CHANGES IN EFFECTIVE NEURAL CONNECTIVITY FOLLOWING A CHIROPRACTIC ADJUSTMENT

by

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(Under the Direction of Rebecca Shisler Marshall)

ABSTRACT

Individuals who receive chiropractic care often report improvement in cognitive performance, yet little is understood about how the improvements occur. In this study a secondary analysis of electroencephalography (EEG) data from a previous chiropractic randomized controlled trial was analyzed at three time points. The purpose of this study was to assess changes in brain communication patterns following a single chiropractic adjustment. Brain communication changes were measured using Phase Slope Index, a measure of the direction and magnitude of communication between two brain regions. Fourteen Brodmann areas were assessed that had either shown previous responses to chiropractic or were related to cognitive task performance. Similar to previous chiropractic research, the results for the adjustment group demonstrated changes within the brain in areas associated with executive function, attention, and spatial awareness. These included the prefrontal cortex and posterior cingulate cortex, with unique changes in the dorsal lateral prefrontal cortex. Contrary to expectations, changes similar to previous chiropractic research were also noted in the sham group; these included the somatosensory cortex and posterior cingulate, with a unique presentation in the visual association area. Both the adjustment and sham groups demonstrated

changes in regions associated with cognitive task performance: anterior brain regions for the adjustment group and more posterior regions for the sham group. While the brain demonstrated different changes between the groups, more research is needed to delineate the effects of sham related factors such as touch from the adjustive force effects. Relative to time, few changes were noted between the baseline and post assessment, and in some instances the additional observation of the one-week time point demonstrated lack of sustained changes. Regional brain connectivity changes were most noted at the one-week time point. Overall, the results of this study suggest that a single session of chiropractic can change brain communication patterns, that those patterns are different from an applied sham adjustment, and that the changes occur over one-week. Further, additional insight was provided into the need for more research in the development of a sham adjustment protocol that accounts for individual complex elements of the chiropractic adjustment, such as touch.

INDEX WORDS: Chiropractic, Adjustment, Sham, Spinal manipulation, Phase Slope Index, Electroencephalography, Effective connectivity

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DEDICATION

This dissertation is dedicated to the patients of chiropractic – past, present, and future – that I and other chiropractors have the privilege of serving.

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CHAPTER 1

INTRODUCTION

Chiropractic from its early beginnings as a profession was based on the belief that the chiropractic adjustment of the articulations of the spine influenced the function of the central nervous system. (1,2) In fact, the first adjustment was said to restore hearing to a man who became deaf following a fall from a ladder. (3) Clinically, chiropractic research has documented changes in such symptoms as attention, memory, reaction time, spatial cognition and executive function. (4-7) In one study using a series of eight standardized psychometric tests, 157 developmentally delayed children were assessed before and after chiropractic care. The study noted improvement post-care in twenty domains of cognitive function (4); however, little is understood about how these observed changes occur. This lack of research and understanding may be one reason for chiropractic's limited acceptance as an applied neurologic therapy for pathologic conditions or as tool for cognitive performance enhancement. Instead, chiropractic is predominately relegated to musculoskeletal conditions and pain syndromes. (8)

Recent chiropractic neurophysiology research is beginning to address this lack of understanding. One method used to gain a deeper understanding is the use of a stimulus-locked paradigm, such as somatosensory evoked potentials. (9-11) This approach applies an external input, such as an electrical impulse on a peripheral nerve. The impulse is tracked through the peripheral and central nervous systems (CNS), providing data relative to changes in location, latency, and magnitude of the neural response. (9-11) Using the stimulus-locked model, chiropractic researchers have been able to demonstrate neuroplastic changes in the brain

following a single instance of spinal adjustment. (9-11) For example, using somatosensory evoked potentials (SEP) of the median nerve, changes were observed in the cortical peaks known as the parietal N20 and frontal N30. These peaks are associated with early sensorimotor integration. (9-11) To identify the regions of the brain responsible for changes in the N30 peak amplitude, a follow up study was performed using electroencephalography (EEG) source localization technique. (11) The N30 peak demonstrated the most consistent changes following chiropractic; therefore, it was utilized in the study. The regions assessed by Lelic in the follow up N30 peak study were the primary and secondary somatosensory cortices, cingulate and prefrontal cortex. Lelic found that only the prefrontal cortex was a significant contributor to the N30 peak changes. (11)

