EFFECTS OF TACTILE AND PROPRIOCEPTIVE FEEDBACK ON MANUAL FUNCTION IN PATIENTS WITH TYPE II DIABETES

A Thesis

Presented to

The Faculty of the Department

Of Health and Human Performance

University of Houston

In Partial Fulfillment

Of the Requirements for the Degree of

Master of Science

By

Nereyda Ochoa

August 2015

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ABSTRACT

Control of manual function requires optimal integration of sensory and motor systems. Pathology to either of these systems may lead to sub-optimal object manipulation. A growing body of literature has identified changes to sensory function in individuals with Type II Diabetes (T2D); however, the impact of the disease on the motor system has not been thoroughly investigated. The purpose of this study is to evaluate the effects of tactile and proprioceptive feedback on manual function in patients with T2D compared to age- and sex-match control subjects. Both groups of participants will have sensory deficits induced through median nerve block at the wrist (treatment 1) and at the elbow (treatment 2). This method allows for safe and effective temporary removal of tactile sensation distal to the wrist (treatment1) and tactile and proprioceptive sensations distal to the elbow (treatment 2). If sensory deficits due to neuropathy in T2D are the sole contributors to changes in manual function in T2D, then both groups should display equal reduction in manual motor function. If, however, another physiological mechanism is responsible for said motor changes than it can be expected that the T2D group will display greater reductions in manual motor performance than the control group. Overall, tactile sensation measurements suggested differences between the T2D group and the healthy cohort; however, tactile sensation in the T2D group at baseline was found to be equivalent to tactile function of the control group in the anesthesia conditions. Clinical assessment of gross motor movements suggested the sensory system as the primary component responsible for sensorimotor changes, while tasks of fine motor movement indicated another component to be responsible for changes other than those produced by the sensory system. More sensitive kinetic testing also reveals that

another system is at play causing sensorimotor changes, this system however is unknown and further research is required to identify this key component.

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CHAPTER I

PROBLEM STATEMENT

1.1 Introduction

In daily interactions, tactile sensation provides important details ranging from personal safety to intimate touch. An individual's association with the external environment relies on sensory and motor cues that if missing, may generate a significant threat for day-to-day activities. An important link for these interactions is the human hand. The fingertips on the hand provide information from the periphery to the Central Nervous System to initiate or modify motor activities in a given situation. Research suggests that hand grip strength is primarily controlled by feed-forward mechanisms, in which the CNS responds to a stimuli with a general neural pattern. The pattern is continually updated to accommodate task demands and environmental changes through the use of afferent feedback such as vision, tactile sensation, and proprioception (Augurelle et al. 2000, Johansson.2002, Nowak et al. 2003). Damage to these structures, as in Diabetic Peripheral Neuropathy or any sensory neuropathy, can lead to miscommunication between afferent messages and efferent brain commands.

Diabetic Peripheral Neuropathy, DPN, can develop in both Type I (T1D) and Type II Diabetes (T2D). Although its cause is unknown, some researchers believe that it may be due to poor glucose management especially hyperglycemia, or excess glucose in the bloodstream (Valensi 1997, Vinik 2011). Symptoms associated with DPN include numbness, tingling, pain, decrease in muscle strength and decrease in sensation expressed in the distal extremities (Vinik 2011). Recent studies suggest that motor function and manual dexterity are also

impaired in both T1D and T2D; where the degree of impairment may correlate with the severity of neuropathy (Casanova et al. 1991). Specifically, patients with T2D produce significantly less force during maximal grip force production tasks than healthy control participants (Cetinus et al. 2005). Adults with T2D were also found to perform worse than non-diabetics in fine finger movement tasks and mimic daily hand activities; however, appropriate age-matching protocols were not performed in those studies, thereby introducing natural aging as a confounding factor in diabetic hand function (Pfutzner et al. 2011). To control for the effect of aging, additional studies subsequently indicated that adults with T2D did exhibit T2D-related differences in basic hand function during maximal and submaximal force production tasks but not in the widely used clinical evaluation tools for assessing hand function (Gorniak et al. 2014; Ochoa & Gorniak 2014). The changes in maximal force exhibited by the T2D group did not correlate with changes in sensory function or disease severity; whereas changes in submaximal force production did correlate with poorer sensory function in the T2D group (Gorniak et al. 2014; Ochoa & Gorniak 2014). Together, these results suggest that sensory deficits are not the sole contributor to abnormal force production in T2D.

Investigations regarding the role of sensory function with respect to manual dexterity have been ongoing in the field of motor control. Specifically, decreased tactile sensation in the fingertips of healthy individuals has been simulated by use of local anesthesia to investigate the effect of cutaneous feedback on force production during manual tasks. Although visual afferents are primarily responsible for retrieving appropriate neural patterns for manipulative tasks tactile feedback is crucial for continual and efficient object manipulation. In the absence of visual feedback, a secondary system must provide

information pertaining to interactions with the environment. Mechanoreceptors distributed throughout the hand, chiefly in the fingertips, respond to mechanical disturbances on the glabrous, hairless, surfaces of the hand (Lofvenberg 1983, Johansson et al. 1984, 1992, 1993, 1998, 2009). The high density of mechanoreceptors provide information pertaining to frictional contact between objects and the human hand, object shape, and object weight, all of which are essential for updating prehension control by the CNS. In individuals with impaired cutaneous sensibility, this information is lost and the brain lacks the ability to plan and executive motor functions (Johansson et al. 2009).

Previous work has provided evidence of the importance of cutaneous afferent information for motor control of the human hand. In the majority of these studies, proprioception and tactile function of the hand was preserved while the tactile function of the fingertips was temporarily diminished (Johansson et al. 1992, 2002, Augurelle et al. 2003, Shim et al. 2012, Nowak et al. 2013). These temporary sensory deficits were achieved primarily through subcutaneous injection of anesthesia at the metacarpophalangeal joints to fingers 2 – 5 of the hand, also known as a "ring block" of the digits. Early on, Augurelle and colleagues used a ring block to identify significant decreases in grip force production during static and dynamic tests by healthy participants (Augruelle et al. 2003). Other groups have shown that maximum voluntary force in single- and multi-digit tasks decreases significantly after application of anesthesia via ring blocks to digits 2-5 (Shim et al. 2012).

The previously mentioned work in healthy populations suggests that altered force production in healthy control subjects is due to diminished cutaneous sensory feedback of the fingertips. These findings are in contrast to recent evidence indicating that diminished sensory function alone may not account for motor function changes in the hand in the

presence of a systemic metabolic disorder (e.g. T2D). In order to better understand how actions of the hands are controlled in the presence of systemic neural damage, more work is needed to understand the contribution of sensory (tactile and proprioceptive) function to hand function.

1.2 Problem Statement

In light of this gap, the goal of this project is to elucidate the contribution of sensory feedback to manual dysfunction in individuals with T2D as compared to healthy age- and sex-matched controls. This will be achieved by mimicking the effects of tactile and proprioceptive deficits in both adults with T2D and healthy age- and sex-matched control participants via the use of subcutaneous anesthesia. Anesthetization will occur by injection of a local anesthetic at two locations. The first injection, median nerve block at the wrist, will be used to temporarily yet safely remove tactile sensation while preserving proprioception of the portions of hand and forearm innervated by the median nerve. The second injection, median nerve block at the elbow, will be used to temporarily yet safely remove tactile and proprioceptive feedback to the portions of the hand and forearm innervated by the median nerve.

1.3 Specific Aim & Hypothesis

Specific Aim: To evaluate the contribution of tactile and proprioceptive feedback on hand motor function in patients with T2D as compared to healthy age- and sex-matched controls.

Primary Hypothesis: At baseline, patients with T2D will exhibit similar motor behaviors compared to control participants under both anesthetized conditions.

Alternate Hypothesis: At baseline, patients with T2D will exhibit different motor behaviors compared to control participants under either or both of the anesthetized conditions.

Rationale: If diabetic neuropathy affecting tactile function is the primary deficit in T2D affecting hand function, anesthetization of both the T2D group and healthy group will reveal equivalent motor behavior deficits upon temporary removal of tactile and proprioceptive functions. In this case, consistent with our previous studies (Gorniak et al. 2014; Ochoa & Gorniak 2014), the T2D and healthy control groups will still exhibit differences in motor behavior at the pre-anesthetization evaluation; however, these differences will be reduced in the control group with anesthesia. In contrast, if deficits in manual motor behavior with T2D are primarily influenced by physiological mechanisms not related to sensory function (i.e. central control), then the T2D group will produce significantly altered motor behaviors in both the pre-anesthetization and anesthetization portions of this study.

CHAPTER II

BACKGROUND AND LITERATURE REVIEW

2.1 Diabetes: The Disease

Diabetes Mellitus is a metabolic disorder caused by dysfunction of circulating insulin or insufficient insulin production by the pancreas. Diabetes affects 347 million worldwide with 25.8 million people residing in the United States; it is the seventh leading cause of death in the USA (CDC 2011, WHO 2013). The cost of management of the disease was reported to be approximately $174 billion in 2007 with $116 billion related to direct medical expenses and the remaining $58 billion due to indirect costs (CDC 2011). Currently, three types of diabetes exist and are used for diagnostic purposes: Type I, Type II, and Gestational Diabetes. Type I diabetes is caused by insufficient insulin production by the pancreas and may also be known as “juvenile, childhood, or insulin dependent diabetes.” Individuals with Type I Diabetes require daily insulin administration in order to maintain appropriate levels of insulin for the body to use. Insulin is a hormone that regulates circulating blood sugar by providing necessary transport for glucose into the cell. Contrary to Type I Diabetes, in Type II Diabetes, T2D, the pancreas produces an adequate amount of insulin however it is dysfunctional and the body is not able to utilize it. T2D is also known as “non-insulin or adult onset diabetes.” Gestational diabetes has an onset at pregnancy and persists only throughout the 40 weeks of gestation. This type of diabetes shares similar symptoms to Type I and T2D. The focus of this thesis will be on T2D.

T2D is caused by an excessive amount of circulating blood sugar or hyperglycemia resulting in the insensitivity of insulin by insulin receptors located on the cell surface (Tripathy et al. 2010, Ginter et al. 2012). Insulin resistance threatens cell survival,

metabolism, and neuronal plasticity (Ginter et al. 2012). Ginter et al. suggests that diseases of peripheral insulin resistance such as T2D can result in insulin resistance in the brain (Ginter et al. 2012). T2D may be diagnosed at any age. Given the comorbidities, this disease can be exceptionally detrimental during old age (Kaylani et al. 2013) and result in loss of independence and decreased quality of life. Symptoms associated with the disease range from excessive thirst and urination to weight loss, fatigue, and loss of muscle mass (WHO 2013, Kaylani et al. 2013). Macrovascular diseases associated with T2D include cardiovascular disease, hypertension, and stroke. Microvascular diseases associated with T2D are foot ulcerations, gangrene, and amputations (Ginter 2012, Vinik 2011, Kaylani 2013). T2D impacts the Peripheral Nervous System via autonomic, sensory, and motor neuropathies (Zochodne 2007, CDC 2011, Vinik 2011). Risk factors for this disease include genetics, smoking, alcohol consumption, obesity, and the normal aging process (Ginter et al. 2012, Vinik 2011, Kaylani et al. 2013).

Obesity and excessive regional visceral adiposity are strongly associated with the prevalence of T2D; the surplus of glucose due to overeating results in metabolic stress and low grade inflammatory response known as “metaflammation” (Ginter et al. 2012). Currently, obesity is considered the most important cause of T2D (Ginter et al. 2012). The natural aging process also results in decreases in insulin efficiency. Kaylani and colleagues (2013) have suggested that this decrease in functionality could be due to increased abdominal fat mass, decreased physical activity, sarcopenia, mitochondrial dysfunction, hormonal changes, and increased oxidative stress all concurrently occurring with advanced age (Kaylani et al. 2013). The convergence of these factors and physiological changes due to T2D may result in decreased quality of life. Some of the previously stated risk factors can be

managed through lifestyle changes albeit others such as genetics and aging are out of the individual's control

2.1.1. Diabetes and the Peripheral Nervous System.

Diabetic Neuropathy (DN) is a progressive neurodegenerative complication associated with T2D. Two distinct theories are posed by Zochodne (2007) to explain the progression of neuronal degeneration of the disease. The first theory is characterized by a "dying back" of neurons that initiates at the axons and progressively degrades until the cell body is reached and decomposed. The second theory consists of neuronal degradation that occurs simultaneously at both the axon and cell body until the cell has withered and is no longer functional (Zochodne et al. 2007).Valls-Canals and colleagues (2002) suggest that neuronal degeneration in DN is due to a combination of both dymyelination and axonal retraction that occur concurrently, yet independent of each other (Valls-Canals et al. 2002). Furthermore, they suggest that the demyelination process occurs prior to axonal loss and may or may not present with symptomatic neuropathy; axonal loss is the primarily responsible for the associated symptoms (Valls-Canals et al. 2002). This damage to the Peripheral Nervous System (PNS) can be localized as in mononeuropathy or widespread as in polyneuropathy (Zochodne et al. 2007).

