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ABSTRACT

It is known that disorders of the cerebellum have the potential to affect coordination of movements. The purpose of this thesis is to examine changes in motor coordination in individuals with olivopontocerebellar atrophy (OPCA) during multi-finger force production tasks. In particular, maximum forces, multi-finger synergy (the ability to show error compensation among finger forces), and enslaving (index of finger independency) were examined in three multi-finger pressing tasks.

Seven OPCA subjects and seven age and gender matched control subjects participated in this study. Task 1 required maximum voluntary contraction (MVC) of all fingers simultaneously. Task 2 required a single finger (task-finger) to produce a linearly increasing amount of force while non-task finger forces were measured to quantify finger force enslaving (E). Task 3 required production of a constant level of total force by four fingers followed by production of a force pulse in order to examine properties of synergy (steady-state value ($\Delta V_{Z,SS}$), change prior to impulse ($\Delta\Delta V_Z$), time of change initiation prior to impulse (t_{ASA})) amongst the fingers. .

In OPCA subjects, higher non-task finger force production (enslaving) and lower maximal finger forces were observed as compared to the control subjects. The OPCA data is in conflict with several previous studies where MVC and enslaving were found to be proportional. Additionally, $\Delta V_{Z,SS}$, $\Delta\Delta V_Z$, and t_{ASA} all decreased in OPCA patients relative to control subjects. Future studies must gather more data from the OPCA patients to further characterize gender effects, develop a disease progression model of OPCA, and understand the altered MVC-enslaving relationship.

Table of Contents

List of Figures

List of Tables

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Chapter 1: An Introduction to Motor Control and the Brain

Olivopontocerebellar atrophy (OPCA) is a neurologic, degenerative condition known to affect the cerebellum. Several previously developed force production tasks were tested on OPCA patients to clarify some of the involuntary motor control difficulties that arise as a result of this diseased state. Because the cerebellum plays a large role in movement regulation and production, its structures and functions will be discussed further to better understand potential ramifications of OPCA on movements. Following the discussion of OPCA, motor control history and several current studies will be introduced to provide context for the work presented. The purpose of the thesis is to determine what, if any, changes in motor control are elicited by OPCA.

1.1 The Cerebellum

The cerebellum is a structure of the brain located on the inferior and posterior portion of the brain. It is slightly superior to the spinal cord.

1.1.1 Structures of the Cerebellum

The cerebellum is made up of four nuclei.[1] Each nucleus, fastigial, globose, emboliform, and dentate, has gamma aminobutyric acid (GABA) receptors. GABA is a neurotransmitter involved in many neurophysiological processes. The fastigial nucleus is an efferent nucleus located near the apex of the fourth ventricle but may not be directly affected by OPCA, as it does not connect to the olives or the pons. The globose and emboliform nuclei receive signals from medial and dorsal accessory olivary nuclei as part

of a web of afferent neurons entering the cerebellum. The dentate nucleus is the main efferent nucleus of the cerebellum projecting on cortical structures.

1.1.2 Functions of the Cerebellum

The dentate nucleus of the cerebellum contains GABA receptors that receive input from the pons (pontine nuclei) and the inferior olive (olivary nuclei).[1] The inferior olives communicate with the cerebellum via the olivocerebellar tract that originates in the inferior and accessory olivary nuclei. The climbing fibers of this tract have been postulated to relate to quick, impulsive movements and detecting or mediating error in voluntary movement. In contrast, the non-olivary afferent inputs (mossy fibers) to the cerebellum are thought to be responsible for slow or steady state movements as well as processing audio, visual, and motor-related signals. The ventral lateral nucleus of the thalamus, along with the red nucleus, receives the primary outputs of the cerebellum from the dentate nucleus.

Several studies have been done examining the cerebellum's responsibilities in motor control. A study of cerebellar activity during force production described relationships between cerebellar regions, force production, and force production rate.[2] Functional magnetic resonance imaging (fMRI) done in conjunction with force production tasks determined that, in general, both the superior and medial portions of the cerebellum were responsible for the amplitude of force while the lateral and inferior portions of the cerebellum were responsible for the rate at which force was able to be produced. Depending on the force production results of this study, postulations can be made about regions of the cerebellum responsible for affected performance.

Also relevant is a study of volume deficit in the pontocerebellar tract of alcoholics.[3] The deficit was shown to be responsible for lower body gait ataxia and a general ataxia disturbing balance in men; alcoholic women were also ataxic relative to their control subjects, just not with statistical significance. In OPCA, full control of movements is typically first lost in the legs. The ataxia progresses upwards into the arms and eventually the musculature of the mouth. On a side note, it would be interesting to find out if severe alcoholic damage to the pontocerebellar tract caused the extent of the ataxia to progress into the upper limbs and mouth, mimicking OPCA.

1.1.3 Spinocerebellar Degeneration: Olivopontocerebellar Atrophy

Olivopontocerebellar atrophy is a spinocerebellar degenerative disease that causes ataxia.[4] The degenerations of the olivocerebellar and pontocerebellar tracts are predicted to adversely affect different types of movement production as the olives are thought to be responsible for impulsive movements and the pons is thought to be responsible for slow or steady state movements.

OPCA can be categorized as a subset of a more extensive degenerative condition, multiple system atrophy (MSA).[5] MSA is a combination of three conditions: Shy-Dragers, striatonigral degeneration, and olivopontocerebellar atrophy. In MSA patients whose OPCA symptoms were more pronounced than the symptoms of the other two conditions, a neuropathology and pathophysiology investigation discovered a characteristic loss of white matter in the cerebellum. White matter of the brain is myelinated neurons; myelin is important in neural signal conduction. The dentate nucleus, the primary output of the cerebellum, was shown preserved.

In addition to changes in the cerebellum, there were also changes in two upstream inputs to the cerebellum, the pons and the olivary nuclei. The size of the pons was reduced and changes in the olives were seen as lesions formed in both nuclei and in the fibers connecting them to cerebellum.[6]

Of the fibers merging into the cerebellum, various efferent olivary nuclei neurons have been associated with regions of the cerebellum and can be considered part of the olivocerebellar tract.[7] The lateral olivary nuclei connects to the lateral cerebellum; medial inferior and accessory olivary nuclei connect to the lateral lobes of the cerebellum; the dorsal fold of the olivary nuclei sends its efferents to the superior surface of the cerebellum; the ventral fold of the olivary nuclei is connected to the inferior cerebellum. The other neural tract relevant to OPCA is that between the pons and cerebellum. The pons has neurons running to both the lateral cerebellar cortex and the dentate nucleus of the cerebellum.[8]

Although the two neural pathways, olivocerebellar and pontocerebellar, are degraded, proprioception (the ability to perceive one's body) of OPCA patients is unaffected while the regulation of movement production becomes increasingly affected.[2]

1.2 Motor Control

Motor control starts in the central nervous system and ends in movement production.

1.2.1 A Brief History of Motor Control

The history of motor control begins with Nikolai Bernstein.[9] His fascination with the changes small variations in a single joint had on the end results of multi-joint actions,

regional organization of the brain and their corresponding movement and sensory responsibilities, and theory of parallel processing involved in movements opened up a field that has branched, branched again, and continues to grow. Today, motor control includes studying the central nervous system's responsibilities in movement initiation, duration, and strength.

Of particular interest is digital motor control. Performance of everyday tasks from writing, to opening a jar, to playing an instrument requires precise coordination of forces in the fingers. Previous finger coordination studies done at The Pennsylvania State University have shown that individual fingers do not perform tasks only as distinct entities[10]; this thesis is working to further clarify their relations in OPCA patients. The foundations of muscular production of forces in the digits have been laid; changes in motor control caused by pathologies remain to be understood.

1.2.2 Force Production in the Digits

The ability to produce forces with digits 2-5 is dependent on muscles of the hand with bellies in the forearm (extrinsic) and in the hand (intrinsic).[11] Several of the flexors and extensors responsible for digital force production include flexor digitorum profundus (*2-5*) and superficialis (*2-5*), and extensor digitorum (*2-5*), extensor indicis (*2*), flexor and extensor digiti minimi (*5*). Additional muscles of the hand stabilize the fingers mediolaterally, two of which are the dorsal and palmar interosseus muscles (*2-5*).

Force production in the digits is able to be quantified using variance.[12] Given a force production task requiring two digits to produce 50 N, there is a linear solution space. Variation along this line ("good variance") does not affect total force and complies with the uncontrolled manifold hypothesis' assertion that there is variability in the space

of elemental variables (those produced by digits) that stabilizes a value of a task-specific performance variable. Variation orthogonal to the solution space ("bad variance") does not lend well to task completion. Ideally, muscles of the hand are innervated by the central nervous system in a manner that maximizes good variance and minimizes bad variances. These variances are measured in motor control studies of the digits and can be used to determine how well fingers work together in certain populations, be it age or gender, etc.