From this line of research, a sensorimotor integration model evolved that attempts to explain how a chiropractic adjustment produces neuroplastic change. (12-13) It is suggested that regions of spinal dysfunction, such as those experiencing diminished mobility, generate altered afferent input to the CNS. (12-13) This altered afferent input interferes with the body's ability to know where it is in space. (12-13) When a force is applied, such as a high-velocity, low amplitude chiropractic adjustment, that force restores the normal movement pattern of the articulation and the central afferent input. (12-13) Neuroplastic changes in the brain occur quickly, and disrupted movement patterns lead to regional alterations in brain sensory perception. (14-15) Just as the brain changes within days of immobility, such as when a nerve is severed, (14-15) regional and whole brain networks may change as a consequence of spinal dysfunction, commonly called a subluxation within the chiropractic profession.

Studies evaluating the consequences of the subluxation on regional and whole brain networks have yet to be done. Although, based on a series of studies designed to test the

sensorimotor integration model, it is understood that the chiropractic adjustment influences early sensorimotor integration and centrally initiated motor responses, which can influence motor behavior. (9-10,16-17) Using transcranial magnetic stimulation, motor evoked potentials of the gastrocnemius muscle were measured before and after chiropractic spinal manipulation. Following spinal manipulation motor evoked potentials were increased compared to control participants. (17) This line of research further supports the sensorimotor integration model, but does not provide a mechanism for understanding changes in cognitive function in relation to sensorimotor integration.

An additional area of chiropractic research related to cognitive efficiency evaluates the ability of the brain to gate (filter) sensory information entering the brain. (18-20) In studies using dual somatosensory evoked potential stimulation to the median and ulnar nerves simultaneously and consecutively, the researchers were able to evaluate how the brain gated sensory information during simultaneous stimulation. (18-20) The studies showed that chiropractic improved the ability of the brain to filter incoming information, suggesting improved cognitive efficiency. (18-20)

Improved cognitive efficiency has been related to alteration in regional and whole-brain activation patterns. (21) Thatcher compared brain effective connectivity to intelligence quotient scores (IQ); effective connectivity provides both the direction and magnitude of communication flow between brain regions. In the study, improved regional connectivity with reduced distant brain communication was observed in the higher IQ children. The lower IQ children exhibited greater communication with distant neural resources. (21) This suggests that when local networks (hubs) are inefficient, compensatory hubs send information to the weak hubs to improve function of the network as a whole. (21) Only one study in chiropractic has examined

network connectivity following an adjustment, and that study focused only on the pain processing network. Using functional magnetic resonance imaging (fMRI) to evaluate functional connectivity between regions of the brain in the pain processing network, spinal manipulation was found to alter connections between the cingulate cortex, anterior insula, posterior insula, periaqueductal gray and primary somatosensory cortex. (22) Different from effective connectivity, functional connectivity only demonstrates whether a connection exists, not the direction and magnitude of the connectivity. (21-22)

To date, no chiropractic study evaluates changes in effective connectivity following an adjustment. In order to uncover the possible mechanism of action for the chiropractic adjustment in relation to neural connectivity, evaluation of both regional and whole brain network changes is needed. Therefore, this study proposes a secondary analysis of previously collected chiropractic data in order to perform an effective connectivity analysis assessing regional brain network changes following chiropractic care. In the previous clinical study (NCT01953614), resting state EEG data was collected on thirty participants randomized to one of three groups of ten: chiropractic, sham (placebo), or control group. The previous analysis of this data demonstrated significant changes in surface activation patterns in the chiropractic adjustment group compared to the sham and control groups, and these changes were sustained at one-week post. Similar to the Thatcher effective connectivity and IQ research, this study will use Phase Slope Index (PSI) as the effective connectivity assessment protocol. (21) The purpose of this investigation is to identify the effect of a single dose of chiropractic spinal manipulation on brain communication patterns of healthy individuals immediately after and one-week post spinal manipulation, and also to determine if the effects immediately after spinal manipulation are similar to the effects one-week post.