Prevalence of DN has not been accurately assessed due to lack of awareness. Failure to seek medical attention may be due in part to the gradual onset of neuropathic symptoms, as well as perception of limb function. Casanova and colleagues states that often individuals with T2D generally perceive their hand function to be better than the actual performance of the hand (Casanova et al. 1991). Additionally, diagnosing neuropathy in the upper

extremities can be confounded and difficult due to compounding diseases such as Ulnar Neuropathy at the elbow (UNE) and Carpal Tunnel Syndrome (CTS) (Zochodne et al. 2007). Due to these comorbidities, DN is commonly misdiagnosed. DN presents with an array of symptoms such as pain, paresthesia, pin-pricks, tingling, numbness, and ulcerations to the distal extremities (Vinik 2011). Allodynia, pain caused by mechanical disturbances to the body is especially worsened at night by weight of bed covers, can significantly alter quality of life, emotional, and mental wellness (Vinik 2011, Zochodne et al. 2007)

DN targets sensory and motor nerve fibers throughout the body. Large diameter nerve fibers have thick myelination and allow for rapid propagation of action potentials. Small diameter nerve fibers are thinly myelinated or lack myelination resulting in slower conduction of action potentials (Kandel et al. 2013). Excitability of the cell is directly associated with diameter of nerve fiber; small-diameter conduction velocities may be as small as 1 m/s compared to conduction velocities of large-diameter nerve fibers of approximately 120 m/s. Currently, testing of nerve conduction velocity (NCV) is used as a diagnostic tool for identifying neuropathic symptoms and differentiating between mononeuropathy and polyneuropathy. NCV evaluations may provide a link to the location of the damage and to structures affected by the disease. Loss of NCV is estimated to occur at a rate of approximately 1 m/sec/year. Vinik suggests that at diagnosis, patients with T2D already have symptoms of slowing nerve conduction velocities and the degree of damage is correlated with disease duration of diabetes (Vinik 2011).

Another gold standard for neurophysiological testing used in conjunction with NCV is assessment of the Sensory Nerve Action Potential (SNAP). This test is commonly administered behind the heel to evaluate function of the Sural nerve; however, it can be used

for evaluation of nerves throughout the body. Degradation of axonal integrity is suggested if presented with more significant decreases in SNAP than decreases in NCV (Zochodne et al. 2007). Taken together, NCV decreases suggest primary demyelination and abnormal amplitude during SNAP suggest axonal damage.

Physiological changes concurrent with the progression of diabetes result in local syndromes of the upper extremities such as (CTS) and (UNE). CTS is a compressional mononeuropathy, resulting from median nerve entrapment at the wrist. CTS is diagnosed by physicians through sensory testing in areas of median nerve innervation. Most commonly, CTS is diagnosed after observation of a reduced conduction velocity during NCV assessment. Presentation of CTS includes sensory losses in the hands include pain, and paresthesia especially in digits 1-4 (Papanos et al. 2008, Somaiah et al. 2008). In some cases CTS, will also present with reduced NCV in the median nerve (Papanos et al. 2008). Chronic CTS commonly results in muscle weakness (Papanos et al. 2008, Zochodne et al. 2007, Somaiah et al. 2008). Severity of CTS is also associated with age and duration of diabetes if diagnosis of diabetes is present (Papanos et al. 2008, Zochodne et al. 2007).

UNE is another mononeuropathic syndrome caused by ischemia or compression of the ulnar nerve. Sensory dysfunctions associated with UNE include paresthesia at digit 4 and 5 and at the medial border of the hand, low amplitude SNAP, and reduced NCV (Boulton et al 2004). Motor deficits include muscle wasting of the hypothenar and weakness of intrinsic muscles innervated by the ulnar nerve (Boulton et al. 2004, Papanos et al. 2008, Zochodne et al. 2007). UNE can be a late complication of T2D. Both sensory and motor deficits significantly affect the quality of life in individuals with T2D and are main targets for future research (Nowak et al. 2003, Cetinus et al. 2005, Zochodne et al. 2007, Papanos et al. 2008,

Melchior et al. 2009, Vinik et al. 2011, Ginter et al. 2012, Allen, M.D., Kimpinski, K., Doherty, T.J., et al. (2013b.), de Freitas et al. 2013, Gorniak et al, 2014).

2.1.2. Sensory Function and Diabetes

2.1.2a. Physiology of Normal Hands during Object Manipulation

Functionality of the hand determines how humans interact with the environment. Although sensory feedback is important for maintaining object manipulation, the primary control behind manual action works in a feed-forward manner (Johansson et al. 2002, Kendel et al. 2013, Nowak et al. 2003, Witney et al. 2000, Melchior et al. 2009). Object manipulation begins by observation of the object, for example a coffee cup's properties such apparent weight, size, shape, and external forces that will concurrently act on the cup (Johansson et al. 2002, Mackenzie & Iberall. 1994). If the visual system is dysfunctional an alternative sensory system will provide pertinent information regarding interactions with the environment. The CNS retrieves a neural representation known as an internal model that is based on previously observed properties to grip the coffee cup. This is known as use of Anticipatory Control Parameters (APC) (Johansson et al. 2002). APC's are determined based on upon prior experiences under similar conditions and with similar objects. This message termed an "efference copy," is sent to the cerebellum to monitor the expected outcome and the actual outcome (Johansson et al. 1992, Manto et al. 2012). This model is continuously updated through tactile feedback and moment-by-moment comparison of the intended response with the actual response during initial contact with the cup (Johansson et al. 2002, Mackenzie & Iberall. 1994). Discrete Sensory Driven Control (DESC) is the mismatch between intended and actual movements based on tactile and proprioceptive

feedback via mechanoreceptors in the hand (Johansson et al. 1984, 1992, 1993, 1998, 2004, 2009). As little as one trial or update by the DESC is required for a new APC to be generated and stored for later use. Mechanoreceptors in the periphery, particularly the fingertips send information to the cerebellum for corrective action (Lofvenburg et al 1983, Johansson et al. 1984, 1992, 1993, 1998, 2004, 2009, Manto et al. 2012). Interactions between APC and DESC are essential for conducting movements in the absences of visual feedback. An APC can be retrieved and used based on the tactile properties of the object (Johansson et al. 2002, Witney et al. 2000).

Mechanoreceptors in the fingertips vary by function, size, and density within the skin of the hand. Meisner's Corpuscles are mechanoreceptors associated with large nerve fibers that respond to light touch, and perturbations of the skin surface at high frequencies and are insensitive to static force (Figure 1) (Johansson et al. 2009, Vinik 2011). Merkel cells lie just deeper to the Meissner's Corpuscle (see Figure 1) and are stimulated by edges, points, or shear forces (Kandel et al.2013). Ruffini endings are deeper than Merkel cells (see Figure 1) and are responsive to vibration, static force, and stretch on the surface of the skin; these mechanoreceptors are also associated with large nerve fibers (Johansson et al. 2009, Vinik 2011). The Pacinian Corpuscles lie deepest in the dermis of the skin (see Figure 1), are associated with large nerve fibers, and are responsive to vibration of 40-400 Hz and static force. Nociceptors and thermoreceptors are dispersed throughout the dermis and are both associated with small nerve fibers as they are responsive to pain and temperature (hot/cold), respectively (Vinik 2011).

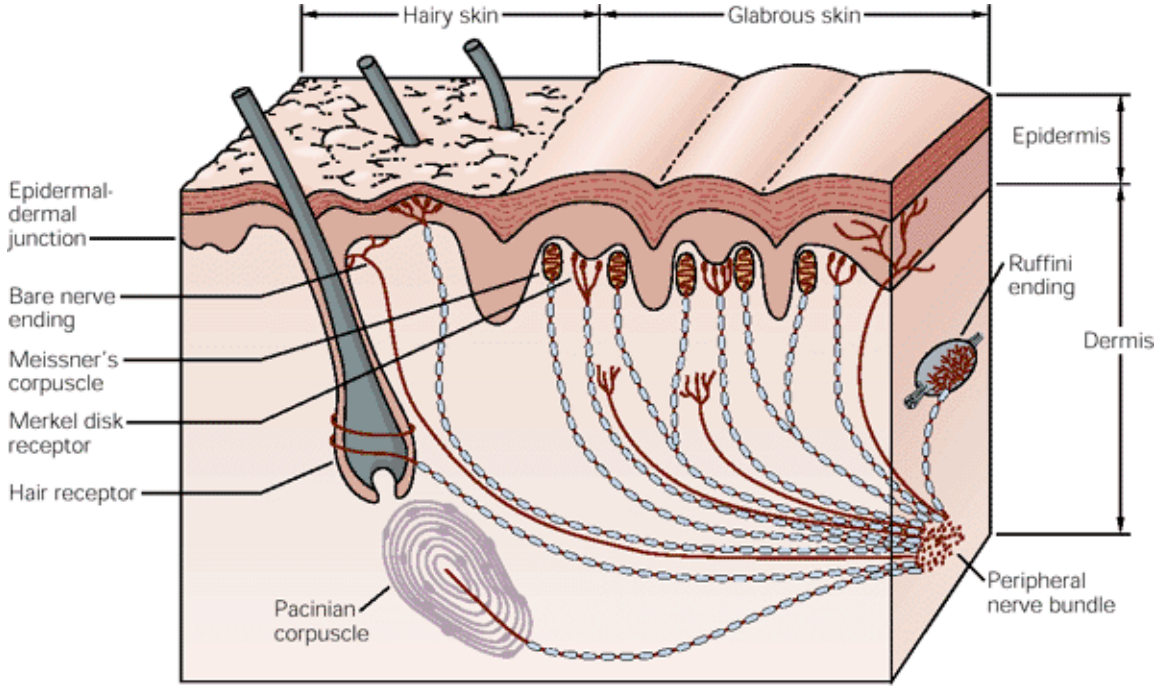

Figure 1. Mechanoreceptors in the glabrous and hairy skin that provide afferent feedback regarding the current state. In order from superficial to deepest Meissner's Corpuscle, Merkel Cells, Ruffini Endings, and Pacinian Corpuscle. Adapted from Kandel et al. 2013.

Furthermore, functional classifications of the mechanoreceptors have been established to describe the role of each as fast- acting or slow-acting, during object manipulation (Johansson 2009, Kandel et al. 2013). Fast- acting type I (FA-I) and slow-adapting type I (SA-I) lie superficially within the dermis of the skin and are densely located in the fingertips of the hand. Meissner's Corpuscles are FA-I and Merkel Disk are SA-I (Figure 2). Fast- acting type II (FA-II) and slow-acting II (SA-II) lie deeper in the dermis of the hand and are uniformly distributed through the palmar surface (Figure 2). Pacinian Corpuscles are classified as FA-II and Ruffini- Endings are SA-II (Figure 2).

Fast-acting fibers are also known as Rapidly-adapting fibers (RA-I or RA-II), these classifications are used interchangeable and the naming varies depending on the literary source. These mechanoreceptors are critical for encoding information about the environment

such as object weight, shape, and surface friction (Johansson et al. 1984, 1992, 1993, 1998, 2004, 2009). If the hand reaches for an object that has a slippery surface, such as a water bottle with condensation around the exterior, FA-I/ RA-I fibers will be strongly activated in response to the frictional change (Johansson et al. 2009). This suggests that FA-I/ RA-I fibers are most important during initial contact between the fingertips and the surface of objects (Johansson et al. 2009) and that they are more responsive during manipulations that involve slipperier surfaces, lower coefficients of friction. Control of grip is dependent on contact between fingertip and object, resulting in changes in force production that vary with each individual lift. During these modifications of grip force the amount of force produced is independent between of the digits (Johansson et al. 1994). Object shape contributes to the firing rates of FA-I/ RA-I, SA-I, and SA-II fibers that are distributed throughout the fingertips of the hand. Furthermore, SA-II are more responsive to objects that have coarse properties and are curved in shape (Johansson et al.2009).