1.2.3 Motor Control Tasks and the Digits

With respect to the tasks performed to develop this thesis, there were three phenomena studied that may not necessarily be familiar to readers: maximum voluntary contraction, enslaving, and synergy.

1.2.3.1 Maximum Voluntary Contraction

Maximum voluntary contraction (MVC) is the largest amount of force able to be produced by a muscle or group of muscles. Frequently, these forces are used as baselines for other tasks whose results are then reported as a percentage of the MVC. Scaling allows for comparison between people who differ in force production abilities; a body builder may be able to produce an MVC of 100 N compared to a librarian who is only able to produce an MVC of 30 N. Either person would have the potential to reach 10, 30, 50 or any percent of their individual MVC in a follow-up task.

1.2.3.2 Enslaving

As described by Latash in *Synergy*[13] enslaving of the fingers is their lack of individuality, that is, one finger does not produce force without related, unintended force

production in the other digit(s). A common example of enslaving is that of the little and ring fingers. Movement of the little finger cannot be done independently of movement of the ring finger. Should one carefully observe their fingers while the little finger is being moved intentionally, one may also notice that the middle and perhaps even the index finger move as a results of enslaving innervations. The movement of, and forces produced by, the middle and index finger will likely be much smaller than that of the ring finger.

1.2.3.3 Synergy

Broadly defined, synergy[13] is the cooperation of elements (fingers) during force production that is characterized by task-dependence, error compensation, and sharing. The sharing component of synergy requires that all the involved effectors, in this case the fingers, contribute to the performance of the tasks. Error compensation of fingers relates to negative co-variation of finger forces across trials. Lastly, synergy requires task dependence; this means that the same set of fingers can be organized to stabilize different performance variables in different tasks. To illustrate a synergy, one may choose to hold an open water bottle upright; the forces and moments are balanced, and the bottle is still. Lifting the little finger from the bottle causes the other three fingers to share force production in a new way within a new, three-finger solution space but the bottle does not spill.

1.2.3.4 Studies in Motor Control

Sans consideration of pathology or other damage to the brain, motor control is a field expanding on the foundations laid by neurology, neurophysiology, and kinesiology, among others.

There are certainly changes in motor control during various tasks due to natural phenomena in the absence of injury or illness. For instance breathing affects, and actually increases, force production[14,15]; this was demonstrated in two studies. In one, the force production seen in flexor digitorum superficialis is increased during inhalation and exhalation compared to maintenance of a static lung volume. This was observed while maintaining force at 10% of a four finger MVC. Changes were observed near minimal force production values in the former case; a similar study showed that MVC increased by 10% when performed during inhalation or exhalation.

If something as primal as breathing affects force production, other natural variables certainly have the potential affect digital movements and coordination. Simply performing a task with both hands simultaneously causes a reduction in the total force as compared to the sum of each hand's respective maximum contraction force value (known as force deficit).[16] Other natural variables such as age and gender are known to affect motor control; for instance, women's fingers exhibit less enslaving than their male counterparts and elderly people exhibit less enslaving and produce smaller MVCs than younger people.[17]

Good health aside, studies have been done to characterize how brain or spinal injuries and afflictions affect the production of force in the digits. Stroke and injuries to the spinal cord have been found to negatively affect enslaving and MVC, and enslaving respectively.[18,19] Surprisingly, in the spinal cord injury study, the patients with spinal cord injuries exhibited enslaving in paralyzed fingers not participating in the task even though they could not produce force in the same finger when it was tasked to do so. While there is no telling whether this study will produce results as surprising as any of

the aforementioned, learning about the changes in finger coordination of OPCA patients provides measureable ways to examine the disease and understand its effects more completely.

Chapter 2: Quantifying Force Production: Experimental Methods

Procedures for testing OPCA patients and control subjects using three force production tasks are documented, as is the experimental set up. Variable definitions and calculations are outlined briefly. It has been shown that OPCA does not affect learning or retention of force scaling tasks.[20] Thus, during all tasks, learning will not contribute to error as all patients and subjects were allowed to practice until they stated they were comfortable performing the task.

2.1 Experimental Setup

A maximum voluntary contraction (MVC), the largest possible force using index (I), middle (M), ring (R), and little (L) fingers was recorded and used as the baseline for the remaining tasks. The two other tasks required I, M, R, and L fingers to act simultaneously (IMRL) or separately. The person being tested was always seated at a comfortable distance from the force sensors such that the distal phalanges of digits two through five rested comfortably on the force sensors. Their shoulder was flexed at roughly 45˚ and abducted to the same angle; the elbow was flexed to approximately 135˚; the wrist was neither flexed nor extended. Data was collected with Labview and analysis was done in MATLAB, Minitab, and Excel.

The person being tested was seated at a counter had a computer monitor directly in front of them. To one side, a wooden board C-clamped to the counter had a curved

wrist support block attached to it. Figure 2-1 highlights the setup directly around their hand and fingers. Past the wrist support, away from the person being tested, four force sensors were fastened. A Velcro strap was under the wrist support and held the force producing hand in place during the task. The hand slid naturally over the wrist support block so that the Velcro could be easily tucked under the thumb and secured across the knuckles of the index, middle, ring, and little fingers.

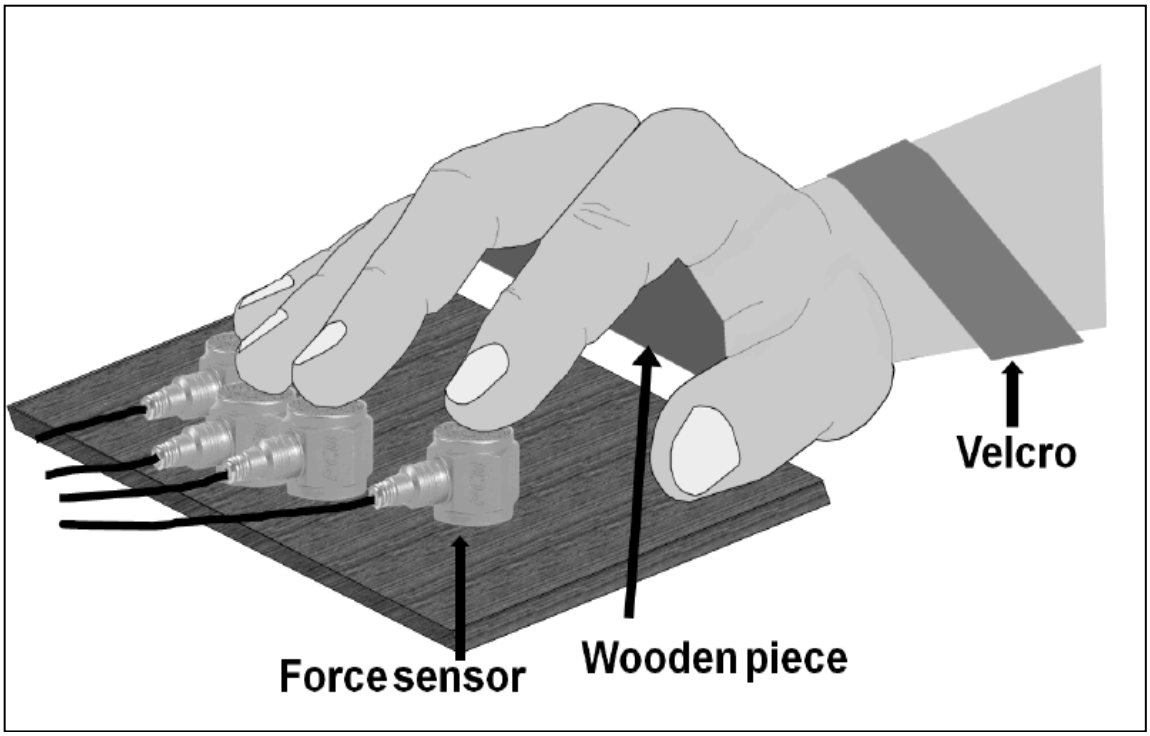

Figure 2-1: Experimental Setup. A board extended (not shown) under a person's elbow for support. A curved, wooden piece (also not shown) was attached to the board and rested under the palm of the hand for support. In front of the wooden piece, four force sensors were fastened to the board with double-sided tape to allow for person-to-person adjustments in placement. The Velcro strap wrapped around a person's knuckles to prevent movement.

The subjects were verbally instructed to always keep their elbow on the board and shoulder still; keeping all four fingers on the sensors at all times was also stressed. No matter which task was being performed, the person being tested was allowed to practice

the task until they were familiar with the task goals and became accustomed to the force production necessary for correct completion. Each person performed Tasks 1 through 3 with one hand after which the apparatus was moved to the other side and each subject performed Tasks 1 through 3 with their other hand.

2.2 Experimental Procedures

Procedures for the three force production tasks are outlined below. Force production goals are stated as percentages of MVC in Tasks 2 and 3.