CHAPTER 2

REVIEW OF LITERATURE

Chiropractic is a profession founded on the premise that correction of abnormal joint position and motion restores proper function to the nervous system. (1-3,26-27) Research is beginning to explore the effects of chiropractic care on the brain, although little attention has been given to how the care changes brain communication patterns. Considering the interdependence between brain regions and diminished brain function that can occur with damage (23-25), understanding the effects of chiropractic care on communication patterns within the brain may provide insight into the role of chiropractic as a therapeutic intervention for pathology or improved human performance.

The following will provide insight into the history and development of chiropractic as a nervous system related profession and discuss research on two foundational hypotheses related to joint level mechanisms that may underlie cortical changes in the brain. The two foundational hypotheses discussed are the nerve compression hypothesis and the sensory insult hypothesis. Based on the sensory insult hypothesis a proposed model will be discussed along with associated research suggesting that the presence of joint dysfunction leads to a breakdown in sensorimotor integration as a result of aberrant sensory input. (12-13) Then, the implications of the model and research will be discussed in relation to cognition, the forward model and sensory gating as a connection between previous chiropractic research and proposed changes in brain communication patterns that are the focus of this research. Finally, information regarding the

technology and system of analysis being used to assess potential brain communication changes following chiropractic care will be provided along with the study aims and hypotheses.

Introduction to chiropractic: a neurologically focused branch of manual therapy.

From the Shamans of Central Asia to the Greeks and bone setters of Nepal, the practice of manipulating the spine emerged as a therapeutic intervention across several different cultures and times. (26-29) Manipulation descriptions and techniques used by such early pioneers in the field of medicine as Hippocrates (460-385 BCE), Galen (131-302 CE) and Avicenna (980-1037 CE) were preserved and continue to be represented in modern medical texts. (26) While these writings influenced scholars and Western medicine, it wasn't until the 19th century that varying perspectives and philosophies related to manipulation of spinal articulations began to formalize. (26-29) This ultimately moved the practice from the domains of folk healing and bone setting to those of licensed and acknowledged professions.

Emerging in relative isolation, the three main contemporary professions practicing manipulation in the early 1900s were medicine, osteopathy and chiropractic. (26-27) Chiropractic's primary philosophical focus is the effect of spinal manipulation on the nervous system. (1-3)

While medical writing provided much of the foundation for the technique of spinal manipulation, it was DD Palmer who was credited with the establishment of the discipline of chiropractic; he applied the therapy based on past experience and study. (3) In addition to studying manipulation from the writings of medical doctor Jim Atkinson, DD Palmer was a magnetic healer and avid student of science and anatomy. (26) Following the application of a manual thrust to a misaligned vertebra that restored hearing to a deaf janitor, Palmer reasoned

that the out-of-place bone decreased nerve impulses, affecting remote body systems and thereby causing deafness. (3)

Based on his study of anatomy, the nervous system in particular, Palmer established chiropractic on the premise that the cause of disease was impingement or irritation of the nerve leading to an alteration in the tone or vibration wave of the nerve. (3,26-27) Palmer proposed that the skeletal system acted as a nerve-tension frame. (1-3,26-27) When a vertebra was displaced from a normal position, the nerve would be impinged or stretched, causing tension and change in the vibration properties of the nerve. (1-3,26-27) The proposed change in neural tone and vibration lead to altered communication within the nervous system, brought about by the displacement of a vertebra – termed a subluxation. Palmer suggested that the neural effects of subluxation was the cause of all disease. (1-3,26-27)