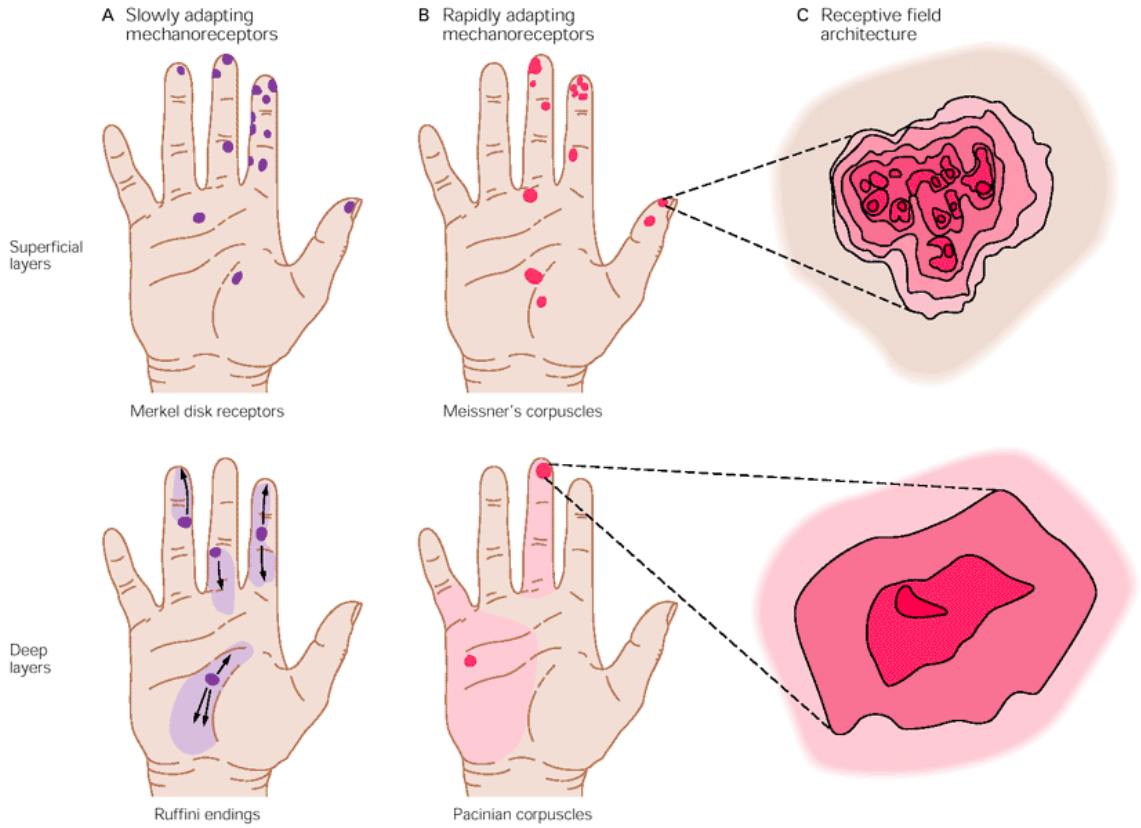

Figure 2. Mechanoreceptor distribution within the plantar surface of the hand. Slow-adapting fibers Merkel Disks (SA-I) and Ruffini Endings (SA-II). Fast-adapting fibers Meissner's Corpuscle (FA-I/RA-I) and Pacinian corpuscle (FA-II/RA-II). Adapted from Johansson and Vallbo 1983.

2.1.2b Abnormal Sensory Function of the Hands

Progression of typical sensory deficits is explained by a "glove- and – stocking pattern" where the distal extremities have more deterioration than the proximal areas of the body (Rothwell et al. 1982, Kandel et al. 2013). The physiological explanation for this pattern is that the distal portions of the nerve endings are the farthest from the neuronal cell bodies and therefore the most susceptible to damage (Kandel et al 2013). Research suggests that individuals with impaired sensory function will perform tasks requiring fine grip and manual dexterity more slowly and with greater difficulty (Melchior et al. 2009). Holding a

cup and writing are still manageable despite losses in sensory function; however, buttoning a shirt, picking up coins and other fine manipulations remain extremely challenging (Rothwell 1982) suggesting dysfunction of a motor component occurring concurrently with loss of sensory function. Sensory perception is also altered in individuals with sensory impairments. Diminished vibratory perception is associated with dysfunction of large nerve fibers; this clinical finding is a gold standard sign for diagnosis of large fiber peripheral DM neuropathy (Dahlin et al. 2008). Loss of cutaneous feedback and its effect on motor performance in individuals with T2D has begun to be established in the literature (Casanova et al 1991, Neeling et al 19966, Walk et al 2003, Capellari et al 2005, Cetinus et al 2005, Andersen et al 2006, Dahlin et al 2008, Cederlund et al 2009, Papanos et al 2011, de Freitas et al 2013, Gorniak et al 2014).

Dysfunction of the small and large sensory nerve fibers has become paramount in identifying the effects of DM on the motor system. Small fiber dysfunction has been suggested to be the earliest sign of neuropathic symptoms (Walk et al 2003, Capellari et al 2005, Papanos et al 2011, Gorniak et al. 2014, Ochoa & Gorniak 2014.). Such dysfunction is attributed to prolonged abnormalities of glucose homeostasis that cause physiological changes to nerve fibers (Capellari et al 2005). Small nerve fibers are more susceptible to damage due to their lack or limited amount of myelination and their propensity to osmotic damage caused by hyperglycemia. Large amounts of myelin in large- nerve fibers are suggested to be used as a protective barrier against such damage (Papanos et al 2011). Hyperglycemia has been implicated in causing impaired blood flow to the distal tissues resulting in tissue hypoxia (Papanos et al. 2011) and impaired sensory and motor functions in T2D.

An early study by Rothwell investigated the case of a male, G.O., whom developed peripheral deafferentation secondary to an influenza-like illness (Rothwell et al. 1982). This was the first time researchers were able to investigate the role of diminished sensory function on motor actions. In this case, the man had difficulty conducting fine motor tasks such as buttoning his shirt and holding a pencil; however, his motor skills were minimally affected provided that some form of feedback, such as visual feedback, was present (Rothwell 1982). Additionally, G.O was unable to maintain a constant force output for an extended period of time. (Rothwell et al.1982). During tasks that required G.O to maintain constant force production, such as holding a pencil or cup, visual feedback was required to reassure him that he was still grasping object. After some time visual feedback was insufficient because this feedback did not provide information pertaining to the pressure being applied on the object. Lack of tactile feedback resulted in objects slipping or excessive force application on the objects which may have contributed to his difficulty in writing tasks. Physiological examinations of G.O. suggested a decrease in motor unit activation of the Abductor Pollcis Brevis and the Extensor Digitorum Brevis muscles; however, the shape and size of the individual potentials were conserved from these muscles. Median and ulnar nerve sensory nerve action potentials (SNAP) were concurrently reduced.

2.1.3. Hand Function and Diabetes

If tactile perception is disturbed, as is the case with individuals with sensory deficits, object manipulation may be compromised. Sensory deficits obtained by anesthesia in healthy controls have resulted in decreases in grip forces (Augurelle 2002) and increases in grip forces (Nowak et al. 2003) alike; thus the influence of sensory deficits to motor function

remain ambiguous. In motor tasks involving grasping objects, groups with diminished sensory feedback produce less amounts of force during testing (Nowak et al. 2003, Augurelle et al. 2003, Shim et al. 2012, de Freitas 2013). An inability to provide an adequate amount of force by the individual on a handheld object results in the slippage of the object (Augurelle et al. 2003), posing safety risks and threatening independent living.

Safety risks can threaten independent living and should be maintained at a minimum. During object manipulation, the safety margin describes the minimum amount of force required to just exceed the slip ratio and prevent object slippage (Augurelle et al. 2002). At the extremes, safety margin may be dangerous. A low safety margin may cause an object to slip out the hand while a large safety margin may induce crushing of the object and/or muscle fatigue (Gorniak et al. 2010, 2011). Individuals with T2D produce stable grip forces and maintain a lower safety margins during grasping task as compared to healthy controls (de Freitas et al. 2013).

In populations with impaired sensation due to anesthetization of the digits, the results are inconclusive. Augurelle's work suggests that sensory deficits result in lower grip force production and lead to object slipping (Augurelle 2002). Contrary to these findings, Nowak suggests that impaired sensation of the digits increases the amount of grip force exerted and increases the safety margin resulting in stable maintenance of the object (Nowak 2003). Both of these conclusions were reached based on tasks involving both static and dynamic components as well as before and after digital anesthesia, although the anesthetic method varied. The age range in these studies is also variable, leading to the discrepancies and inconclusive results.

While the sensory system is suggested to be the primary target during hyperglycemia, evidence is emerging that the motor system may also be affected. The motor system is more resilient to hyperglycemic- associated physiological changes than is the sensory system (Li et al 2004). Evidence of functional dexterity and muscle force production in patients with T2D to date has been contradictive and inconclusive at best (Casanova et al 1991, Cetinus et al 2005, Cederlund et al 2009, Andersen et al 2012, de Freitas et al 2013, Gorniak et al 2014). Decreases in sensory function and tactile afferents have been identified as a source of manual dysfunction in T2D; however this alone may not be the sole cause of the physiological changes in the diabetic hand (Gorniak et al 2014, Ochoa & Gorniak 2014).

Similar to sensory dysfunction, dysfunction of the motor system occurs in a distal to proximal fashion. Motor dysfunction is primarily associated with muscle weakness and muscle atrophy (Allen, M.D., Choi, I.H., Kimpinski, K. et al. (2013a), Allen, M.D., Kimpinski, K., Doherty, T.J., et al. (2013b.). A motor unit is the functional unit of motor control, it involves a motor neuron and all the muscle fibers it innervates. The amount of innervation fibers is dependent upon the type of muscle. A study by Allen et al. provided evidence that individuals with T2D provide approximately 60% less force than their matched control group. These results imply that the amount of denervation in T2D is greater than the naturally occurring collateral reinnervation (Allen 2013). The distal axonal retraction of α-motor neurons results in greater rate of denervation of the muscle fibers than the rate of compensatory reinnervation by neighboring motor neurons (Allen 2013). This process results in a decrease in Motor Unit Number Estimates (MUNE) and concurrent decrease in motor unit firing rate in individuals with T2D. Such changes in motor unit numbers and characteristics were associated with age and disease duration (Allen 2013).

In an earlier study, Casanova et al. evaluated manual dexterity using the Purdue Pegboard Test, O'Connor Tweezer Test, and the Smith Hand Function Test. The results from this work suggest longer time to completion during these tests, with the exception of the zipper and block components, for T2D compared with healthy controls (Casanova et al. 1991). The scores for the zipper and block tests were comparable to the healthy controls suggesting dysfunction of fine motor movement but not gross motor tasks (Casanova et al 1991). Accordingly, Gorniak et al. used the Purdue Pegboard test to evaluate manual changes in T2D and identified abnormal function only in the assembly building portion of this test; the remainder of evaluation components within the Purdue Pegboard Test were non-significant (Gorniak et al. 2014). Additionally, Gorniak et al did not find a significant difference during assessment of manual dexterity via the Jebsen-Taylor Hand Function test for T2D versus age-and sex- match controls (Gorniak et al 2014). Similarly, de Freitas et al. did not see any significant differences in manual dexterity in a group of T2D compared with age- and sexed- matched controls when evaluated with the Jebsen Taylor Hand Function test or the 9-Hole Peg test (de Freitas et al 2013).

Further testing on hand function has been evaluated by testing maximal force production (Cetinus et al 2005, Cederlund et al 2009, Andersen et al 2011, de Freitas et al. 2013, Gorniak et al 2014, Ochoa & Gorniak 2014). Andersen et al. classified motor dysfunction as muscle weakness and atrophy in the distal extremities caused by diabetic neuropathy. It was concluded that upper extremity muscle strength was preserved but lower extremities presented with decreases in muscle strength at the knee and ankle (Andersen et al 2011). Later studies have presented similar results that indicate that the T2D group does not present with changes in manual force production as compared with the respective controls

groups (Cederlund et al 2009, de Freitas et al 2013). Contrary to these findings, evidence has been presented to suggest that grip strength (Cetinus et al 2005, Gorniak et al 2014) but not pinch strength is diminished (Gorniak et al 2014, Ochoa & Gorniak 2014) with T2D.

The case study of the deafferented man described by Rothwell et al, identifies the inability to maintain constant force production with the upper extremities, particularly the hands, throughout a tracking test by subject G.O. due to the neuropathic symptoms (Rothwell et al. 1982). Recent work has evaluated the effect of sensory deficits in T2D using a similar force tracking task. Results from these studies indicate larger force production errors and reduced signal complexity (Gorniak et al. 2014) with T2D. These changes seem not be associated with disease severity or presence of neuropathy in T2D patients. Differences in tracking test results may be due to severity of muscular system involvement. Rothwell et al. suggest that subjects in tracking tests experiencing upper extremity anesthesia are able to maintain constant force production, unlike G.O, because anesthesia does not seem to affect the efficiency of the muscle spindles or Golgi Tendon Organs, which lie in the muscles compared to subcutaneously anesthetized features (Rothwell et al 1982).

