterity', *Am J Occup Ther* **39**(6), 386–91.

Mathiowetz, V., Weber, K., Volland, G. & Kashman, N. (1984), 'Reliability and validity of grip and pinch strength evaluations', *J Hand Surg Am* **9**(2), 222–6.

Mathiowetz, V., Wiemer, D. M. & Federman, S. M. (1986), 'Grip and pinch strength: norms for 6- to 19-year-olds', *Am J Occup Ther* **40**(10), 705–11.

McComas, A. J., Sica, R. E. P. & Petito, F. (1973), 'Muscle strength in boys of different ages', *Journal of Neurology, Neurosurgery & Psychiatry* **36**(2), 171–173.

Milner-Brown, H. S., Stein, R. B. & Yemm, R. (1973*a*), 'Changes in firing rate of human motor units during linearly changing voluntary contractions', *The Journal of Physiology* **230**(2), 371–390.

Milner-Brown, H. S., Stein, R. B. & Yemm, R. (1973*b*), 'The contractile properties of human motor units during voluntary isometric contractions', *The Journal of Physiology* **228**(2), 285–306.

Milner-Brown, H. S., Stein, R. B. & Yemm, R. (1973*c*), 'The orderly recruitment of human motor units during voluntary isometric contractions', *The Journal of Physiology* **230**(2), 359–370.

Mosier, K. M., Lau, C., Wang, Y., Venkadesan, M. & Valero-Cuevas, F. J. (2011), 'Controlling instabilities in manipulation requires specific cortical-striatal-cerebellar networks', *Journal of Neurophysiology* **(In Press)**.

Muir, R. B. & Lemon, R. N. (1983), 'Corticospinal neurons with a special role in precision grip', *Brain Research* **261**(2), 312–316.

Muller, K., Homberg, V. & Lenard, H. G. (1991), 'Magnetic stimulation of motor cortex and nerve roots in children. maturation of cortico-motoneuronal projections', *Electroencephalogr Clin Neurophysiol* **81**(1), 63–70.

Nagi, S. Z. (1964), 'A study in the evaluation of disability and rehabilitation potential: Concepts, methods, and procedures', *Am J Public Health Nations Health* **54**(9), 1568–1579.

Nakajima, K., Maier, M. A., Kirkwood, P. A. & Lemon, R. N. (2000), 'Striking differences in transmission of corticospinal excitation to upper limb motoneurons in two primate species', *J Neurophysiol* **84**(2), 698–709.

Nathan, P. W. & Smith, M. C. (1982), 'The rubrospinal and central tegmental tracts in man', *Brain* **105**(Pt 2), 223–69.

Newell, K. M., Liu, Y. T. & Mayer-Kress, G. (2001), 'Time scales in motor learning and development', *Psychol Rev* **108**(1), 57–82.

Nudo, R. J. & Masterton, R. B. (1990), 'Descending pathways to the spinal cord, iii: Sites of origin of the corticospinal tract', *The Journal of Comparative Neurology* **296**(4), 559–583.

O'Brien, T. D., Reeves, N. D., Baltzopoulos, V., Jones, D. A. & Maganaris, C. N. (2010), 'In vivo measurements of muscle specific tension in adults and children', *Experimental Physiology* **95**(1), 202–210.

Oxford Grice, K., Vogel, K. A., Le, V., Mitchell, A., Muniz, S. & Vollmer, M. A. (2003), 'Adult norms for a commercially available nine hole peg test for finger dexterity', *Am J Occup Ther* **57**(5), 570–3.

Parikh, P. J. & Cole, K. J. (2012), 'Handling objects in old age: forces and moments acting on the object', *Journal of Applied Physiology* **112**(7), 1095–1104.

Paus, T., Zijdenbos, A., Worsley, K., Collins, D. L., Blumenthal, J., Giedd, J. N., Rapoport, J. L. & Evans, A. C. (1999), 'Structural maturation of neural pathways in children and adolescents: in vivo study', *Science* **283**(5409), 1908–11.

Peng, C.-K., Havlin, S., Stanley, H. E. & Goldberger, A. L. (1995), 'Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series', *Chaos: An Interdisciplinary Journal of Nonlinear Science* **5**(1), 82–87.

Pharoah, P. O., Platt, M. J. & Cooke, T. (1996), 'The changing epidemiology of cerebral palsy', *Arch Dis Child Fetal Neonatal Ed* **75**(3), F169–73.

Pieperhoff, P., Hömke, L., Schneider, F., Habel, U., Shah, N. J., Zilles, K. & Amunts, K. (2008), 'Deformation field morphometry reveals age-related structural differences between the brains of adults up to 51 years', *The Journal of Neuroscience* **28**(4), 828–842.

Pierrot-Deseilligny, E. (2002), 'Propriospinal transmission of part of the corticospinal excitation in humans', *Muscle & Nerve* **26**(2), 155–172.

Platz, T., Pinkowski, C., van Wijck, F., Kim, I. H., di Bella, P. & Johnson, G. (2005), 'Reliability and validity of arm function assessment with standardized guidelines for the fugl-meyer test, action research arm test and box and block test: a multicentre study', *Clin Rehabil* **19**(4), 404–11.

Plautz, E. J., Milliken, G. W. & Nudo, R. J. (2000), 'Effects of repetitive motor training on movement representations in adult squirrel monkeys: role of use versus learning', *Neurobiol Learn Mem* **74**(1), 27–55.