Although the field of chiropractic began in 1895, the concept of relating the cause of pathology to the spine was not new. (27) In 1871, William Hammond released his book *Treatise on Diseases of the Nervous System*, which discusses the growth and history of the "spinal irritation" concept. (27) Spinal irritation embraces the idea that pathology of the spinal cord can lead to disease. Similar to chiropractic, the spinal lesion was diagnosed through tenderness upon palpation of select vertebrae associated with particular spinal nerves or sympathetic ganglia. (27) The medical profession at that time associated irritation of the spine to diseases such as mania, vertigo, colic, asthma and diabetes. (27) The treatment for the patient included leeching, irritants to induce blistering, or galvanic current to the site of tenderness. (27) In contrast, Palmer's approach was simply to manipulate the spine (also called an adjustment) to restore the normal juxtaposition of the vertebrae. (1-3)

D.D. Palmer, along with his son B.J. Palmer, continued to grow and advance the profession of chiropractic, opening schools, establishing chiropractic professional organizations, and defending chiropractic in the court system as a distinct healing art. (1-3,30-33) The distinction being that chiropractic adjusted the spine and articulations with the intent to influence the nervous system. (1-3,30,34) This was contrary to osteopathy, which is another branch of manual therapy, that manipulated the spine, but in an effort to influence the vascular system of the body, as opposed to the nervous system. (26)

Currently, chiropractic is one of the most commonly utilized forms of complementary and alternative therapy - practiced in over one hundred countries. (8, 35-36) The practice has evolved to include various forms of manipulation, both of the spine and the extremities. (8) These range from traditional hand application of high velocity low amplitude thrusts using patient bony landmarks as levers for force application to low force instrument adjustment of the spine and extremities. (37-40) Some methods even apply the adjustment through use of an instrument mounted on a frame for placement on a specific vertebral location, such as the C1 (atlas) vertebral transverse process. (37-41) Through the evolution of the various manipulative techniques, much has been learned about the biomechanics of the spine and how best to deliver a therapeutic thrust; however, remaining at the core of the profession is the philosophy that the adjustment is delivered to influence the nervous system. (3,30,37)

In summary, since the establishment of the profession in 1895 and identification through the court system as a separate and distinct health care profession, (42) the influence of the subluxation on the nervous system has been acknowledged and represented in state and other legal doctrines related to scope of practice. (43) Thus, maintaining DD Palmer’s initial premise that adjustment to a vertebra out of alignment influences the nervous system. (1-3,34) The field

of chiropractic has evolved to include a number of different techniques to adjust the spine and influence the nervous system, and while much of the research in the profession focuses on delivery of the adjustment and clinical outcomes, basic science research designed to gain understanding of the mechanisms of action related to the adjustment are beginning to evolve. (37,44) Current research provides insight into the basic science research related to joint level neurophysiologic research.

Joint level chiropractic neurophysiologic research:

Neurophysiologic research within the chiropractic profession is still relatively young. (12-13,16,31) The evolving science of chiropractic was initially based on adoption of related basic science studies as an explanation for the results obtained through care. (33) For instance, it was believed that a vertebra out of alignment with the vertebrae above or below impinged upon the intervertebral foramen (IVF) created between the two vertebrae, leading to compression of the nerve root as it exited the foramen. (1-3,31,34) It was further believed that this compression on the nerve root led to afferent (sensory) changes that influenced reflex systems within the body or resulted in efferent (motor or secretory) changes with potential visceral or skeletal consequences. (1-3,31,34) This was called the nerve compression hypothesis, and this hypothesis is one of two main hypotheses in chiropractic literature. (1-3,31,34) Understanding the prevailing research related to joint level mechanism of action for the chiropractic profession provides the foundation for further interpretation of the research regarding changes observed in the brain following an adjustment.

Nerve compression hypothesis: The nerve compression hypothesis was initially proposed by DD Palmer, who believed that the abnormal position of a vertebra impinged upon the nerve exiting the intervertebral foramen between the abnormally positioned vertebra and a neighboring