2.1.4 Digital Anesthesia

Research groups have identified techniques to imitate conditions such as sensory and motor deficits. Popular techniques include nerve blocks along the forearms, wrists, or single digits via ischemia, digital cooling, and injection of anesthesia (Shim et al 2012, Reilly et al 2008, Augurelle et al 2003, Nowak et al 2003, Li et al 2004, de Freitas et al 2013). Digital cooling has been established using ethyl chloride during dynamic and static gripping tasks (Nowak 2003). Ethyl chloride was applied to the palmar surface of the hand and the effect

lasted approximately two minutes, reapplication was necessary after every trial. Application of the topical agents was halted when sensory deficits had been established by loss of sensation to pin-prick, touch, and squeezing. Digital cooling does not result in changes to surface friction or proprioception (Nowak 2003).

Temporary sensory blocking of the hand via ischemic block has also been highlighted as a method to alter sensory function. In this method, the block is achieved through the application of a sphygmomanometer to the upper extremity. This action impairs perfusion of the extremity distal to the cuff. The ischemia method has been used to assess selectivity of finger flexion (Reilly et al. 2008). This study required inflation of the blood pressure cuff at the wrist to approximately 200 mmHg. Loss of tactile sensation was evaluated through Von Frey Filaments at three sites: just distal to the cuff, at the base of the index finger, and at the tip of the index finger. An additional method that was used to confirm complete paralysis of the hand was surface EMG at the First Dorsal Interosseous (FDI) of the hand (Reilly et al.2008). The time for the full effect of ischemia ranges from 39-73 minutes. Reperfusion begins immediately after deflation of the cuff (Reilly 2008). Although this method was effective for providing sensory deficits and evaluation of selective finger force flexion in a healthy sample, it can be dangerous to use in a sample of T2D who already have vasculature issues resulting in permanent damages.

A more invasive yet better controlled method that has been utilized in research applications is injection of anesthesia subcutaneously to achieve median nerve blocks and digital ring blocks. These procedures introduce a subdermal anesthetic into pre-established site while maintaining safe and aseptic procedures. The difference between median nerve block method and the ring block method pertains to the sites of administration. For the

median nerve block at the wrist, the carpal tunnel compartment of the wrist is the site of injection. For the digital ring blocks, the metacarpal joint for the particular digit selected is the site of injection. These procedures provide a well- controlled and sterile anesthetic environment. Limitations of this method include resources such as medical professionals to carry out the procedure and participants willing to take part in such an invasive procedure. Median nerve at the wrist and ring block of the digits will induce sensory deficits preserving proprioception and functionality of the intrinsic muscles of the hand. Median nerve block at the elbow induces tactile sensory deficits and proprioceptive deficits distal to the site of administration.

In a study by Li et al, median nerve block at the wrist was used to assess the functionality of the thumb after trauma to the median nerve; loss of tactile sensation was verified with Semmes- Weinstein Monofilaments (Li et al 2004). Results of this study suggest that median nerve block result in force deficits in all direction of thumb movement (Li et al 2004).

Previously, ring blocks have been used to investigate the effects of loss of cutaneous sensation during pressing tasks (Shim et al 2012) and during dynamic and static gripping tasks (Augurelle et al. 2003). Shim and colleagues conducted the procedure by applying a topical anesthetic to the all digits followed by an additional injection of anesthesia solution at the middle phalanges of digits 2 through digit 5 (Shim et al 2012). Loss of cutaneous sensation was verified with Von Frey Filament at the distal pad of the fingers (Shim et al. 2012). Augurrelle et al. managed the ring block procedure by application of the anesthetic injection at the base of the index finger and the thumb. Anesthesia was verified through the use of Semmes-Weinstein Monofilaments (Augurelle et al. 2003). Results from these studies

suggest that cutaneous sensation is important for integrating information between the external environment and the body, establishing and maintain grip forces during daily activities and for maximum voluntary muscle contraction (Augurelle et al 2003, Shim et al 2012).

Tactile deficits induced by anesthesia have served to establish the importance of sensory feedback for hand manipulation. In tasks such as precision pinch, the lack of sensory afferents results in an inability for the index finger and the thumb to coordinate the force modulation that occurs during initial contact between two surfaces (Monzee et al 2002). Object slippage occurs more often with weights heavier than expected and low friction surfaces (Monzee et al 2002). Additionally, anesthesia results in decreased sweat production of the skin and a reduction in skin-surface friction. Grip force changes that result from local anesthesia include an increase in the tangential forces between the fingertips and the object resulting in a greater propensity of object slippage because the grip force is no longer applied perpendicular to the object (Monzee et al 2002).

Collectively taken, the purpose of the investigation in this thesis is to evaluate the contributions of tactile and proprioceptive feedback upon hand function of patients with T2D and non-T2D healthy controls. The non-T2D sample will provide a benchmark for the suspected physiological deficits of the diabetic population, in the presence and absence of injected anesthesia. Anesthesia injections will be applied at both the wrist, to induce tactile deficits, and at the elbow, to induce tactile and proprioceptive deficits in the extrinsic muscles of the forearm that contribute to manual function. Manual function will be assessed through sensory and motor evaluations. Sensory evaluations will be conducted using the Semmes-Weinstein monofilament test. Motor evaluations will include maximal grip and

pinch tests, submaximal testing force production. Additionally, the clinical testing will be conducted using the Jebsen-Taylor Hand Function Test (JTHFT) and Functional Dexterity Test (FDT).

CHAPTER III

METHODS

3.1. Participants

Eight (8) individuals with T2D and eight (8) healthy age- and sex-matched individuals were recruited to participate in this experimental study. Patient information for the T2D group can be found in Table 3.1. The average age of the participants was 56 ± 5 years and 55 ± 5 yearsfor the T2D group and the healthy cohorts, respectively. The average BMI for the T2D group was 34.5 ± 6.4 and that of the control group is 27.77 kg/m^2 ± 3.62. Furthermore, the average %HbA1c for the T2D and healthy groups were, 8.9 ± 1.4 % and 5..9 ± 0.4%, respectively. All subjects with the exception of one from each of the groups were strongly right-handed (LQ average = +98), the exception was strongly left-handed (LQ average = -100). Participants were recruited from the general population through the use of flyers and from our database from previous participation in our lab. T2D participants must have confirmed diagnosis of T2D either with or without diagnosis of peripheral neuropathy per physician. Healthy individuals recruited to participate in this study did not have a diagnosis of T2D, Type I Diabetes, or pre-diabetes. Study participants were excluded if they reported a history of neurological disorders (Parkinson's disease, Stroke, Multiple Sclerosis, etc.), chemotherapy treatments, and/or hereditary neuropathies. The protocol was reviewed and approved by the Committees established for the Protection of Human Subjects (CPHS) at the University of Houston. In accordance with the Declaration of Helsinki, participants provided informed consent according to the regulations established by the CPHS at the University of Houston.

Table3.1 : Participant Demographics

Patient #	Gender	Age (years)	BMI	%HbA1c	LQ	Diagnosis of peripheral Neuropathy
1	F	60	23.8	9.5	(+)100	-----
2	M	56	30.5	9.3	(+)100	-----
3	F	55	37.8	-----	(+)100	-----
4	F	65	29.4	9.5	(+)90	-----
5	F	46	41.0	6.4	(+)60	-----
6	M	55	43.5	9.0	(-)50	Yes
7	F	58	39.0	11.1	(+)100	-----
8	M	53	30.6	7.6	(+)100	-----
Mean	-----	56	34.4	8.9	+62.5	-----
SD	-----	5	6.3	1.4	-----	-----

Table 3.1 Age, gender, percent hemoglobin (%HbA1c) values, Laterality Quotient, and clinical diagnosis of peripheral neuropathy for the T2D group. Values are presented for individual participants as well as mean and standard deviation for the sample.

3.2. Experimental Procedures

All participants were evaluated with each test at a baseline condition prior to the injection of anesthesia. Testing was conducted with the dominant hand only. Hand dominance was established using the Edinburgh Inventory (Oldfield, 1971) which ranges from a laterality quotient (LQ) of –100 (which indicates strong left-handedness) to +100 (which indicates strong right-handedness). Participants were re-evaluated on each sensory and motor test for the identification of behavioral changes during temporary loss of tactile sensation to the hand (via median nerve wrist block) and temporary loss of tactile and proprioceptive function to the forearm and hand (via median nerve elbow and wrist block).

3.2.1. Sensory Evaluations

The Semmes-Weinstein Monofilament test was used to evaluate tactile sensation of the hands. Monofilament testing sites included: tip of the thumb (median nerve), tip of the index finger (median nerve), tip of the middle finger (median nerve), hypothenar eminence (ulnar nerve), and dorsum of the hand near metacarpal 1 (radial nerve). Testing of non-median nerve sites assisted in monitoring unintended anesthetic side effects. Administration of anesthetic at the wrist may also result in decreased sensory deficits in regions of the hand not innervated by the median nerve due to cross contamination during application (Li et al. 2004). During the test, participants kept their eyes closed and verbally indicated if and where they perceive monofilament touch. The monofilament size was increased until the subject was able to detect its touch a minimum of two times at the same location.

Proprioception was evaluated by two different examinations. The first examination utilized tuning forks to assess vibratory perception thresholds. A standard 128 Hz tuning fork was struck inducing vibration of the device and then applied to testing sites (1) tip of digit 1, (2) tip of digit 2, (3) tip of digit 5, (4) thenar eminence. And (5) forearm, superficially with the intent of stimulating the flexor digitorum superficialis. Vibration detection thresholds for the intrinsic musculature within the thenar eminence, as well as the flexor and extensor compartments of the forearm were evaluated. The examination was assessed as a pass/fail for the ability to discern vibration in the absence of visual feedback. Additionally, participants underwent a kinesthesia examination in which the testers produced the following movements in the participant's non-dominant hand, (1) touch of tip of digit 1 and digit 2, (2) touch of digit 1 and digit 5, (3) abduction and adduction of digit 1. The purpose of this examination was to have the participant reproduce the movement on the dominant hand in the absence of

visual stimuli (eyes closed). Proprioception was assessed (1) prior to the application of any anesthesia, (2) after application of anesthesia to the wrist injection site only, and (3) after application of anesthesia to both the wrist and elbow injection sites.

3.2.2. Laboratory-based Motor Evaluations

All laboratory evaluations were conducted three times: at baseline, after wrist block (treatment 1), and after elbow block (treatment 2) (Figure 3.1).

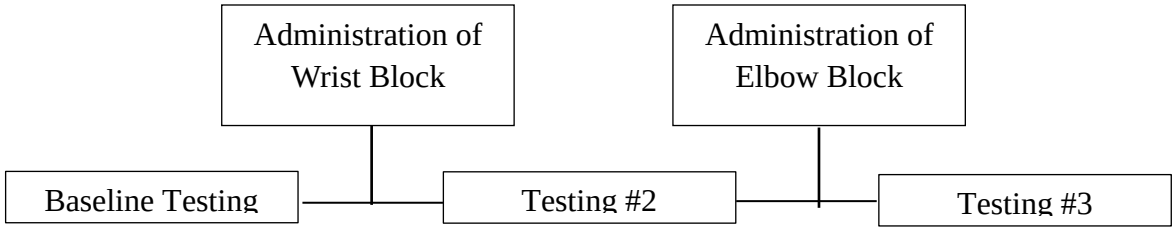

Figure 3.1. Schedule of laboratory evaluations. Initial baseline testing occurred toestablish normative values for all participants. After wrist block, we expect to see decreased tactile sensation in the hand and preservation of proprioceptive input. After elbow block, we expect continuous tactile deficits and diminished proprioception distal to the elbow.

Maximal hand grip strength was evaluated using a Biometrics Hand Dynamometer and wireless DataLOG system (Dynamometer Model G200, DataLOG model MWX8, Biometrics Ltd., Newport, UK). Participants were seated in a position of comfort with their elbow flexed at 90° and directed to relax grip on the device until prompted by the examiner. Once the word “begin” was announced, participants exerted maximal grip and held this force production for approximately 2-3 seconds before relaxing grip. Verbal encouragement was provided throughout each trial. After each trial, a break was permitted for approximately 2

minutes. Three maximal grip strength trials were collected with the dominant hand. The maximal force produced across all three trials was considered in subsequent analysis.