Poole, J. L., Burtner, P. A., Torres, T. A., McMullen, C. K., Markham, A., Marcum, M. L., Anderson, J. B. & Qualls, C. (2005), 'Measuring dexterity in children using the nine-hole peg test', *Journal of Hand Therapy* **18**(3), 348–351.

Porter, R. (1985), 'The corticomotoneuronal component of the pyramidal tract: Corticomotoneuronal connections and functions in primates', *Brain Research Reviews* **10**(1), 1–26.

Randall, M., Carlin, J. B., Chondros, P. & Reddihough, D. (2001), 'Reliability of the melbourne assessment of unilateral upper limb function', *Dev Med Child Neurol* **43**(11), 761–7.

Ranganathan, V. K., Siemionow, V., Sahgal, V. & Yue, G. H. (2001), 'Effects of aging on hand function', *Journal of the American Geriatrics Society* **49**(11), 1478–1484.

Rathelot, J. A. & Strick, P. L. (2006), 'Muscle representation in the macaque motor cortex: an anatomical perspective', *Proc Natl Acad Sci U S A* **103**(21), 8257–62.

Rose, J. & McGill, K. C. (2005), 'Neuromuscular activation and motor-unit firing characteristics in cerebral palsy', *Developmental Medicine & Child Neurology* **47**(5), 329–336.

Sakzewski, L., Boyd, R. & Ziviani, J. (2007), 'Clinimetric properties of participation measures for 5- to 13-year-old children with cerebral palsy: a systematic review', *Developmental Medicine & Child Neurology* **49**(3), 232–240.

Schieber, M. H. & Santello, M. (2004), 'Hand function: peripheral and central constraints on performance', *J Appl Physiol* **96**(6), 2293–2300.

Schmidt, M. & Lipson, H. (2009), 'Distilling free-form natural laws from experimental data', *Science* **324**(5923), 81–85.

Smith, Y. A., Hong, E. & Presson, C. (2000), 'Normative and validation studies of the nine-hole peg test with children', *Percept Mot Skills* **90**(3 Pt 1), 823–43.

Steenbergen, B. & Utley, A. (2005), 'Cerebral palsy: recent insights into movement deviation', *Motor Control* **9**(4), 353–6.

Stein, R. B., French, A. S., Mannard, A. & Yemm, R. (1972), 'New methods for analysing motor function in man and animals', *Brain Research* **40**(1), 187–192.

Stephens, J. A. & Usherwood, T. P. (1977), 'The mechanical properties of human motor units with special reference to their fatiguability and recruitment threshold', *Brain Research* **125**(1), 91–97.

Stucki, G., Ewert, T. & Cieza, A. (2002), 'Value and application of the icf in rehabilitation medicine', *Disability & Rehabilitation* **24**(17), 932–938.

Sutherland, D. (1997), 'The development of mature gait', *Gait & Posture* **6**(2), 163–170.

Talati, A., Valero-Cuevas, F. J. & Hirsch, J. (2005), 'Visual and tactile guidance of dexterous manipulation tasks: an fmri study', *Percept Mot Skills* **101**(1), 317–34.

Taylor, N., Sand, P. L. & Jebsen, R. H. (1973), 'Evaluation of hand function in children', *Arch Phys Med Rehabil* **54**(3), 129–35.

Thomas, C. K., Bigland-Richie, B. & Johansson, R. S. (1991), 'Force-frequency relationships of human thenar motor units', *J Neurophysiol* **65**(6), 1509–16.

Thomas, C. K., Ross, B. H. & Stein, R. B. (1986), 'Motor-unit recruitment in human first dorsal interosseous muscle for static contractions in three different directions', *Journal of Neurophysiology* **55**(5), 1017–1029.

Tiffin, J. & Asher, E. J. (1948), 'The purdue pegboard; norms and studies of reliability and validity', *J Appl Psychol* **32**(3), 234–47.

Valero-Cuevas, F. J., Smaby, N., Venkadesan, M., Peterson, M. & Wright, T. (2003), 'The strength-dexterity test as a measure of dynamic pinch performance', *J Biomech* **36**(2), 265–70.

van de Ven-Stevens, L. A., Munneke, M., Terwee, C. B., Spauwen, P. H. & van der Linde, H. (2009), 'Clinimetric properties of instruments to assess activities in patients with hand injury: a systematic review of the literature', *Arch Phys Med Rehabil* **90**(1), 151–69.

Vandermeeren, Y., Sebire, G., Grandin, C. B., Thonnard, J. L., Schlogel, X. & De Volder, A. G. (2003), 'Functional reorganization of brain in children affected with congenital hemiplegia: fmri study', *Neuroimage* **20**(1), 289–301.

Venkadesan, M., Guckenheimer, J. & Valero-Cuevas, F. J. (2007), 'Manipulating the edge of instability', *J Biomech* **40**(8), 1653–61.

Vollmer, B., Holmström, L., Forsman, L., Krumlinde-Sundholm, L., Valero-Cuevas, F. J., Forssberg, H. & Ullén, F. (2010), 'Evidence of validity in a new method for measurement of dexterity in children and adolescents', *Developmental Medicine & Child Neurology* **52**(10), 948–954.

Westling, G. & Johansson, R. S. (1984), 'Factors influencing the force control during precision grip', *Exp Brain Res* **53**(2), 277–84.

Wolpert, D. M., Diedrichsen, J. & Flanagan, J. R. (2011), 'Principles of sensorimotor learning', *Nat Rev Neurosci* **12**(12), 739–751.

Wolpert, D. M., Miall, R. C. & Kawato, M. (1998), 'Internal models in the cerebellum', *Trends in Cognitive Sciences* **2**(9), 338–347.