vertebra. (1-3,31,34) This hypothesis gained strength from such basic science studies as those conducted by Sharpless, Gelfan and Tarlov, who studied the susceptibility of spinal roots to compression. (45-46) One study by Sharpless in the early 1970s demonstrated that pressures as little as 10 mmHg resulted in a nearly fifty percent reduction in compound action potential values in rat and cat dorsal nerve roots (L4-L7) dissected free of surrounding tissue. (45) Compression as a mechanism for decrease in compound action potential propagation was supported by further animal studies such as those performed by Gelfan and Tarlov in the 1950s, who studied anoxia and compression in the spinal nerve roots of animals, determining that compression more so than anoxia was responsible for conduction block within the nerve. (46) Nerve root studies in the 1960s and 1970s demonstrated additional consequences such as axonal degeneration and metabolic alterations in the nerve root following compression or irritation. (47-50) These early studies on changes in compound action potential propagation following compression, while not directly assessing joint level changes following displacement of a vertebra, provided the chiropractic profession with a potential mechanism through which vertebral level changes could lead to remote consequences.

To advance the nerve compression hypothesis, anatomical studies of the IVF and other vertebral structures illustrated regions with potential to compress the nerve root and associated vascular supply. (37,47) For instance, natural extension movement narrows the IVF, and under normal conditions the nerve root creates a smooth piston movement; however, development of fibrous adhesions within the tissues due to lack of movement can fix the nerve trunk in its bed, reducing mobility, limiting tolerance to deformation. (51) Cadaver and magnetic resonance imaging (MRI) studies noted that changes within the discs, facet joints, joint capsules and ligamentous structures of the spine have the potential to lead to compression of the spinal nerve

root or spinal cord. (37, 44, 52-53) The compression may be a result of direct insult or inflammation, including edema. (44)

Cadaver and MRI research also identified transforaminal ligaments. (37,44,54-56) These ligaments traverse the IVF and significantly decrease available space within the IVF – an average 31.5% decrease in superior to inferior space. (54-56) The decrease in space as a result of the transforaminal ligaments, could lead to compression or irritation of the nerve root. (37,44,54-56) While none of the studies were designed to directly test the effects of joint malposition on nerve root compression, one MRI research study conducted by Cramer et al. assessed the dimensions of the 5th lumbar spine IVF before and after an adjustment to the vertebrae. Following the adjustment, the participants exhibited gapping of the target zygapophyseal joints, suggesting improved IVF space following application of the 5th lumbar spinal manipulation. (57-58)

While the nerve compression hypothesis still presents a plausible explanation for the effects of abnormal joint position and motion on the nervous system, it has been acknowledged in the profession that direct compression, especially due to direct vertebral pressure, is an extreme simplification. (31) Further, research on this topic seemed to shift towards understanding the sensory consequences of a displaced or immobile joint. A 2006 review of the basic science literature for the chiropractic profession from 1995 to 2006 only listed four studies of relevance to the nerve compression hypothesis. (37) Two studies were on the transforaminal ligaments, demonstrating that the transforaminal ligaments are present in 60% of lumbar vertebrae and that the ligaments may calcify. (54, 59) The third study measured the pressure between a herniated disk and the nerve root. This study was performed in 34 individuals undergoing surgery for lumbar disk herniation; it was found that the pressure between the

herniated disc and nerve root averaged 53 mmHg. (60) When paired with the previous studies on the changes in nerve compound action potential with as little as 10 mmHg, it may be too soon to completely rule out the nerve compression hypothesis. The fourth study by Song used a reversible IVF encroachment and inflammation model at the 4th and 5th lumbar vertebra and observed increased excitability of the dorsal root ganglion, which resolved upon reversal of the IVF encroachment. (61). Although the studies by Cramer, Song and Takahashi continue support for the nerve root compression hypothesis, it is unknown why the field of chiropractic research appears to have migrated more towards the sensory insult hypothesis. Perhaps, it was the acknowledgement that the subluxation is more complex than just compression of a nerve and that more research needed to be conducted through exploration of other areas. In particular, one area of research for the sensory insult hypothesis serves as a foundation for a series of studies on sensorimotor integration at the cortical level.