2.2.1 Task 1: Maximum Voluntary Contraction

Task 1, MVC, was performed with IMRL. OPCA patients and control subjects were instructed to press down on the sensors as hard as they could without compromising shoulder, elbow, or wrist positioning as best they could. Individual finger maxima were output, as was the sum of the individual maxima.

Task 1 was performed twice with each hand per person. For each hand, the averages of the five values were used to scale force production requirements for Tasks 2 and 3. Average individual finger maxima were used to scale the maxima of Task 2. The average, summed maximum was used to scale the IMRL force production needed for Task 3. A representation of the MVC output is shown in Figure 2-2.

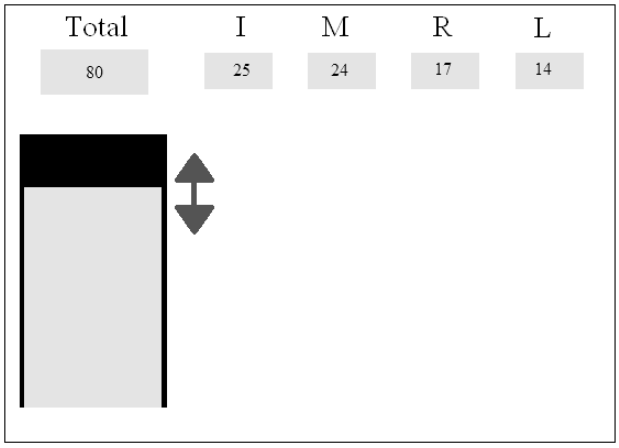

Figure 2-2: An Illustration of the MVC Task. The arrow indicates the increase or decrease in force production. The total (IMRL) force and individual finger forces (I, M, R, L) are shown as well.

2.2.2 Task 2: Ramp Force Production

Task 2 required a linear increase in force production over 10 seconds from 0 N to 40% of an individual finger's MVC. All fingers needed to remain on the sensors; the task finger was the only finger whose force changed the value seen by the subject. Force output was also recorded for the non-task fingers. Each finger, I, M, R, and L, was tested twice per hand, per person. An example of a correctly performed Task 2 is shown in Figure 2-3.

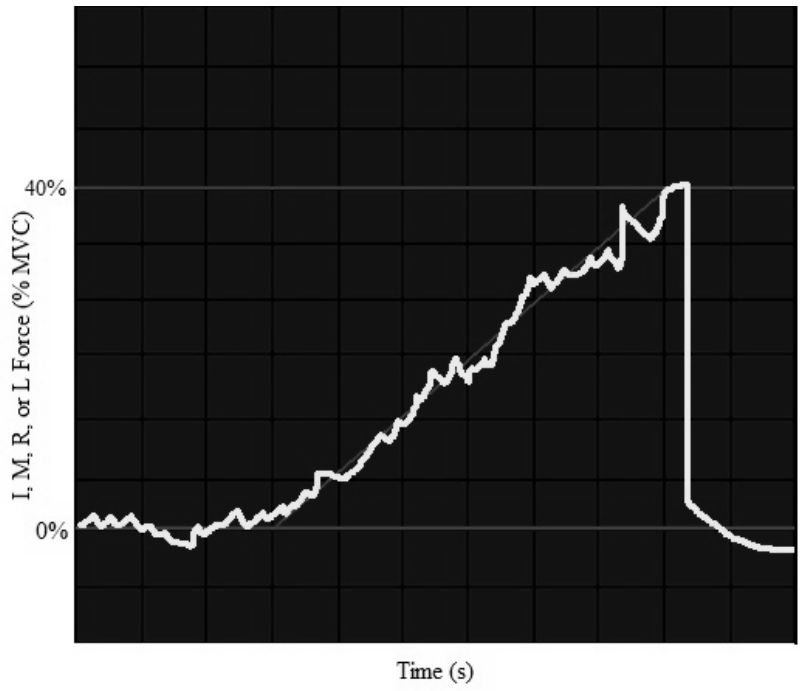

Figure 2-3: An Illustration of the Ramp Task. The force shown was only produced by the task finger as a percentage of the task finger's MVC taken from Task 1. The ramp begins at 0% MVC and ends at 40% MVC. Non-task finger forces did not contribute to the values seen.

The result of this task was an enslaving index (E), reflecting involuntary force production in non-task fingers. For each trial using one task finger *j* and three non-task fingers *i*, where *i* and *j* = {I,M,R,L} respectively, regression coefficients $k_{i,j}$ were calculated (Equation 1).

$$F_{i,j} = F_i^0 + k_{i,j} * F_{Tot,j} \quad (1)$$

$F_{i,j}$ is the individual finger force when *j* is the task finger. F_{Tot} is the total force when *j* is the task finger. The enslaving index was calculated as the average of all task finger, non-task finger combinations $k_{i,j}$ where $i \neq j$ (Equation 2).

$$E = \sum k_{i,j}/12 \quad (2)$$

2.2.3 Task 3: Impulse Force Production

Task 3 required steady state force production at 5% of the MVC. Sometime after the 5-second, steady state period the OPCA patients and control subjects were asked to produce a force impulse that came within ±5% of 25% of the MVC. The task was carried out between 20 and 30 times per hand, per person. Figure 2-4 shows the task performed correctly.

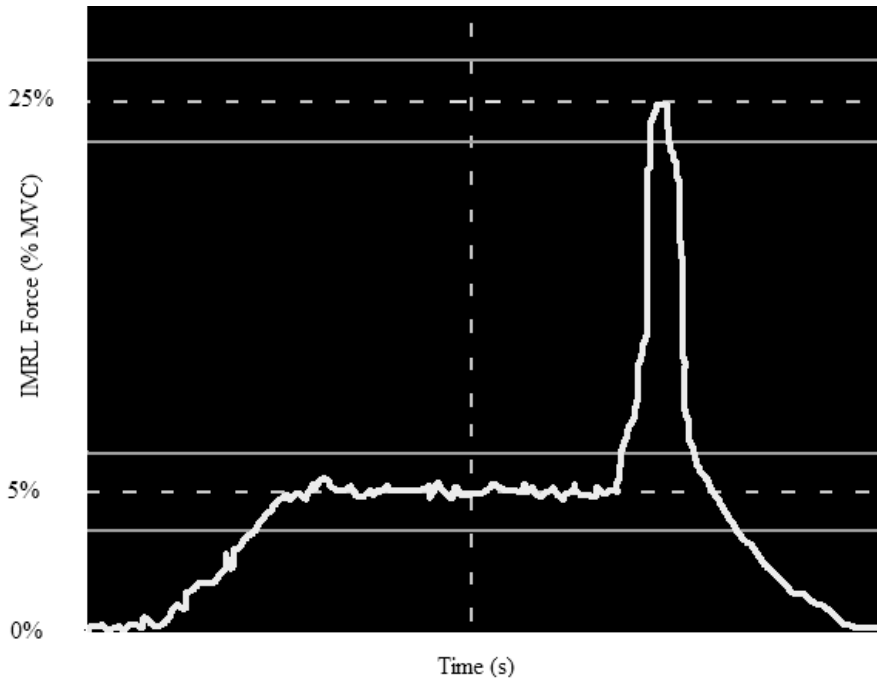

Figure 2-4: An Illustration of a Correctly Performed Impulse Task. After the task begins, the IMRL force was brought up to 5% MVC (lower horizontal dashed line). Any time after 5 seconds (vertical dashed line), a force impulse was produced in an attempt to reach 25% MVC (upper horizontal dashed line) after which force production could drop to zero.

It was important that steady state is maintained prior to the impulse. The patients and subjects were told that decreased force production prior to impulse, shown in Figure 2-5, was incorrect.

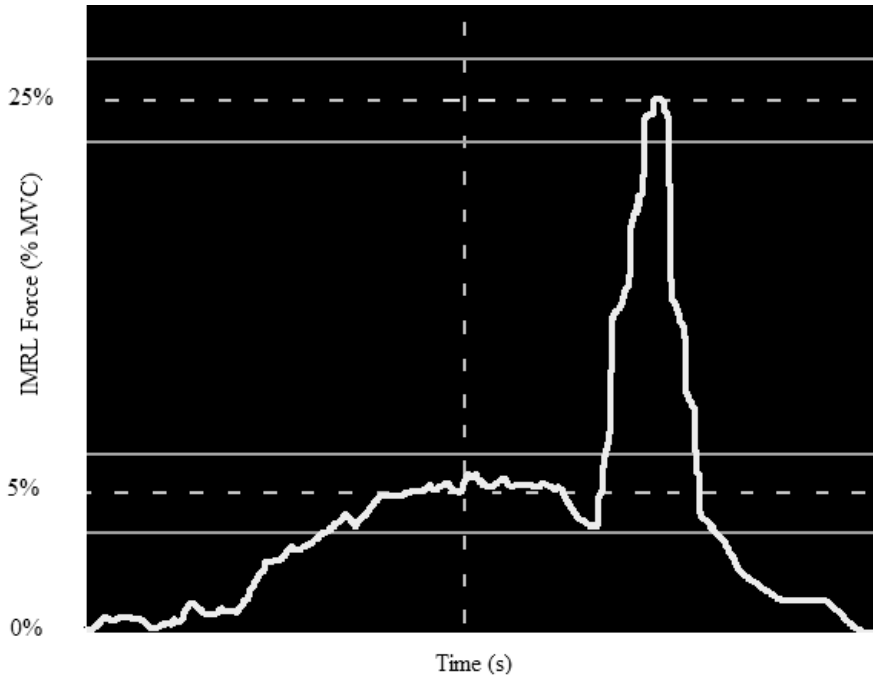

Figure 2-5: An Illustration of an Incorrectly Performed Impulse Task. The dip in force production just prior to the impulse is the incorrectly performed portion of the task.