Maximal pinch evaluation was conducted using a Biometrics Pinch Dynamometer and wireless DataLOG system (Precision Pinchmeter model P200, DataLOG model MWX8, Biometrics Ltd., Newport, UK). Participants remained seated during this evaluation. The testing device was held vertically with the hand not being tested. At the instruction of the examiner, the participant pinched the device using a precision pinch for approximately 2-3 seconds before relaxing. A precision pinch grasp was obtained by pressing the testing device using the finger pads of index finger and the thumb. Again, a 2-minute break was permitted after each of three trials. The maximal force produced across all three trials was considered in subsequent analysis.

A system, illustrated in Figure 3.2, was created to determine force characteristics exhibited during submaximal force production. This task involves using the index finger and thumb together in a precision pinch grip to produce a constant level of grip force, with feedback indicated by a computer screen. All forces and moments of force produced by both digits are recorded simultaneously using two identical six-component force-moment transducers (Nano-25 transducers; ATI Industrial Automation, Garner, NC, USA) during the submaximal force production task (Submax). The grip width of the object (defined as the distance between the contacts surfaces of the Nano-25 sensors) was 0.04 m. The total mass of the object was 0.680 kg. The transducers were mounted to a fixed aluminum device throughout the entire testing session. Sandpaper (320-grit) was attached to the contact surfaces of each sensor to increase the friction between the digits and the transducers.

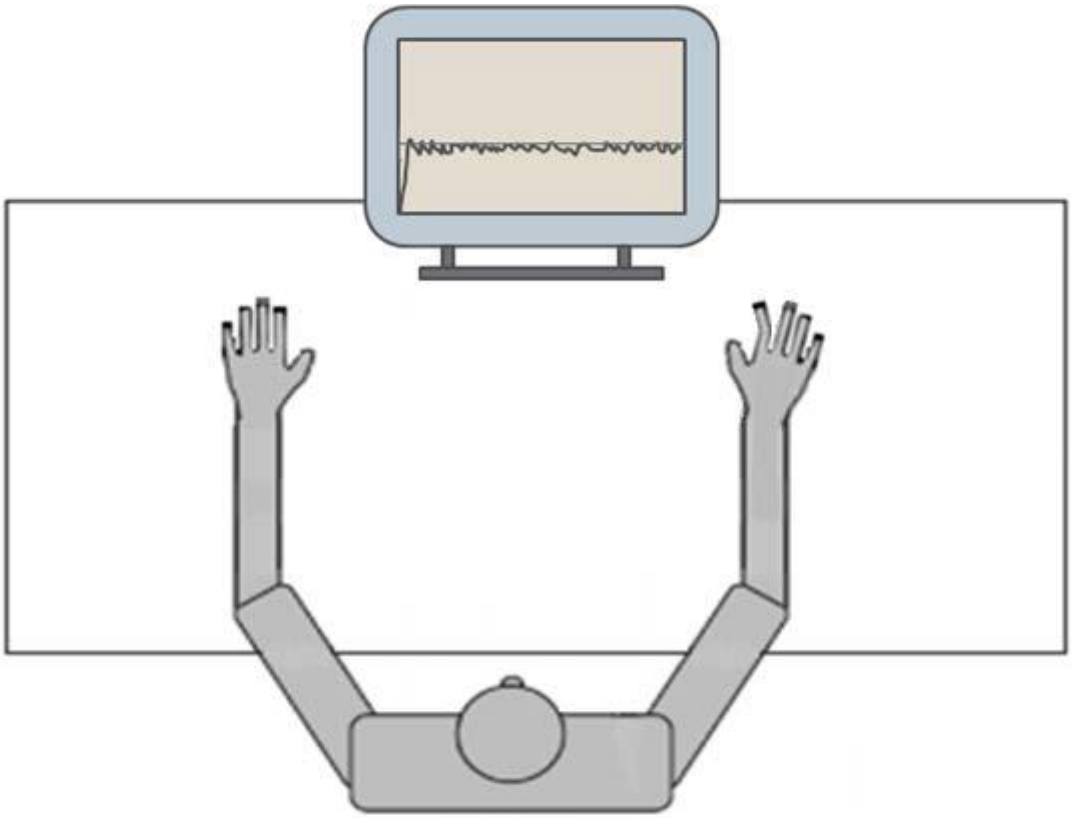

Figure 3.2. Experimental setup for Submaximal force production test. Participants sit directly in front of a computer screen. The screen provides visual feedback pertaining to the amount of force applied to the sensor. The feedback will consists of two lines, one white and one red, indicating the desired amount of force to be applied and the actual amount of force applied by participant.

Subjects sat with an erect posture, arms unsupported, in a chair facing a small table. They were instructed to grasp the object using the dominant hand. No contact of either transducer was permitted prior to trial onset; subjects were instructed to begin each trial with both hands placed palm down on the surface of the table. Up to three practice trials were offered to each subject prior to the onset of data collection for each condition. The MVC values for pinch force production were determined from the maximal pinch evaluation (see previous paragraphs). Each participant performed three trials for each Submax condition (20% and 40%), lasting 15 seconds each.

Transducer signals were amplified and multiplexed using ATI hardware prior to being routed to an analog to digital converter (via cDAQ-9174 chassis and NI-9205 input modules, National Instruments, Austin, TX, USA). A customized Labview program (National Instruments, Austin, TX, USA) was used for data acquisition and customized MATLAB (Mathworks Inc., Natick, MA, USA) programs were written for data processing. Signals were sampled at 100 Hz and low-pass filtered at 10 Hz using a 2nd order, zero-lag Butterworth filter. The temporal region of interest in the force data consists of the final 10 seconds of each trial. Participants were required to reach and maintain the indicated force production level within the first five seconds of each trial. If participants are unable to reach the target force, or fail to maintain the target force for the duration of the trial, such trials were repeated.

3.2.3. Clinical Evaluations

3.2.3.a. Jebsen-Taylor Hand Function Test

The Jebsen-Taylor Hand Function Test is a performance based evaluation used to assess ability to perform common daily motor skills (Jebsen et al. 1969). It consists of seven timed tests of manual activities. Participants wqwewill be instructed to perform each of the seven tasks as rapidly and accurately as possible. All tests are assessed by time to completion using a standard stopwatch. Times for the participants are reported in seconds (s).

Jebsen Taylor Hand Function Test (JTHF) is comprised of the following battery tests: writing, card turning, moving small common objects, simulated feeding, stacking checkers, moving large light objects, and moving large heavy objects. The writing portion of the test requires participants to write a sentence composed of 24 characters, not previously seen, as

quickly and efficiently as possible. The sentence is written at a third grade level for ease of administration. The card turning test is intended to simulate page turning and involves the turning of five vertically-oriented index cards from one side to the next. The moving small common objects portion includes moving two vertically oriented paper clips, two bottle caps, and two cent coins. Participants are required to lift each item from the table and place them in a designated container at a prescribed location on the table. Participants must lift the small objects in the order that they are placed on the table and may not lift more than one object at a time. The simulated feeding test consists of using a table spoon to move five kidney beans. Participants are instructed to pick up each kidney bean with the spoon and insert them into a designated container. Again, they may not lift more than one kidney bean at a time. The stacking checkers test consists of 4 checker pieces placed horizontally on a table. Participants must stack the checkers into a column directly in front of the,. Once again only one checker may be manipulated at any given time. Last, the moving large light objects and moving large heavy objects tests are similar with the exception of the weight of the objects. During each test, participants will lift one object (can) at a time and place it on top of a board placed directly in front of them. When the last object has been placed upon the board, the test will be complete.

3.2.3.b. The Functional Dexterity Test

The Functional Dexterity is designed to assess three components of functional dexterity: speed, accuracy, and manipulation (Dorit et al. 2003). The test apparatus consists of 16 wooden pegs inserted into a 4x4 grid. Participants are required to lift, rotate, and reinsert each peg into its appropriate location. The first peg must be completed before the

participant may continue onto the next peg. Once the top row of pegs has been manipulated, the participant will move onto the next row in a zig-zag pattern. Participants will be instructed to perform the task as rapidly and accurately as possible. All tests will be assessed by time to completion using a standard stopwatch. Time to completion will be recorded in seconds (s). Ten (10) second penalties will be added to total performance time for dropping a peg, using the board for assistance in rotation of the peg, and for turning the hand toward the ceiling (supination) during rotation of the peg.

3.3. Administration of Median Nerve Blocks

Two median nerve blocks were conducted on each participant using aseptic procedures on the dominant hand of both T2D and age-and sex-matched controls. Median nerve block was achieved by injection of anesthesia at two different sites. The first injection of 2% lidocaine solution was administered at the wrist as a means to temporarily remove tactile sensation from the hand. The second injection was administered at the elbow as a means to achieve temporary removal of tactile and proprioceptive information from the forearm and hand. The Semmes-Weinstein Monofilament test was used to determine median nerve block effectiveness. See Figure 3.1. for the schedule of sensory and motor evaluation.

CHAPTER IV

RESULTS

4.1 Sensory Function

4.1.1. Semmes-Weinstein Monofilament Test

Tactile detection thresholds were assessed using the Semmes-Weinstein Monofilament test; sites of interest were areas innervated by the median and ulnar nerves. As in our previous work (Gorniak et al. 2014, Ochoa & Gorniak, 2014) multiple sites were assessed; however, for statistical analysis we focused on digits 1 and 5. These sites are innervated by the median and ulnar nerves, respectively. Monofilament values were log transformed for our statistical analysis due to the logarithmic scaling structure of the monofilament range. Monofilament data were retransformed and presented as gram-Force(g) for reporting and interpretation purposes. Repeated measures analysis of variance indicated a significant difference in tactile detection threshold for *Group* ($F_{1,7} = 11.64$, $p < 0.05$), *Site* ($F_{1,7} = 37.31$, $p < 0.001$), and for *Condition* ($F_{1,7} = 29.14$, $p < 0.001$). The results indicate a significant interaction of *Site x Condition* ($F_{2,14} = 7.74$, $p < 0.05$). Bonferroni post-hoc analysis (three comparisons, $\alpha = 0.05/3 = 0.0167$) indicated significant differences among all three *Conditions*: baseline vs. wrist block ($p = 0.013$), baseline vs. elbow block ($p = 0.001$), and wrist block vs. elbow block ($p = 0.003$). All effects can be found in panels A and B of Figure 4.1. In reference to our hypothesis, the mean value of tactile perception in digit 1 (thumb), innervated by the median nerve, by the T2D group at baseline (0.59 +/- 0.07 g), was within the 95% confidence intervals of the mean tactile perception in digit 1 values generated by the healthy control group in the wrist block (95% CI = 0.39 – 0.73 g) and elbow block (95% CI = 0.57 – 1.27 g) conditions. The mean value of tactile perception in digit 5 (little

finger), innervated by the ulnar nerve, by the T2D group at baseline (0.54 +/- 0.08 g), was within the 95% confidence intervals of the mean tactile perception in digit 5 values generated by the healthy control group in the wrist block (95% CI = 0.39 – 0.63 g) and elbow block (95% CI = 0.39 – 0.76 g) conditions.

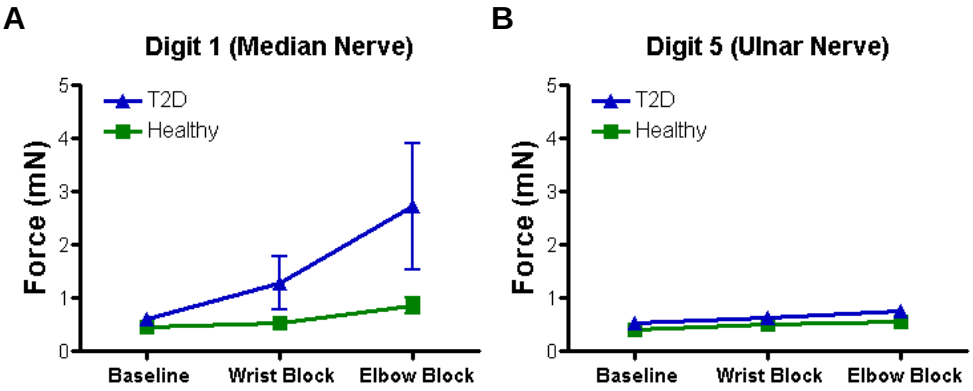

Figure 4.1. Mean and standard error bars tactile detection thresholds for the median and ulnar nerves. **A:** *Group* and *Condition* averages for the tip of digit 1, innervated by the median nerve. **B:** *Group* and *Condition* averages for the tip of digit 5, innervated by the ulnar nerve.

4.1.2. Kinesthesia

Proprioception was assessed via a kinesthesia test. During this testing, the tasks of interest were digit 1 abduction/adduction, touching of tip of digit 1 to tip of digit 2, and touching tip of digit 1 and tip of digit 5. The Kruskal-Wallis non-parametric test was used to identify the following the results, as successful task completion was coded as pass/fail. No significant differences were noted between the T2D and healthy *Groups* nor for the different *Conditions* (i.e. baseline, wrist block, and elbow block) during the digit 1 abduction/adduction task. In Table 4.1, were observed during the baseline *Condition*, no detection mistakes were performed during the baseline or elbow blocks for either *Group*.