Sensory insult hypotheses: Understanding of the relationship between sensory innervation of paraspinal structures and the spinal manipulative thrust was aided by the development of animal models paired with a servo-driven motor system. (37) The servo-driven motor allowed for application of a specified force to a vertebra; the force was designed to mimic the force applied during an adjustment. (37) The animal model enabled the researcher to record the effects of force application on the following: the neural activity of the dorsal roots, the discharge properties of paraspinal tissue primary afferents and the remote physiologic and neurophysiologic changes within the animal. (37)

In order to demonstrate changes in the afferent firing patterns of muscle spindles and GTOs following simulated spinal manipulation, Pickar and colleagues utilized the animal model in a series of single unit electrophysiologic recordings. (62-66) Muscle spindles and GTOs are

considered proprioceptive sensory fibers, providing information about body position. (62-66) In a series of studies, firing patterns of the muscle spindles and GTOs were measured following varying durations of simulated spinal manipulation. It was found that paraspinal GTOs and muscle spindles experience different discharge frequencies depending on the duration of the manipulative force. (62-63,66-68) When force duration approximates that of a traditional chiropractic spinal manipulation (100 to 150 ms) the discharge frequency increases, also GTOs and muscle spindles are co-activated, indicating a stronger response due to the increased firing from both sensory fibers. (62-63,66-69) With slower force-time profiles, co-activation of the sensory fibers does not occur. The co-activation with increased responsiveness of GTOs and muscles spindles to high speed (short-duration) forces in the animal model was reflected in human studies by Herzog that used electromyography (EMG) to assess changes in paraspinal muscle tone with varying speeds of manipulation. (37,69) Manipulations approximating 100 to 150 ms resulted in consistent and predictable EMG responses. (37,69) This means that the standard high velocity, low amplitude thrust may provide a predictable mechanism of influencing the nervous system.

The studies above provide information on the potential proprioceptive consequences of a chiropractic manipulation; however, not addressed are the consequences of the actual subluxation. Meaning, what effect do the vertebrae out of alignment have on afferent firing patterns? (37, 62,67,66,69-70) Pickar's lab also examined this question. In cats with lumbar vertebrae held in a position that stretches (holds-long) the paraspinal muscles, activation of muscle spindles decreased in mean discharge rate by -2.0 to -16.1 impulses per second. (71) The hold-long position simulates a vertebral misalignment, where the vertebra is positioned abnormally, stretching the proprioceptive fibers. In the study, two-seconds in the hold-long

position resulted in decreased discharge frequency of the muscle spindles by -5.7 to -10.0 impulses per second with movement of the vertebra. (71) When the simulated spinal manipulation was applied to the previously held-long motor unit, a partial reversal of the muscle spindle decreased discharge rate occurred. (64,72) This has two potential implications for chiropractic. First, this research suggests that a vertebral misalignment, a subluxation, held for as little as two seconds decreases the rate of firing for the proprioceptive muscle spindles. Second, if a spinal manipulative thrust, a chiropractic adjustment, is applied to the misaligned segment, then some return of the normal firing pattern is restored. While this research was just assessed in an animal model, it does indicate a potential mechanism describing the consequences in afferent proprioceptive firing patterns of a subluxation and the potential for improvement related to the adjustment. (64,71-72) The work conducted by Pickar and colleagues has been instrumental in providing understanding of the potential proprioceptive response to chiropractic care. (37) Prior to this work it was only speculated that proprioception was influenced through spinal adjustment. (1-3,49,73)

Beyond chiropractic, this phenomenon of altered proprioceptive sensitivity and responsiveness following sustained stretch or contraction has been studied for over thirty years in relation to properties of the muscle. (74) A review by Proske in 2014 even cautions researchers studying proprioception to be mindful of this inherent striated muscle characteristic, which includes the intrafusal fibers of the muscle spindle. (74) When a muscle is held in a stretched position, approximately one percent of the actin and myosin in the sarcomeres spontaneously form new, non-force generating cross-bridges. (75) Following release from a sustained stretch, slack is generated in the muscle because of the bound cross-bridges. Further, when a muscle is released from extended shortening, the non-force generating cross-bridges lead to a more taught