The results of this task were three-fold: a steady-state synergy index (ΔV), a value (ΔΔV) for the change in ΔV between steady-state force production and the beginning of impulse force production, and t_{ASA}.

In general, the relative amount of good variance (V_{good}) to bad variance (V_{bad}) with respect the total variance (V_{tot}, $V_{tot} = V_{good} + V_{bad}$) is defined as ΔV (Equation 3).

$$\Delta V = (V_{good} - V_{bad})/V_{tot} \tag{3}$$

The larger the ΔV, due to some combination of large V_{good} and small V_{bad}, the better the ability to coordinate force production a person has. Due to differences in degrees of freedom needed to normalize the good and bad there are upper and lower limits to ΔV. The statistical analysis performed requires normal distribution of data and

the boundaries prevent ΔV from obtaining such a distribution. Thus, a Fischer transformation was done to ΔV in order to present ΔV_z, a synergy index with a normal distribution.

To calculate $\Delta\Delta V_z$, defined as the difference between the mean steady-state synergy $\Delta V_{Z,SS}$ and the synergy at the time of impulse (defined as the time at which (dF/dt), the rate of change of force, reaches 5% of $(dF/dt)_{max}$) $\Delta V_{Z,I}$ was calculated using Equation 4.

$$\Delta V_{Z,I} - \Delta V_{Z,SS} = \Delta\Delta V_z \quad (4)$$

T_{ASA} is defined as the time at which the steady-state synergy changed by at least two standard deviations prior to impulse production.

Chapter 3: Meet the Patients

Fourteen subjects, seven OPCA patients and seven control subjects, completed the task battery. Information for age and gender matching, among other qualitative categories for comparison, are included for OPCA patients and control subjects.

3.1 Olivopontocerebellar Atrophy Patient Information

Seven OPCA patients completed the series of tasks. Four were male and three were female. Ages ranged from 54 to 75 with illness duration ranging from 3 to 12 years. The youngest OPCA diagnosis occurred at 42 years of age, the oldest at 69. Only one OPCA patient (ID 1, Table 3-1) developed symptoms unilaterally. For the remaining patients, diagnoses were based on a bilateral gait or balance problem. Table 3-1 details OPCA patient information. Appendix A contains a complete archive of OPCA patient information.

Table 3-1: OPCA Patient Information. Relevant personal information of the seven OPCA patients used for comparison purposes.

Subject	Gender	Age (Years)	Handedness
1	F	60	R
2	M	60	R
3	F	54	N/A
4	M	60	R
5	M	75	L
6	F	59	R
7	M	73	R

3.2 Control Subject Information: Age and Gender Matched

More than seven control subjects finished the series of tasks. Of the control subject population, seven were chosen based on similarities in ages and genders to the OPCA patients for comparison in Tasks 2 and 3, the ramp and impulse. Table 3-2 provides their basic information.

Table 3-2: Ramp and Impulse Control Subject Information. Information useful for identifying control subjects who would be useful in making appropriate conjectures about OPCA patients' deviation from normal motor control.

ID	Group	Gender	Age (Years)	Handedness
8	Control	M	73.7	R
10	Control	M	59.8	R
11	Control	F	54.3	R
14	Control	F	65.8	R
17	Control	F	69.1	R
18	Control	M	66.9	R
24	Control	M	67.3	R

In comparison of MVC, data from subject 8 is not considered and replaced with from data three other subjects. Their ID numbers are 1, 3, and 21 and basic information on them is shown in Table 3-3.

Table 3-3: MVC Control Subject Information. Information useful for identifying control subjects who would be useful in making appropriate conjectures about OPCA patients' deviation from normal motor control.

ID	Group	Gender	Age (Years)	Handedness
1	Control	M	58.4	R
3	Control	M	53.9	R
21	Control	M	74.3	R

Chapter 4: Results and Discussion of Motor Control Tasks

There are five variables by which the affects OPCA has on motor control of digits two through five were measured: mean force, enslaving, mean steady state synergy, change in synergy from steady state to impulse production, and anticipatory synergy adjustment. Seven OPCA age patients were tested and a corresponding number of age and gender matched control subjects selected from a larger pool of control subjects were used for comparing Tasks 2 and 3; removal of one of these seven control subjects and addition of three other control subjects was done for MVC comparison due to rejection criteria. Matching the populations by age and gender allows for better comparisons between the task variable means. Mixed-design ANOVAs with repeated measures were done in Minitab (MVC: n = 6 OPCA patients, n = 9 Control subjects; Ramp and Impulse: n = 6 OPCA patients, n = 7 Control subjects). In particular, how outcome variables were affected by group (OPCA and Control), finger (four fingers), and hand (left and right), was examined.

4.1 Task 1: Maximum Voluntary Contraction Results

Understanding the changes OPCA causes in digital motor control begins with examination of differences in maximum voluntary contractions, (MVC). The MVC, per finger and summed across all four fingers, provide baselines from which Tasks 2 and 3 are scaled for OPCA patients and control subjects alike. Complete, numerical results are found in Appendix B.

Figure 4-1a and Figure 4-1b show the measured changes in average force production between the OPCA patients and control subjects for the I, M, R, L, fingers and the IMRL total.

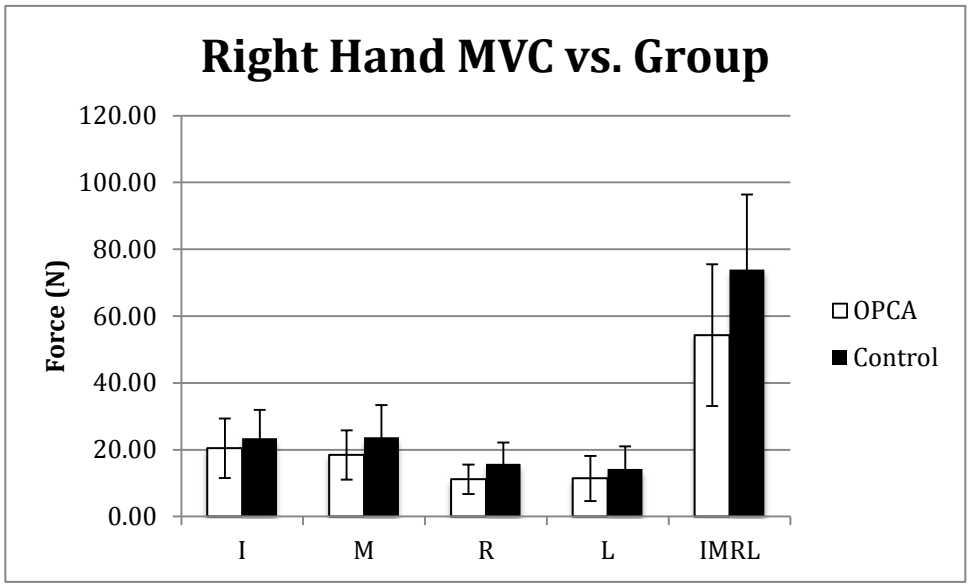

Figure 4-1a: Right Hand Maximum Voluntary Contraction vs. Finger. The mean (± standard deviation) MVC force for index (I), middle (M), ring (R), little (L), and all (IMRL), fingers is shown for the right hand of both groups.