During the first anesthetized *Condition*, wrist block, we note one error in each group, two total overall total errors.

Table 4.1 Kinesthesia : Digit 1 Abduction/Adduction

	Baseline	Wrist Block	Elbow Block	Total Errors
Healthy	0	2	2	4
T2D	0	5	2	7

Table 4.1. Number of kinesthesia errors produced by the T2D and healthy *Groups* in each of the three *Conditions* (Baseline, Wrist Block, Elbow Block) during digit 1 abduction / adduction.

The results for the tip of digit 1 and digit 2 suggested no difference between *Groups*; however, differences were significant among the *Conditions* such that baseline differed from wrist block and from elbow block ($Z = -2.97$, $H_2 = 13.26$, $p < 0.001$). As shown in Table 4.2, we observed one error during baseline examination that corresponded to the healthy *Group.* During the wrist block *Condition*, a total of 11 errors were noted of which 4 were in the healthy group while the remaining seven were presented in the T2D group. In the elbow block *Condition*, we observed a total of 8 errors with 4 occurring in each *Group.*

Table 4.2 Kinesthesia : Digit 1 to Digit 2

	Baseline	Wrist Block	Elbow Block	Total Errors
Healthy	1	4	4	9
T2D	0	7	4	11

Table 4.2. Number of kinesthesia errors produced by the T2D and healthy *Groups* in each of the three *Conditions* (Baseline, Wrist Block, Elbow Block) during digit 1 to digit 2 touch.

Assessment of touch for tip of digit 1 and 5 resulted in no significant difference between *Groups*; however, a significant difference among *Conditions* ($Z = 1.92$, $H_2 = 8.55$, p

= 0.05). Again we note that the baseline *Condition* was different from both of the anesthetized *Conditions.* As shown in Table 4.3, zero total errors occurred at baseline, 7 total errors during wrist block 2 for healthy and 5 for T2D, and 4 total errors during the elbow blocks trials 2 corresponding to each *Group.*

Table 4.3 Kinesthesia : Digit 1 to Digit 5

	Baseline	Wrist Block	Elbow Block	Total Errors
Healthy	0	2	2	4
T2D	0	5	2	7

Table 4.3. Number of kinesthesia errors produced by the T2D and healthy *Groups* in each of the three *Conditions* (Baseline, Wrist Block, Elbow Block) during digit 1 to digit 5 touch.

4.1.3. Vibration Perception

Vibratory perception was assessed using tuning forks. The examination assessed participant's ability to detect vibration utilizing a 128 Hz tuning fork in different sites of the hand and arm. The areas of interest, similar to the monofilament test, focused on sites innervated by either the median and ulnar nerves. Results were listed and coded as pass/fail for sensation of vibration or lack thereof. No significant differences were noted with respect to: *Group, Condition, Site,* or any interactions. All participants, with the exception of one T2D participant who lacked the ability to detect one site under two *Conditions,* sensed the vibratory sensation in all sites during all *Conditions.* Kruskal-Wallis statistical evaluation confirmed no significant effects among *Group, Site,* and *Condition* for the vibratory perception data.

4.2. Kinetics

4.2.1. Maximal force production

Analysis of maximal grip force production revealed that the T2D *Group* (mean ± SE; 179.7 ± 47.3N) produced significantly less force than age- and sex-matched healthy controls (302.6 ± 51.2N) ($F_{1,7} = 5.97$, $p < 0.05$). There was a significant difference in max grip force among *Conditions* ($F_{2,14} = 4.07$, $p < 0.05$), as shown in panel A of Figure 4.2. The interaction of *Condition x Group* was not significant. Despite the significant finding of *Condition*, Bonferonni corrected post-hoc analysis did not reveal significant differences across *Conditions*. In reference to our hypothesis, the mean value of max grip by the T2D group at baseline (210.37 ± 47.01 N), was within the 95% confidence intervals of the mean max grip values generated by the healthy control group in the wrist block (95% CI = 166.96 – 412.27 N) and elbow block (95% CI = 180.20 – 417.43 N) conditions.

Analysis of maximal pinch force production revealed no significant differences between *Groups* ($F_{1,7} = 1.76$, $p = 0.226$). Maximum pinch were significantly different among *Conditions* ($F_{2,14} = 10.72$, $p < 0.01$), without a significant interaction term. Bonferroni corrected post-hoc analysis revealed a significant decrease in pinch forces produced in the elbow block *Condition* as compared to baseline values. All data are shown in panel B of Figure 4.2. In reference to our hypothesis, the mean value of max pinch by the T2D group at baseline (45.91 ± 6.22 N), was within the 95% confidence intervals of the mean max pinch values generated by the healthy control group in the wrist block (95% CI = 33.60 - 62.67 N) and elbow block (95% CI = 27.41 – 56.00N) conditions.

Approximate entropy (ApEn) and detrended fluctuation analysis (DFA) for the maximal force production tasks did not display significance regarding differences between *Groups* nor among *Conditions*.

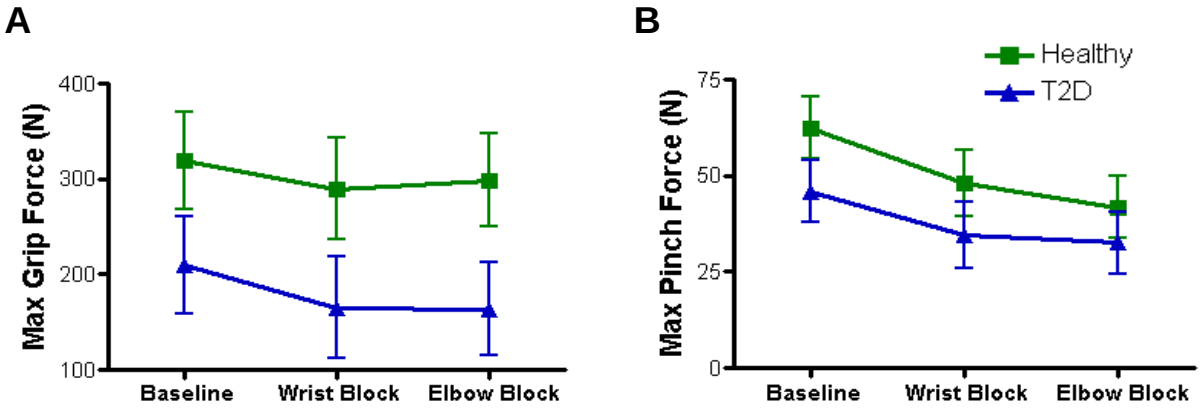

Figure 4.2. Mean and standard error bars for maximal force production tasks. **A:** *Group* and *Condition* averages for maximal grip force production. **B:** *Group* and *Condition* averages for maximal pinch force production.

4.2.2. Submaximal force production

In the submaximal force production tasks, root mean squared error (RMSE) of the forces produces with respect to the target value increased significantly between 20% MVC and 40% MVC submaximal force production *Tasks* ($F_{1,6} = 6.40$, $p < 0.05$). Additionally, RMSE decreased significantly with *Condition* ($F_{1,6} = 6.93$, $p < 0.05$). Bonferonni corrected post-hoc analysis did revealed larger RMSE values at baseline as compared to the elbow block *Condition*. While the main effect of *Group* was not significant, the interaction of *Group x Condition* was significant ($F_{2,12} = 5.50$, $p < 0.05$), such that T2D participants tended to produce larger RMSE values across all tested *Conditions,* shown in panels A and B of Figure 4.3. In reference to our hypothesis, the mean value of RMSE by the T2D group at baseline (1.20 ± 0.40N), was not within the 95% confidence intervals of the mean RMSE values generated by the healthy control group in the wrist block (95% CI= 0.37 – 0.956N) and elbow block (95% CI = 0.22 – 0.78N) conditions.

Similarly, the coefficient of variation (CV, no units, errors normalized to mean force production), results indicated significant differences between the two *Tasks* (20% and 40% MVC) ($F_{1,6} = 14.82$, $p < 0.01$). CV values were noted to be considerably lower between for 40% MVC than for 20% MVC. The main effects of *Condition* and *Group* were not significant, but the interaction *Group x Condition* was significant ($F_{2,12} = 6.18$, $p < 0.05$). The interaction data indicates that T2D participants produced significantly larger errors in the two anesthesia (wrist block and elbow block) *Conditions* as compared to healthy controls, as shown in panels C and D of Figure 4.3. In reference to our hypothesis, the mean value of CV by the T2D group at baseline (0.09 ± 0.02 (no units)), was not within the 95% confidence intervals of the mean CV values generated by the healthy control group in the wrist block (95% CI = 0.03 - .07 (no units)) and elbow block (95% CI = 0.02 - .06 (no units)) conditions.

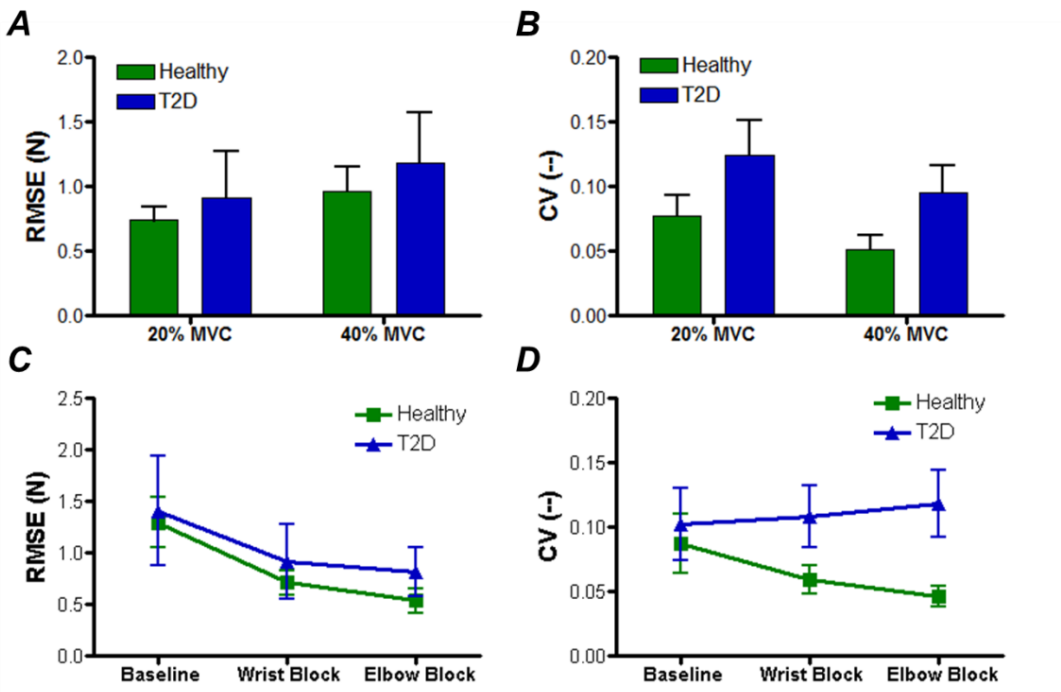

Figure 4.3. Mean and standard error of Root Mean Square Error (RMSE) and Coefficient of Variation (CV) values. ***A:*** *Group* and *Task* RMSE data. ***B:*** *Group* and *Task* CV data. ***C:*** *Group* and *Condition* RMSE data. ***D:*** *Group* and *Condition* CV data.

Approximate entropy (ApEn), a measure of output variability was almost significant for the interaction of *Group x Condition x Task* ($F_{2,12} = 3.78$, $p = 0.054$), but no significance was noted for any of the main effects, shown in panel A of Figure 4.4. In reference to our hypothesis, the mean value of ApEn by the T2D group at baseline (0.186 ± 0.028 (no units)), was within the 95% confidence intervals of the mean ApEn values generated by the healthy control group in the wrist block condition (95% CI = 0.177 – .358 (no units)) but not the 95% confidence interval of the healthy control group in the elbow block condition (95% CI = 0.190 – 0.354 (no units)).

De-trended fluctuation analysis (DFA) was noted to be significantly higher in the T2D *Group* when compared to healthy controls ($F_{1,6} = 8.02$, $p < 0.05$), as shown in panel B of Figure 4.4. In reference to our hypothesis, the mean value of DFA by the T2D group at baseline (1.11 ± 0.07 (no units)), was within the 95% confidence intervals of the mean DFA values generated by the healthy control group in the wrist block (95% CI = 0.94 – 1.22 (no units)) and elbow block (95% CI = 0.98 – 1.13 (no units)) conditions.