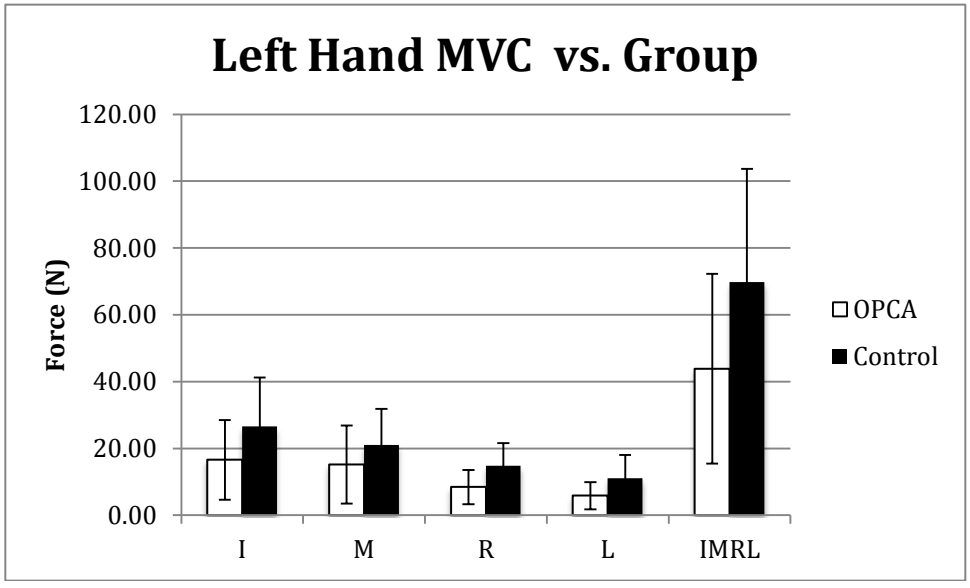

Figure 4-1b: Left Hand Maximum Voluntary Contraction vs. Finger. The mean (± standard deviation) MVC force for index (I), middle (M), ring (R), little (L), and all (IMRL), fingers is shown for the left hand of both groups.

OPCA had an adverse effect on maximal force production as I, M, R, L, and IMRL MVCs decreased in the left (13%, 22%, 29%, 20%, 27%) and right (38%, 28%, 43%, 48%, 37%) hands relative to control subjects.

Table 4-1 documents the statistical relevance group, hand, and fingers had on the MVC results. Group and fingers were found to be significant factors in differences in MVC. The hand the task was performed with was not significant.

Table 4-1: Factors Contributing to Variation in MVC and Significance. The smaller the p-value the smaller the probability the variable changed by chance and the greater the probability the factor was responsible for change.

MVC Factor	Significance
Group	$p < 0.001$
Finger	$p < 0.001$

Individual finger and IMRL force maxima obtained from MVC, while necessary baselines for testing subjects using Tasks 2 and 3, do not necessarily provide information about interdigit force production relationships.

4.2 Task 2: Ramp Force Production Results

Task 2, a linear increasing force from 0 N to 40% of MVC, is a single finger task determining the degree of dependence, enslaving (E), the three non-task fingers have with respect to the task finger. Complete, numerical results are found in Appendix C.

Figure 4-2 shows the tiny difference between the enslaving of the left and right hands in control subjects and also goes on to illustrate the magnifying quality OPCA had on enslaving. In the left hand, enslaving was increased by 55% in OPCA patients relative

to control; the right hand of OPCA patients saw a 31% increase in enslaving relative to control subjects.

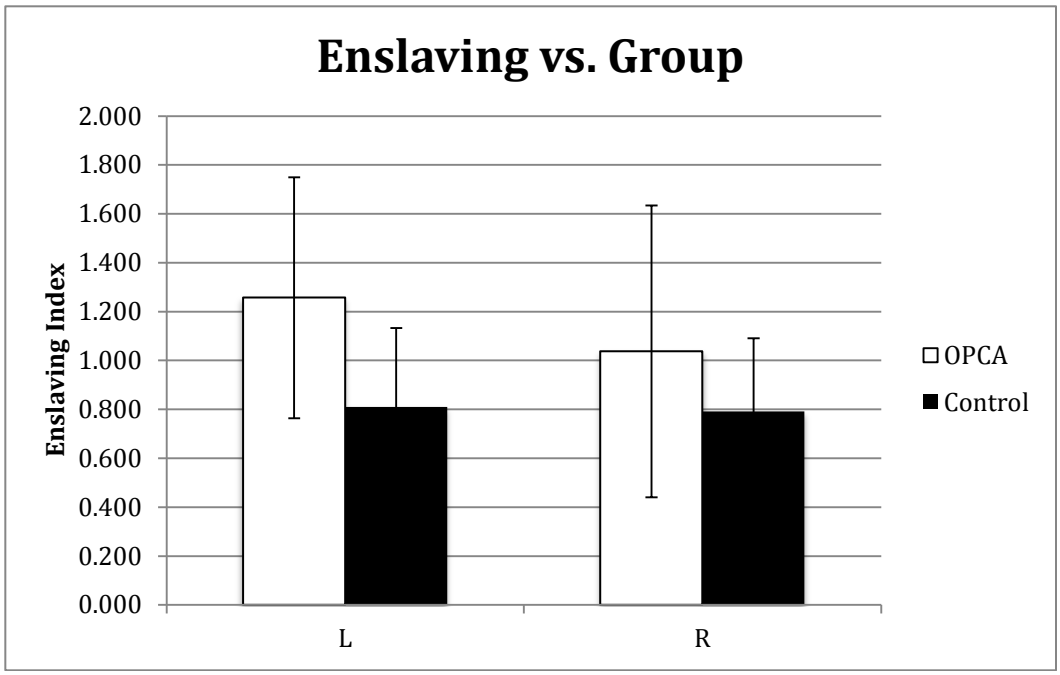

Figure 4-2: Enslaving Index vs. Group. The mean (± standard deviation) enslaving of the three non-task fingers with respect to task finger across all permutations of task finger in the left and right hands of OPCA patients and control subjects.

Table 4-2 documents the statistical relevance group and hand have on the enslaving results. The change in enslaving due to group significant and is unlikely to have happened by chance; the change in enslaving due to hand is not significant.

Table 4-2: Factors Contributing to Variation in Enslaving and Significance. The smaller the p-value the smaller the probability the variable changed by chance and the greater the probability the factor was responsible for change.

Enslaving Factor	Significance
Group	$p < 0.1$

4.3 Task 3: Impulse Force Production

Task 3, a task requiring a transition from steady-state force production to the production of a force impulse, sheds light on how IMRL synergy is affected by OPCA.

The target steady state and impulse force productions are 5% MVC and 25% MVC, respectively. Complete, numerical results are found in Appendix C.

4.3.1 Results: Steady State Synergy

Steady-state synergy index ($\Delta V_{Z,SS}$) is a measure of the relative amount of good variance seen across all four fingers during the production of 5% MVC for the period of time prior to impulse production.

The mean steady-state synergy index of control subjects and OPCA patients is greater in the left hand than the right during steady-state force production. However, finger coordination is present to a lesser degree in OPCA patients (Figure 4-3), evidenced by the decreases (30% and 32%) relative to control subjects.

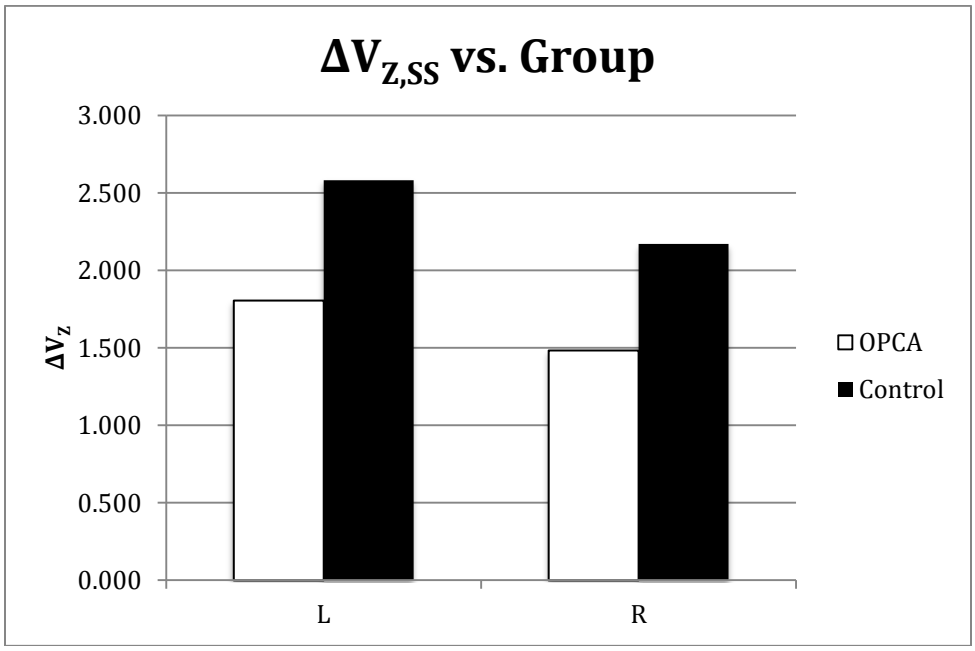

Figure 4-3: Mean Steady-state Synergy Index. A comparison of steady-state synergy index versus group in the left and right hands of OPCA patients and control subjects.

Table 4-3 documents the statistical relevance group and hand have on the synergy results. Group is a significant factor contributing to differences in finger coordination as the difference is improbably due to chance; hand is not.

Table 4-3: Factors Contributing to Variation in ΔV_Z and Significance. The smaller the p-value the smaller the probability the variable changed by chance and the greater the probability the factor was responsible for change.

Steady-state Factor	Significance
Group	$p < 0.05$

4.3.2 Results: Synergy Changes from Steady-state to Impulse Generation

There is a change in synergy index ($\Delta\Delta V_Z$) as steady-state force production changes into the production of a force impulse.

As a whole, and as seen in Figure 4-4, the OPCA patient population showed decreased (Left, 56%; Right 89%) $\Delta\Delta V_Z$ as the transition from steady-state force production to impulse force production was made.

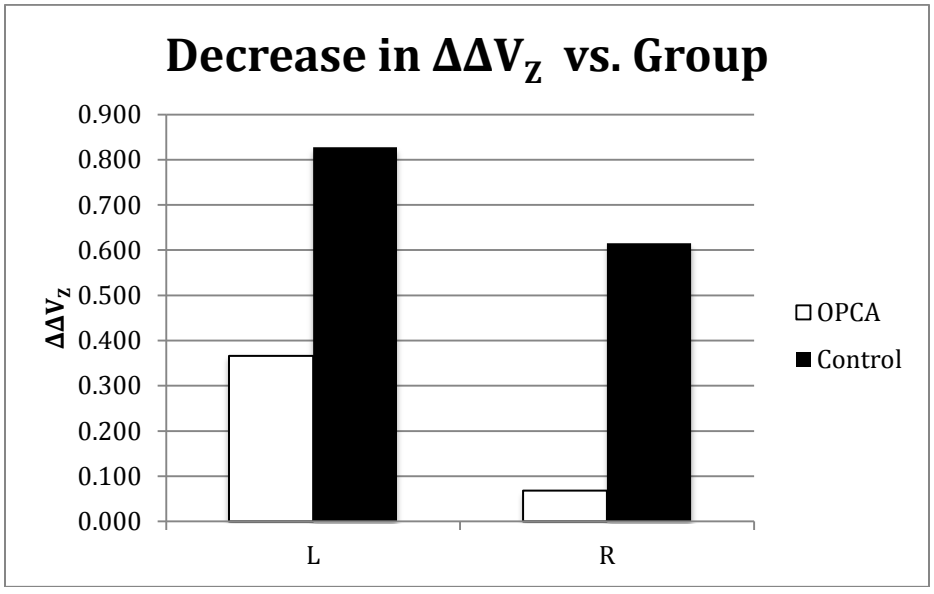

Figure 4-4: $\Delta\Delta V_Z$ vs. Group. Illustrating the mean decrease in synergy index seen between steady-state and impulse production in the left and right hands of OPCA patients and control subjects.

Table 4-4 illustrates the significance hand and group had on the decrease in ΔV_z between steady-state and impulse. Change in steady-state synergy is not likely due to chance when examining differences in group; hand is not significant.

Table 4-4: Factors Contributing to Variation $\Delta\Delta V_Z$ and Significance . The smaller the p-value the smaller the probability the variable changed by chance and the greater the probability the factor was responsible for change.

Change In ΔV_z Factor	Significance
Group	$p < 0.01$

4.3.3 Results: Anticipatory Synergy Adjustment Time

The anticipatory synergy adjustment time (t_{ASA}) is the time at which a change of two standard deviations in ΔV_z is seen between the steady-state force production and impulse force production.

The mean t_{ASA}s (Figure 4-5) for the left and right hands of control subjects (0.29 s, 0.26 s) are greater than those in the left and right hands of OPCA patients (0.13 s, 0.056 s). The effect OPCA has on timing mechanisms is negative, evidenced by decreases in t_{ASA} of 56% in the left hand and 79% in the right.

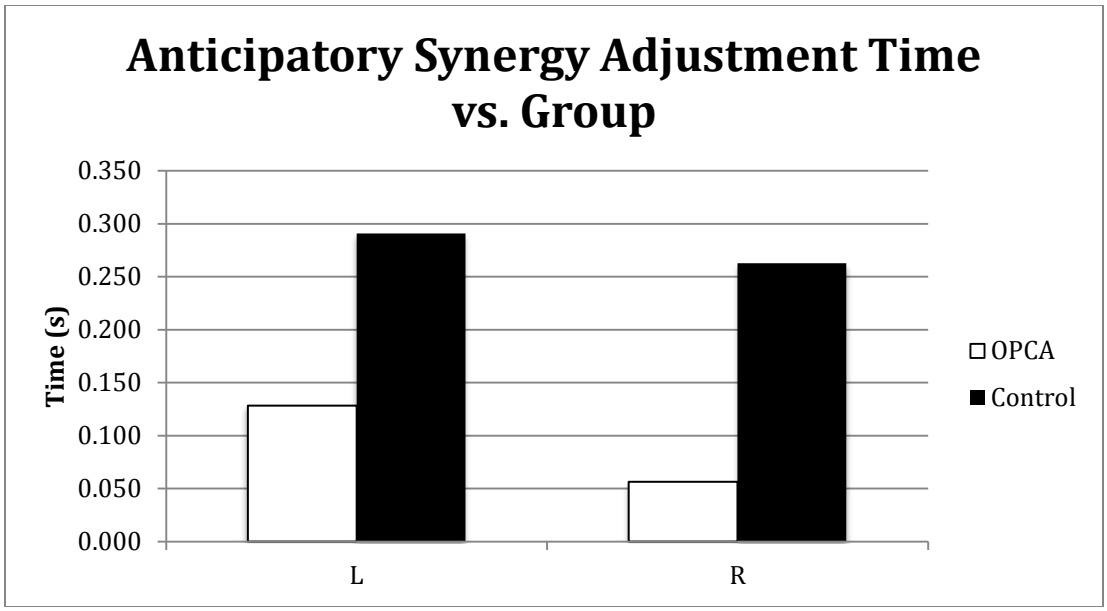

Figure 4-5: Anticipatory Synergy Adjustment Time vs. Group. Illustrating the mean times at which synergy begins to decrease between steady-state force production and impulse production in the left and right hands of OPCA patients and control subjects.

Table 4-5 documents the statistical relevance group and hand have on the t_{ASA} results. Group significantly affects t_{ASA} ; hand is not significant.

Table 4-5: Factors Contributing to Variation in t_{ASA} and Significance. The smaller the p-value the smaller the probability the variable changed by chance and the greater the probability the factor was responsible for change.

t_{ASA} Factor	Significance
Group	$p < 0.01$

4.4 Discussion of Results

There are several aspects of this study that need to be discussed: the changes seen in task variables and notable findings.

4.4.1 Discussion of Task 1: Maximum Voluntary Contraction

In OPCA patients there was a drop in MVC force relative to that of the matched control subjects ($p < 0.01$). This result is seen in I, M, R, L, and IMRL in both hands but the effect of hand on decrease in MVC was not significant.

As force production is linked to regional cerebellar activity, in amplitude's case the lateral and inferior regions, these would be the first places to look for damage in the cerebellum. White matter degradation in these areas may eliminate their ability to do their part in specifying force amplitude. Examining MRIs of OPCA patients' brains in these cerebellar regions for demyelination would help to confirm or refute the notion that this specific type of degeneration was responsible for the loss in force production due to lack of signal conduction. Should the MRI not show unnatural demyelination in these regions, alternate theories on the neural cause of the weakness could be made. Several olivary nuclei (lateral, medial inferior, accessory) pass signals to the lateral cerebellum while the ventral fold of the olives signals to the inferior portion of the cerebellum. Demyelination along the olivocerebellar tract to one of these nuclei could finger one of the olivary nuclei as a controller of force amplitude.

The decline of MVC in OPCA patients was comparable to the 36% percent reduction in MVC seen in the affected hands of stroke patients.[18] All of the reductions (I, M, R, L, and IMRL) in the left hand were less than 36%. In the right hand, all decreases save that of the ring finger (28%) were greater than the affected hand of the stroke patients. A future study of MVC and hand dominance in OPCA patients would help clarify the role hand dominance plays in the decreased of MVC. The stroke study provides a reasonable benchmark for comparison to OPCA data but further study into injury or pathology is warranted. At any rate, OPCA patients saw a decline in their maximal force production capacity relative to control.

4.4.2 Discussion of Task 2: Ramp Force Production

Enslaving is a topic of interest in motor control because the lack of independence is evident during most attempts at moving individual fingers. The index, followed by little, middle, and ring fingers is the most independent of the fingers.[21] Enslaving of OPCA patients' individual fingers are not specifically examined in this discussion; IMRL enslaving is discussed.