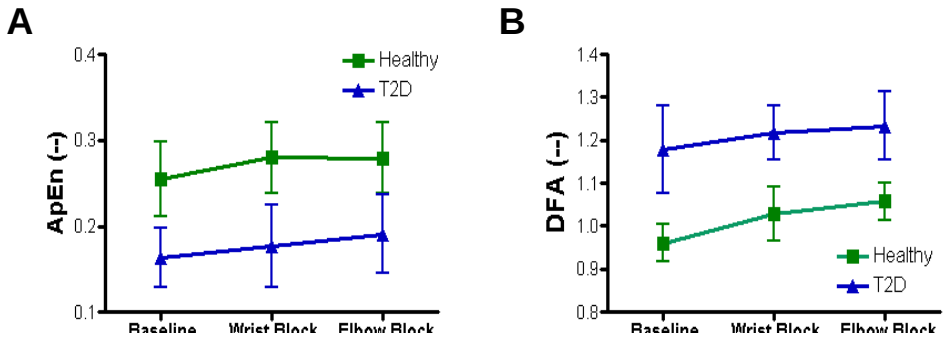

Figure 4.4. Mean and standard error of Approximate Entropy (ApEn) and Detrended Fluctuation Analysis (DFA) values for submaximal force production tasks under baseline, wrist block, and elbow block *Conditions* for T2D and healthy control *Groups.* ***A:*** ApEn. ***B:*** DFA.

4.3. Clinical Motor Evaluations

4.3.1. Functional Dexterity

The Functional Dexterity Test (FDT) was used in conjunction with the JTHFT to assess object manipulation mimicking activities of daily living. Overall, analysis revealed a significant *Group* effect ($F_{1,7} = 13.40$, $p < 0.01$), such that T2D patients were on average significantly slower than age- and sex-matched healthy controls. Additional analysis indicated a significant effect of *Condition* ($F_{2,14} = 8.69$, $p < 0.005$) and of the interaction between *Group x Condition* ($F_{2,14} = 5.69$, $p < 0.05$). Time to completion of task depended on the *Condition*, such that the two *Groups* were similar at baseline, but the time for task

completion increased significantly in T2D group for the wrist and elbow block conditions, but not for the healthy group, as shown in Figure 4.5. Bonferonni corrected post-hocs confirmed significantly longer task times for the wrist and elbow block conditions as compared to baseline values, particularly for the T2D *Group*. In reference to our hypothesis, the mean value of FDT performance by the T2D group at baseline (28.71 ± 1.36 s), was within the 95% confidence intervals of the mean FDT performance values generated by the healthy control group in the wrist block (95% CI = 25.38 - 47.11 s) and elbow block (95% CI = 27.21 – 32.09 s) conditions.

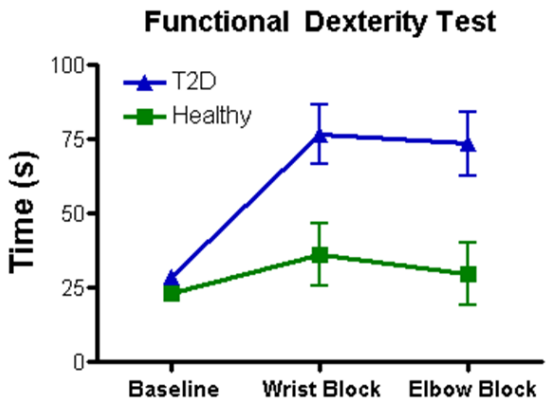

Figure 4.5. Mean and standard error of completion times for the Functional Dexterity Test. Data for T2D and healthy control *Groups* are shown in the three tested *Conditions* (baseline, wrist block, and elbow block).

4.3.2. Jebsen Taylor Hand Function Test (JTHF)

In the first JTHF subtest (JTHF1), a test that task simulates turning of pages, no significant differences were noted between *Groups.* Additional analysis indicated a difference among *Conditions* ($F_{2,14} = 7.55$, $p < 0.05$). Post-hoc analysis of *Condition* did not reveal any significant effects, despite the increase in JTHF1 time increasing in the wrist block *Condition*. Despite the suggestion of a *Group x Condition* interaction in Figure 4.6, no

significant interaction was found. In reference to our hypothesis, the mean value of JTHF1performance by the T2D group at baseline (6.71 ± 0.78 s), was within the 95% confidence intervals of the mean JTHF1 performance values generated by the healthy control group in the wrist block (95%CI= 5.24 - 11.49s) and elbow block (95%CI = 5.03 - 7.80 s) conditions.

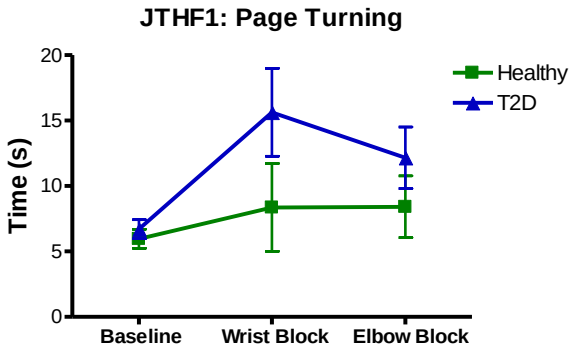

Figure 4.6. Mean and standard error of completion times for JTHF1 (simulated page turning). Data for T2D and healthy control *Groups* are shown in the three tested *Conditions* (baseline, wrist block, and elbow block).

The JTHF2 required four checkers to be individually lifted from a surface and be stacked on top of each other. This test indicated that the T2D *Group*, again, was significantly slower than healthy controls ($F_{1,7} = 23.96$, $p < 0.005$). Once again, *Condition* was significant ($F_{2,14} = 11.913$, $p < 0.01$), as well as the interaction *Group x Condition* ($F_{2,14} = 9.08$, $p < 0.05$). Post-hoc analysis confirmed that the T2D *Group* was significantly slower that the healthy control group in the wrist block condition, particularly as compared to the elbow block condition, shown in Figure 4.7. In reference to our hypothesis, the mean value of JTHF2 performance by the T2D group at baseline (5.59 ± 0.65 s), was within the 95% confidence intervals of the mean JTHF2 performance values generated by the healthy control group in the wrist block (95% CI = 4.57 - 7.32 s) and elbow block (95%CI = 3.79 – 7.21 s) conditions.

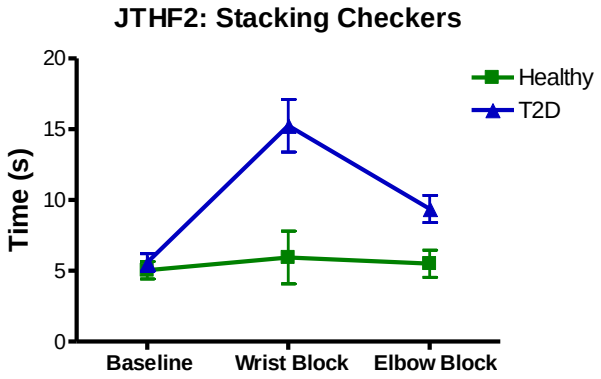

Figure 4.7. Mean and standard error of completion times for JTHF2 (stacking checkers). Data for T2D and healthy control *Groups* are shown in the three tested *Conditions* (baseline, wrist block, and elbow block).

The JTHF3 test included picking up small objects individually and placing them into a large can. This test indicated that the T2D *Group*, again, was significantly slower than healthy controls ($F_{1,7} = 6.68$, $p < 0.05$). Again, the main effect of *Condition* ($F_{2,14} = 10.47$, $p < 0.01$), and the interaction *Group x Condition* ($F_{2,14} = 6.25$, $p < 0.05$) were significant. Post-hoc analysis confirmed that the T2D *Group* was significantly slower that the healthy control group in the two anesthesia *Conditions* (wrist and elbow block), shown in Figure 4.8. In reference to our hypothesis, the mean value of JTHFT3 performance by the T2D group at baseline (10.93 ± 1.58 s), was within the 95% confidence intervals of the mean JTHF3 performance values generated by the healthy control group in the wrist block condition (95% CI = 4.68 - 26.53 s) but was not for the elbow block condition (95%CI = 5.66 - 19.16 s).

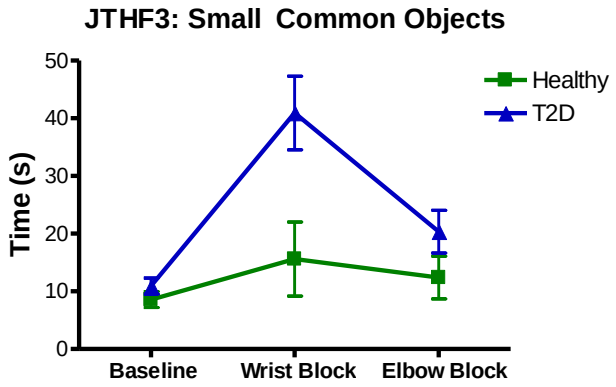

Figure 4.8. Mean and standard error of completion times for JTHF3 (handling small common objects). Data for T2D and healthy control *Groups* are shown in the three tested *Conditions* (baseline, wrist block, and elbow block).

In the JTHF4 test, which involved the lifting of large light objects, only an effect of *Condition* ($F_{2,14} = 10.02$, $p < 0.005$) was found with no interactions. As shown in Figure 4.9, post-hoc analysis of *Condition* indicated that JTHF4 times in the wrist block condition were significantly larger than times in the baseline and elbow block conditions. In reference to our hypothesis, the mean value of JTHF4 performance by the T2D group at baseline (4.54 ± 0.38 s), was within the 95% confidence intervals of the mean JTHF4 performance values generated by the healthy control group in the wrist block (95%CI = 3.85 - 5.20 s) and elbow block (95% CI = 3.65 - 4.80 s) conditions.

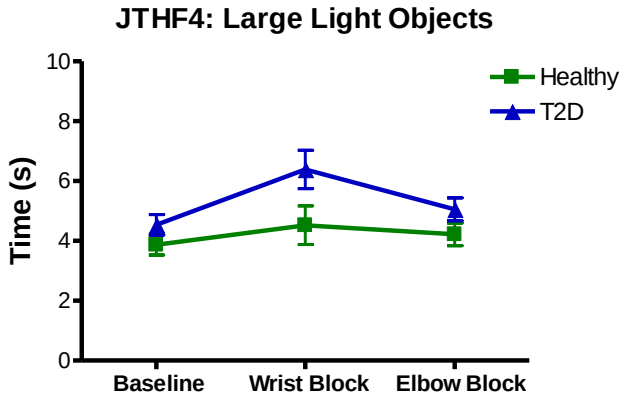

Figure 4.9. Mean and standard error of completion times for JTHF4 (moving large light objects). Data for T2D and healthy control *Groups* are shown in the three tested *Conditions* (baseline, wrist block, and elbow block).

The JTHF5 test was similar to JTHF4 with the exception of utilizing heavy objects instead of light objects for the task. Analysis of data for JTHF5 indicates that the differences between the T2D and controls *Groups* were almost significant ($F_{1,7} = 5.39$, $p = 0.053$) as well as differences among *Conditions* ($F_{2,14} = 3.65$, $p = 0.053$), shown in Figure 4.10. Post-hoc analysis suggested that JTHF5 times in the wrist block condition were longer than in the elbow block condition across all subjects, potentially driving the nearly significant finding. No interactions were found. In reference to our hypothesis, the mean value of JTHF5 performance by the T2D group at baseline (4.82 ± 0.51 s), was within the 95% confidence intervals of the mean JTHF5 performance values generated by the healthy control group in the wrist block (95%CI = 3.66 - 5.45 s) and elbow block (95% CI = 3.58 - 4.86 s) conditions.

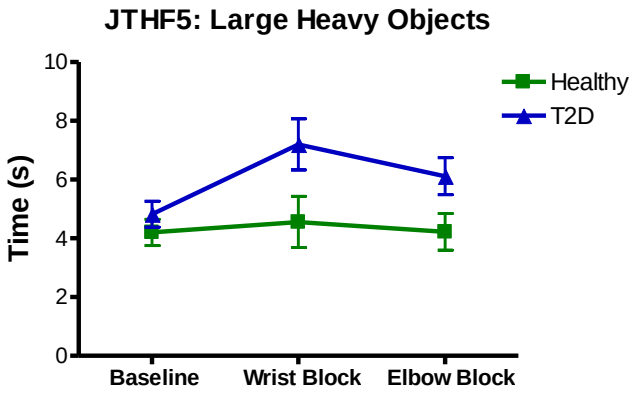

Figure 4.10. Mean and standard error of completion times for JTHF5 (moving large heavy objects). Data for T2D and healthy control *Groups* are shown in the three tested *Conditions* (baseline, wrist block, and elbow block).