OPCA patients saw increased enslaving ($p < 0.1$) relative to control subjects. Although the left hand OPCA patients appeared to be more enslaved than the right, there was no statistical significance found. Previously, Li *et al* found that enslaving is larger in non-dominant hands than dominant hands while performing one-handed tasks.[22] To this effect, control subjects showed slightly larger mean enslaving in the left (non-dominant hand for all subjects) hand. As a group, the OPCA patients were predominantly right handed and exhibited larger enslaving in the left hand as well, although the amplification of enslaving in non-dominant hands was more pronounced than in the control subjects. As the cerebellum is partially responsible for force production it is possible that the demyelination characteristic of OPCA is at the root of enslaving but for a different reason than suggested in MVC discussion. While a higher MVC may require a strong or more frequent neural signal provided by a myelinated neuron, greater force production in non-task fingers may be caused by demyelinated neurons accidentally triggering action potentials (neural signals) in nearby neurons positioned along the axon (extended portion of a neuron carrying signal away from the neuron) and not only the intended neurons at the axon terminals (point of connection of a neuron to the next). Any secondarily

triggered action potentials could provide unwanted innervations to digits local to the assigned task finger during the completion of the ramp force production task.

In addition to supporting the role hand dominance has on enslaving (in both OPCA patients and control subjects), this study confirmed the results of another enslaving study that linked the cerebellar lesions of OPCA to increased enslaving.[25]

4.4.4 Discussion of Task 3: Impulse Force Production

Rounding out the coordination changes of OPCA patients were adversely affected synergy index measures. The steady-state synergy index, ΔV_Z, ($p < 0.05$), the change in index between steady-state and impulse force productions, $\Delta\Delta V_Z$, ($p < 0.01$), and anticipatory synergy adjustment time, t_{ASA}, ($p < 0.01$) all decreased for OPCA patients with respect to control subjects and the changes were significant with respect to group. Changes in task variables due to hand were not significant.

In previously done force production tasks examining a synergy, the right hand showed a greater index of synergy than the left.[23] Contrary to that result, control subjects and OPCA patients tested in this study showed greater mean ΔV_{SS} in their left hands than their right hands. As both populations are predominantly right handed the right hands should have shown more coordination. A larger OPCA population (and control subject population for that matter) should be examined to confirm this trend that is in apparent conflict with previous studies.

The same study[23] also showed that the $\Delta\Delta V_Z$ between steady-state force production to impulse force production was greater in the left hand than the right hand. The OPCA patients and control subjects both showed this larger decrease in synergy in their left hands although the control subjects, with their larger ΔV_{SS}, had larger $\Delta\Delta V_Z$. If

the there is a relation between size of $\Delta V_{Z,SS}$ and $\Delta\Delta V_Z$ prior to impulse production perhaps there is an ΔV_Z minima that is reached and allows all people to produce force as fast as they can while maintaining enough control in production to hit the target range of 25% MVC. As OPCA patients have smaller $\Delta V_{Z,SS}$ than the control subjects, the time it would take for them to reach this minima would be smaller provided that the rates of synergy decrease are roughly the same; looking ahead, t_{ASA} may be predicted to be smaller in OPCA patients than control subjects.

T_{ASA} is a feed-forward mechanism in that it occurs prior to the actual production of force. The ability is to reduce synergy prior to force production is lost as people age[24] but is accounted for in this study. The t_{ASA} is noteworthy because in order to produce greater force production rates, synergy may need to be decreased prior to force production.[13] The smaller t_{ASA} seen in OPCA patients relative to control subjects could lead to lower rates of force production due to the smaller time OPCA patients have to drop ΔV_Z during the transition from steady-state to impulse in Task 3. Examination of the medial and superior cerebellum via MRI could check for OPCA's characteristic damage in these areas, as they are regions associated with rate of force production. It would be interesting to join t_{ASA} and $\Delta\Delta V_z$ to find out if the rate of change, and not just magnitude, of ΔV_Z affected impulse production as a feed-forward mechanism. As group was the significant factor in t_{ASA}, comparisons of force production rates between groups could be done to further examine the effect of t_{ASA} (also ΔV_Z at impulse and the magnitude of $\Delta\Delta V_Z$).

As a comparison between t_{ASA} and cerebellar damage measurements has already been discussed, it is worth mentioning that $\Delta V_{Z,SS}$ and $\Delta\Delta V_Z$ could also be compared to

the physical damage seen in MRI of the OPCA patients' brains. The areas predicted to be damaged would be medial and superior portions of the cerebellum. These areas have already been linked to force production rate, and force production rate may have some dependence on ΔV_Z. A study could clarify this relationship further. If there was found to be no correlation between the damaged cerebellar regions and ΔV_Z, the pontocerebellar tract could be examined as it sends its efferents into some of the regions of the cerebellum responsible for force production rates.

4.4.4 Notable Findings

The study by Shinohara *et al* describes a proportionality between MVC and enslaving; enslaving is smaller in those with smaller MVCs.[17] This was found in two different comparisons of groups: men and women, and the elderly and young. In both comparisons the subjects were healthy.

Combining the results of Tasks 1 and 2, OPCA patients buck this trend. They have smaller MVCs than control subjects but their enslaving is increased. Apparently, neural changes in OPCA patients disrupt a natural relation between the ability to produce large amount of force and lack of finger independence. The combination of increased enslaving and decreased MVC would make activities like playing an instrument (piano for example) much more difficult for patients with OPCA. Fortissimo would be difficult to produce using only the fingers due to decreased MVC. Even if it were to be produced, the enslaving increase would increase the force production of fingers that aren't supposed to strike keys and cause the music to become discordant. Somewhat conversely, if OPCA hampers musical talents (among other things), perhaps prior musical talent of OPCA

patients could attenuate the negative effects seen in the task variables of OPCA patients. It would be worth investigating.

At any rate, the combination of finger weakness and dependency could have adverse effects on daily activities of OPCA patients. Follow-up studies on MVC-enslaving trends should be done in other patient populations (or subsets of the OPCA population provided the sample size increases) to better understand the cause of the deviation from natural MVC-enslaving patterns.

Chapter 5: Proposed Future Work

Throughout the course of the study, there was a major shortcoming in the patient population (size) that hindered a more thorough analysis of the affects OPCA has on finger coordination. The male population (n=4) and female population (n=2 for all tasks due to performance outside of allowable limits) could certainly be increased, provided the tasks could be reproduced in other research facilities as they were limited by the number of the OPCA patients referred to the Milton S. Hershey Medical Center. While OPCA is rare, the sample size of this study prevented more extensive analyses of the effects of gender in OPCA patients has on motor control. An increased OPCA patient population would likely also bring in male and female patients of a greater variety of ages. Available for development would then be a task variable versus age progression model. These motor control tasks cannot be used as a diagnostic tool at this point but they have the potential to provide quantitative disease progression information.

In OPCA patients, MRI could provide additional information about the extent of neural degradations and structural changes in the cerebellum, pons, olives, or tracts connecting them. Documenting the neural changes would potentially enable correlation between the extent of neural damage and its subsequent effects on the motor control processes as proposed in the discussion which would greatly supplement the time since diagnosis (Appendix A) in developing a disease progression model.

Two variable aspects of the OPCA patients, listed in Appendix A as patient information, could also be tested more extensively. Height and weight could be combined to examine the effects BMI has on motor control indices. For the most part, the OPCA

patients were on their medication during these tasks and still performed worse than control subjects. Testing them as medications are nearing complete metabolization would provide an unfiltered look at the effects OPCA has on motor control. If possible this could be done just prior to taking their regimented medicinal doses.

Task specific follow up investigations include (1) checking the changes the MVC-enslaving undergoes in patients with other diseases or conditions affecting the brain or spinal cord, (2) examining the effects t_{ASA}, ΔV_Z, and $\Delta\Delta V_Z$ have on the rate of force production during impulse and subsequent effects the cerebellar pathophysiology of OPCA has on the rate of force production during impulse, and (3) examining patient populations with different pathologies or injury to discover what kinds of problems cause deviation from the healthy MVC-enslaving proportionality.

Chapter 6: Conclusions

The purpose of this thesis was to clarify the effect a rare disorder of the cerebellum, olivopontocerebellar atrophy, had on multi-finger motor control. The analyses required performances of maximum voluntary contraction, ramp, and impulse tasks. After age and gender matching, the test battery results from seven control subjects (4 male, 3 female), combined with the results of the seven OPCA patients allow for postulation on the effects of OPCA on finger coordination.

Of greatest importance (1) is the fact that OPCA patients do not show the typical positive correlation between MVC and enslaving. OPCA patients exhibit smaller MVC than their control subject counterparts but larger enslaving (negative correlation). OPCA also causes (2) a bilateral decrease in MVC OPCA patients, (3) a bilateral increase in enslaving in OPCA patients, (4) a bilateral decrease in $\Delta V_{Z,SS}$ in OPCA patients, (5) a bilateral decrease in the $\Delta\Delta V_Z$ during the transition between steady-state and impulse production OPCA patients, and (6) a bilateral decrease in the t_{ASA} of OPCA patients. In the case of all five task variables the change with group is confirmed ($p < 0.1$).

Future studies in OPCA finger coordination should attempt to draw on a large sample of patients to produce statistically significant comparisons between group/gender combinations of OPCA, control, male, and female. The larger sample size would also enable further study into the effects age has on finger coordination in OPCA patients and provide a model of finger coordination changes over time. MRI examination of neural degradation would provide greater insight into the effect degeneration has on the motor control indices as well as be more useful in the development of a disease progression

model. Determining if other neurologically damaging conditions cause deviation from the MVC-enslaving proportionality would be worthwhile as well.

A greater understanding of finger coordination in a subset of neurological patients, OPCA, has been achieved and the foundations are laid for future work that can clarify finger coordination in neurological patients even further.

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APPENDIX A: OPCA Patient Information

UPID	Group	Gender	DOB	DOV	Age	On/Off
1	OPCA	F	10/22/50	8/17/11	60	On
2	OPCA	M	3/4/50	8/17/11	60	On
3	OPCA	F	11/28/56	9/21/11	54	On
4	OPCA/PSP	M	6/25/50	9/23/11	60	N/A
5	OPCA	M	6/18/36	9/23/11	75	N/A
6	OPCA	F	4/23/52	12/15/11	59	N/A
7	OPCA	M	8/9/38	12/15/11	73	Off

UPID	Date of Diagnosis	Duration of Illness	Side of Symptom Onset	Weight (lbs)	Handedness
1	1999	12 years	Right Side Tremor	241	R
2	2009	3 years	Wavelike Walking	223	R
3	Lithium Tox 1999	12 years	Gait & Tremors	158	N/A
4	2006	5 years	Balance	228	R
5	N/A	N/A	Gait & Balance	169	L
6	2006	5 years	Balance	214	R
7	2007	4 years	Gait & Falls	183	R

APPENDIX B: MVC Data

OPCA	Hand	I	M	R	L	IMRL
1	R	13	10	9	5	34
1	L	5	6	4	2	17
2	R	29	24	16	20	81
2	L	36	32	13	5	78
3	R	9	9	5	5	21
3	L	0	0	0	0	0
4	R	15	19	17	15	60
4	L	21	17	13	9	59
5	R	23	20	8	8	56
5	L	17	28	11	6	62
6	R	20	17	10	7	53
6	L	14	8	6	7	30
7	R	34	30	13	20	75
7	L	23	15	12	12	61
Right Average		20.43	18.43	11.14	11.43	54.29
Left Average		16.57	15.14	8.43	5.86	43.86
Right Standard Deviation		8.94	7.41	4.38	6.75	21.21
Left Standard Deviation		11.93	11.67	5.13	4.06	28.45

CONTROL	Hand	I	M	R	L	IMRL
1	R	9.3	11.6	15.9	10	42.5
1	L	26	23.4	13	5	58.9
3	R	25	38.7	30	10	105
3	L	56.2	38	25.1	10	126.4
10	R	34.9	23	20.3	30	104.1
10	L	38	22.3	19.9	20	101.5
11	R	15.7	15.9	12.4	10	54.6
11	L	17.5	14.5	16.9	10	58.5
14	R	17	15.9	9.3	10	50
14	L	16	13.3	9.8	6	44
17	R	32.2	39.3	10.7	20	85
17	L	27.6	34.4	14.3	8	82
18	R	30.6	22.7	10.8	10	71.7
18	L	25	23.1	12.6	20	70.6
21	R	20.3	21.5	17.1	15	69.2
21	L	28	17.3	20.2	20	74
24	R	26	25	15	13	83
24	L	31	24	16	12	82
Right Average		23.44	23.73	15.72	14.22	73.90
Left Average		26.53	21.03	14.78	11.10	69.79
Right Standard Deviation		8.51	9.65	6.41	6.83	22.48
Left Standard Deviation		14.66	10.78	6.83	6.97	33.84

APPENDIX C: Ramp and Impulse Data

OPCA	T_{ASA} (s)		$\Delta V_{Z,SS}$		$\Delta\Delta V_Z$		Enslaving	
ID	L	R	L	R	L	R	L	R
1	-0.145	-0.178	2.079	0.577	-0.466	-0.444	1.564	0.600
2	0.000	0.000	1.941	2.875	0.082	0.090	0.896	0.601
3	N/A	0.000	N/A	0.578	N/A	0.234	N/A	N/A
4	-0.110	0.000	2.517	2.098	-0.330	0.104	1.111	1.209
5	-0.145	-0.160	2.700	2.486	-1.108	-0.485	1.299	1.632
6	-0.143	N/A	1.046	N/A	-0.358	N/A	2.026	1.801
7	-0.228	0.000	0.552	0.284	-0.015	0.092	0.645	0.381
Average	0.128	0.056	1.806	1.483	0.366	0.068	1.257	1.037
Standard Deviation	0.074	0.087	0.843	1.131	0.421	0.312	0.493	0.597

Control	T_{ASA} (s)		$\Delta V_{Z,SS}$		$\Delta\Delta V_Z$		Enslaving	
ID	L	R	L	R	L	R	L	R
11	-0.398	-0.138	3.441	1.654	-1.829	-0.251	0.800	1.100
14	-0.148	-0.348	2.279	1.857	-0.628	-0.856	1.080	0.890
17	-0.368	-0.278	3.082	2.493	-1.061	-0.347	1.060	1.090
18	-0.338	-0.353	2.776	2.008	-0.239	-0.571	0.770	0.340
24	-0.214	-0.240	2.510	2.143	-0.650	-0.518	0.650	0.550
8	-0.275	-0.090	1.503	1.999	-0.546	-0.620	0.200	0.580
10	-0.298	-0.395	2.485	3.039	-0.840	-1.144	1.110	0.990
Average	0.291	0.263	2.582	2.170	0.827	0.615	0.810	0.791
Standard Deviation	0.088	0.115	0.619	0.462	0.509	0.304	0.323	0.300

ACADEMIC VITA
of T. DOUGLAS SALLADE

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Pennsylvania Furnace, PA, 16865

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814 – 441 – 1205

Education:

Bachelor of Science Degree in Bioengineering, *The Pennsylvania State University*
The Schreyer Honors College, *The Pennsylvania State University*
Honors in Bioengineering

Thesis:

Title: Finger Coordination in Neurological Patients
Supervisor: Mark Latash, *Distinguished Professor of Kinesiology*
Advisor: Peter Butler, *Assistant Professor of Bioengineering*

Work Experience:

Thesis Research — Kinesiology Department, *The Pennsylvania State University*
Neurology Department, *Milton S. Hershey Medical Center*

Description: Examining atypical force production; olivopontocerebellar atrophy patients
Supervisor: Mark Latash, *Distinguished Professor of Kinesiology*
Date(s): May 2011 to May 2012

Teaching Assistant — Biology Department, *The Pennsylvania State University*

Description: Teaching Assistant for Mammalian Anatomy. Directed lab of 24 students.
Supervisor: John Waters, *Lecturer*
Date(s): January 2011 to May 2012

Intern — Applied Research Lab, *The Pennsylvania State University*

Description: MATLAB programming of vehicular environments for visualization.
Supervisor: Andrew Hoskins, *Research and Development Engineer*
Date(s): May 2010 to August 2010

Intern — Engineering Science Department, *The Pennsylvania State University*

Description: Ultrasonic, non-destructive evaluation of concrete. Sponsored by PennDOT.
Supervisor: Joseph Rose, *Paul Morrow Professor of Engineering Science and Mechanics*
Date(s): May 2009 to August 2009

Design Projects:

Team Leader — Bioengineering Senior Design, *The Pennsylvania State University*

Description: Directed construction of MRI Compatible SCR Device for SLEIC.
Supervisor: Margaret Slattery, *Assistant Professor of Bioengineering*
Date(s): January 2012 to May 2012

Software Developer — Bioengineering Junior Design, *The Pennsylvania State University*

Description: Labview program calculating HR & blood oxygenation for pulse oximeter.
Supervisor: Peter Butler, *Associate Professor of Bioengineering*
Date(s): January 2011 to May 2011

Activities:

Investigator — Anatomy Lab, *Mohawk Valley Community College*

Description: Guided observation and dissection of cadavers.
Supervisor: Bill Perrotti, *Professor of Anatomy and Physiology*
Date(s): August 2011, March 2012

Delegate — Undergraduate Curriculum Committee, *The Bioengineering Department at PSU*

Description: Discuss potential problems with, and changes to, bioengineering curriculum.
Supervisor: Margaret Slattery, *Assistant Professor of Bioengineering*
Date(s): September 2011 to May 2012

Volunteer — *Teach For America*

Description: Informed students & clubs, about education inequality and need for teachers.
Supervisor: Jeremy Corbett, *Recruitment Coordinator*
Date(s): September 2011 to December 2011

Member — Student Council, *The Schreyer Honors College*

Description: Director of homecoming float design, coordinator of construction.
Supervisor: Jenny Blew, *Faculty Advisor*
Date(s): September 2010 to May 2012