The JTHF6 test, which simulated spoon feeding, also indicated nearly significant differences between the T2D and healthy control *Groups* ($F_{1,7} = 5.39$, $p = 0.053$), as shown in Figure 4.11. No main effect of *Condition* was found; however, the *Group x Condition* interaction was significant ($F_{2,14} = 3.84$, p , 0.05), illustrated in Figure 4.11. No post-hoc differences were found for *Condition*. In reference to our hypothesis, the mean value of JTHF6 performance by the T2D group at baseline (11.87 ± 0.73 s), was not within the 95% confidence intervals of the mean JTHF6 performance values generated by the healthy control group in the wrist block condition (95%CI = 9.03 - 11.14 s), but was within the 95% confidence interval for healthy control participants in the elbow block condition (95% CI = 8.78 - 13.23 s).

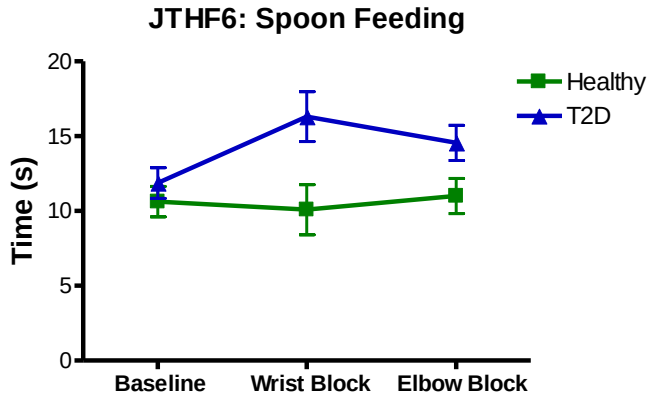

Figure 4.11. Mean and standard error of completion times for JTHF6 (simulated spoon feeding). Data for T2D and healthy control *Groups* are shown in the three tested *Conditions* (baseline, wrist block, and elbow block).

The last JTHF subtest (JTHF7), used to assess handwriting speed, indicated nearly significant differences between the T2D and controls *Group* ($F_{1,7} = 5.54$, $p = 0.051$), depicted in Figure 4.12. No other main effects or interaction effects were found. In reference to our hypothesis, the mean value of JTHF7 performance by the T2D group at baseline (24.86 ± 9.03 s), was not within the 95% confidence intervals of the mean JTHF7 performance values generated by the healthy control group in the wrist block (95% CI = 10.13 - 22.69 s) and elbow block (95% CI = 8.70 - 23.04 s) conditions.

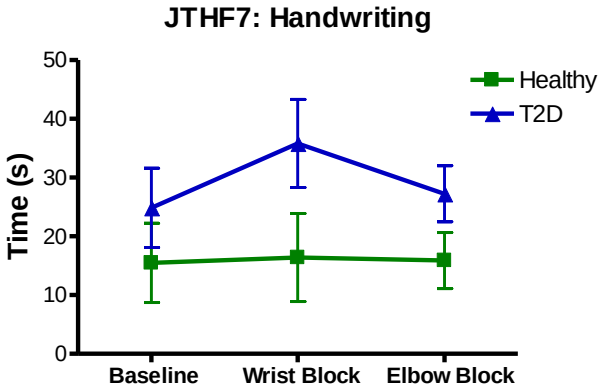

Figure 4.12. Mean and standard error of completion times for JTHF7 (handwriting). Data for T2D and healthy control *Groups* are shown in the three tested *Conditions* (baseline, wrist block, and elbow block).

CHAPTER V

DISCUSSION

5.1. General Discussion

The purpose of this study was to determine the contribution of tactile and proprioceptive feedback on hand motor function in patients with T2D as compared to heathy age- and sex- matched controls. More specifically, in our initial hypothesis, we expected patients with T2D to display similar sensorimotor behaviors at baseline under either or both of the anesthetized conditions of wrist block or elbow block in the healthy control group. Our alternative hypothesis was that patients with T2D will exhibit different motor behaviors at baseline compared to control participants under either or both of the anesthetized conditions. Tactile and proprioceptive functions were assessed using the Semmes-Weinstein Monofilament Test, tuning forks, and digit spatial orientation (kinesthesia). Motor behaviors were assessed via maximal production of grip and pinch forces, submaximal force production, and two dexterity examinations (Functional Dexterity Test and Jebsen-Taylor Hand Function Test). Some variables of interest for each of the motor assessments provided evidence to confirm the primary hypothesis, while other provided evidence that supported the alternative hypothesis. Particularly, the clinical testing batteries supported the primary hypothesis, while the more sensitive kinetic testing measures indicated significant support for the alternative hypothesis.

Sensory measures for the Semmes-Weinstein Monofilament examination suggest that mean tactile threshold of the T2D group was similar to those values produced by the control group during both of the anesthetized conditions, indicating that the delivery of anesthesia to the control group successfully raised their tactile detection thresholds to the level of tactile

impairment of T2D patients at baseline. This confirmation supports the conceptual framework of the primary hypothesis. As expected, and confirmed by our prior work (Gorniak et al. 2014, Ochoa & Gorniak, 2014), tactile difference existed between the groups across all conditions, particularly for the median nerve. Analysis of tactile sensation of the median and ulnar nerves, digit 1 and digit 5 respectively, served as a control establishing the differences in tactile sensitivity. The injection methods used successfully targeted tactile function of the median nerve, while tactile function of the ulnar nerve remained unchanged across all conditions (Figure 4.1).

Additionally, vibratory thresholds were assessed. The findings of the vibratory threshold examinations were based upon assessment of digit 1 and digit 5, as conducted for the Semmes Weinstein monofilament examination. No perceivable differences were noted amongst the sites, conditions, or groups, thus also supporting the theoretical framework for our primary hypothesis. In fact, all participants were able to detect vibratory sensations in all of the sites, with the exception of one T2D participant who failed to sense vibration in both wrist and elbow block. This evidence suggests that the deep Ruffini endings remain intact and responsive to vibratory stimuli despite the medically- induced anesthetized states for the controls group and T2D patients. Concurrently, this evidence provides support for the etiology of Diabetic Peripheral Neuropathy and its initial dysfunction of small nerve fibers that progress into the large nerve fibers with increase in disease severity (Walk et al. 2003, Capellari et al. 2005, Kandel et al. 2013, Papanos et al. 2011, Gorniak et al. 2014, Ochoa & Gorniak 2014). It appears that although small nerve dysfunction was evident in this population as evidenced from tactile dysfunction, whereas the large nerve fibers were preserved from dysfunction.

Proprioception was assessed utilizing a kinesthetic examination specific to this study. Again, assessment of the median and ulnar nerve determined the sites and function to be conducted. Three major tasks were utilized (1) touching of tip 1 and tip 2 which focused primarily on muscle movements innervated by the median nerve (2) touching of tip 1 and tip 5 which utilize muscles innervated by both median and ulnar nerves, respectively and (3) thumb abduction/adduction which utilize muscles again innervated by the median nerve. No difference between the groups was noted; however, the conditions presented significant findings. While at baseline, T2D and healthy groups could correctly manipulate the tasks in the absence of visual feedback, once the diminished sensory induced states were implemented, the corrective mechanisms of each of the groups were distorted resulting in significant amount of errors produced by both groups. Contrary to the preserved proprioceptive function observed in (Nowak et al. 2003), by applying a more general nerve block targeting the function of the entire hand compared to the digital block, we identified loss of proprioceptive function during each of the anesthetized conditions. However, although dysfunction is evident, the lack of group differences once again suggests that motor behaviors of the two groups should remain similar across all tested conditions, as put forth in the primary hypothesis.

5.1.1 Assessment of Motor Deficits induced by Anesthesia

Assessment of motor function via timed clinical measures, namely the Functional Dexterity Test (FDT) and the Jebsen-Taylor Hand Function test (JTHF), were utilized to assess differences in timed manual dexterity and activities of daily living for T2D and healthy groups. Overall, the FDT suggests that the two groups are different throughout the

examinations such that the T2D times to completion are much larger than those for the healthy group. In reference to our hypothesis; however, the average times of the T2D were within the range of time for the anesthetized conditions in the healthy control group, therefore these findings provide evidence to support our primary hypothesis. Similarly, all of the subtests for the JTHFT with the exception of three (JTHF3, JTHF6, and JTHF7), indicated that the average value for the T2D group were included within the range for the anesthetized conditions of the healthy group. These findings also support our primary hypothesis, such that the T2D motor behaviors for clinically validated examinations were unable to detect differences among the T2D group at baseline and the healthy control group in the two anesthetized conditions.

In accordance with our previous work (Gorniak et al. 2014, Ochoa & Gorniak 2014) these clinical tests may not be sensitive to subtle changes in sensorimotor behaviors induced by metabolic diseases such as T2D. The tasks for these examinations focus on combinations of fine and gross motor movements such as the three-jaw chuck grip (FDT) performed by muscles innervated by the median nerve and the lifting of small and large objects (JTHF). While these findings superficially display evidence that the sensory system may be responsible for the differences, i.e. increased time to completion of tasks for the T2D group, a more sensitive measure of physiological changes should be analyzed to reveal a clearer picture of the extent of damage in this T2D group.

The T2D group, overall, displayed reduced force production during the maximal grip production task compared to the healthy group. However, grip forces produced in the anesthetized conditions did drop, suggesting that these differences may be attributed to tactile deficits. The gross tasks of maximal force production may not be the best indicator of minute

physiological difference since the muscle bellies responsible for the greatest amount of force production reside outside the hand and in the forearm. Furthermore, loss of motor function to this degree is typically indicative of large nerve fiber dysfunction (Vinik 2011), and thus cannot detect subtle changes that may be occurring concurrently with the disease process. It is possible that slight muscle paresis did occur with the introduction of a Na+ channel blocking anesthesia (eg. lidocaine), causing a reduction in force output. Furthermore, the maximal pinch tasks displayed similar behaviors to the maximal grip with the exception of absent differences between overall force productions between the groups. Again, the pinch tasks were within the values generated by the medically-induced states such that the loss of force could be attributed to the sensory deficits or the introduction of slight muscle paresis due to Na+ channel blocking. Further analysis utilizing tests that can detect more subtle differences are warranted to properly assess the dysfunction of small nerve fibers rather than large nerve fibers.

Analysis of temporal and complexity components of the submaximal data produced were components of this study that specifically supported the alternative hypothesis. Root mean squared error (RMSE) and coefficient of variation (CV) were much larger in the T2D group, indicating a production of larger tracking errors by the T2D group, potentially related to the firing of motor units and their response to neural excitability. These values were not within the range of the healthy controls during either of the anesthetized states, supporting our alternative hypothesis. More importantly, these results indicate damage beyond the sensory system may be contributing significantly to motor dysfunction in T2D. The exact mechanism(s) responsible are currently unknown; however, the data presented in this thesis provide evidence to rule out the sensory system as the primary contributor to manual

dysfunction. This method of analysis is more detailed and more subtle than gross motor changes as perceived by manual dexterity and/or maximal force production.

Approximate entropy (ApEn) values were noted to be lower in the T2D group while the values for Detrended Fluctuation Analysis (DFA) were larger than those for the healthy group, similar to results found in our previous publications (Gorniak et al. 2014, Ochoa & Gorniak 2014). The differences in both values in the T2D group suggest higher signal predictability in the T2D, indicating significant neural changes occurring with the disease. Although the ApEn values in the wrist block suggest inconclusive changes, those for the elbow block express support for the alternative hypothesis. ApEn increased throughout all the conditions in the submaximal tasks, suggesting significant changes to the motor system affecting motor unit firing rates. While DFA values of the T2D group at baseline were within the range for the anesthetized conditions of the healthy group, the variability exhibited by the T2D group at baseline may have played a significant role in this finding.

5.1.2 Concluding Comments

Although, some of the results presented in this thesis are conflicting in that some are suggestive of sensory dysfunction, while the others are not, combined they indicate a shift in the overall nervous system, not just the sensory system in patients with T2D. Given this evidence, it is likely that changes in motor unit organization and recruitment (Gorniak et al. 2014) as well as subtle changes in the central nervous system are responsible for the changes in manual function exhibited by patients with T2D, consistent with our previous publications (Gorniak et al. 2014, Ochoa & Gorniak 2014). With this new evidence, the next steps of this investigation involve: (1) investigation of how changes to motor units affect manual function

in T2D, and (2) investigation of any changes in the sensory and motor cortices of T2D patients. Results from these future studies may be used to adapt medical management of T2D in relationship to self-care disability in T2D patients.

CHAPTER 6

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