muscle fiber. (76) This altered tension position of the muscle – slack or taught – leads to altered firing patterns. (74,76-77) This property of muscle fibers is known as thixotropy, and while there is still some debate around the theory, especially relative to the role of the titin molecule, application of this concept through muscle conditioning has been shown to change in response to Achilles tendon reflex stimulation, the Hoffman reflex, awareness of body position sense, and cortical excitability as assessed by motor evoked responses following transcranial magnetic stimulation. (76, 78-83) While compression of the slack or taught muscle fibers by adjacent fibers has been proposed as a natural mechanism that breaks the cross-bridges, a series of rapid stretches (5 mm/s) to the muscle have also been shown to break the cross-bridges, restoring the normal firing patterns of the muscle. (84) The concept of thixotropy may aid in explaining some of the muscle spindle and GTO responses observed in the chiropractic experiments performed by Pickar and colleagues, especially given the partial restoration of muscle spindle firing patterns following simulated manipulation. (62-64, 74, 76) More research would need to be conducted examining the effects of chiropractic on muscle fiber tension state, specifically actin and myosin cross-bridge formation, to determine if thixotropic muscle properties are a potential mechanism of action for neurophysiologic responses observed following chiropractic.

Research examining the changes in proprioceptive responses to the adjustment have also been performed in human studies. The Hoffmann Reflex (H-Reflex) was used to test motor neuron response to stimulation of the tibial nerve (Ia afferents) before and after an adjustment. (85-88) The H-Reflex is analogous to the muscle stretch reflex, following the same 1a sensory (afferent) pathway, although instead of being stimulated by muscle stretch, the H-Reflex is triggered by an electrical stimulation. (85-88) The stimulation is transmitted through the spinal cord to synapse onto the alpha motor neuron (efferent fiber) leading to stimulation at the

neuromuscular junction and elicitation of a twitch in the target muscle. (85-88) A study by Floman assessed changes in the latency (time from stimulus to response) and amplitude (level of response in millivolts) of lumbar disc herniation patients before and after side lying lumbar chiropractic adjustments. (85) Patients who presented with an abnormal H-Reflex on the symptomatic side of the body compared to the asymptomatic side experienced a significant increase in H-Reflex amplitude. Latency of the symptomatic side was also improved (decreased) but did not reach statistical significance. (85) Another study assessed H-Reflex changes comparing a chiropractic manipulation to the sacroiliac joint and a sham manipulation. (86) Following the chiropractic manipulation, a 12.9% (statistically significant) attenuation (decrease) of the H-Reflex amplitude was observed, and no significant change was observed following the sham. Uniquely, this study applied a topical anesthetic in a second series of assessments to determine if the response occurred as a result of cutaneous afferent stimulation. A 10.6% (statistically significant) decrease in H-Reflex amplitude was again observed in the chiropractic group and not in the sham. (86) Given that the H-Reflex stimulation is delivered transcutaneously, the fact that the H-Reflex still decreased in the presence of anesthetic further implicates the spinal manipulation as the causative agent as opposed to skin receptor (touch) activation leading to the changes in H-Reflex response.

Beyond changes in the H-Reflex observed in the Murphy and Floman studies, Dishman in a follow up study used transcranial magnetic stimulation (TMS) of the gastrocnemius muscle to examine changes in brain related responses (corticospinal) following lumbar spinal manipulation. (89) This technique assessed the effect of chiropractic on activation of the alpha motor neuron pool through evaluating the amplitude (microvolts) of motor evoked potentials in the gastrocnemius muscle. In the study an adjustment to the lumbar spine in side-lying position

was compared to a control group placed in a similar adjustment position with no thrust. The Lumber adjustment served to facilitate (increase) motor evoked potentials of the gastrocnemius muscle compared to positioned but non-adjusted controls. (89) While opposite the attenuation of the peripherally based H-Reflex, this study suggests that centrally initiated responses can be mediated by the chiropractic adjustment – possibly from muscle spindle and GTO activation. (89) This research adds to the joint related chiropractic literature, suggesting that muscle and joint sensory fibers, such as proprioceptive muscle spindles and GTOs may mediate reflex and cortically initiated motor responses. (85-86, 88-89)

These two hypotheses and the associated research suggest plausible joint related influence on the nervous system, including the brain: the nerve compression hypothesis and sensory insult hypothesis. The nerve compression hypothesis proposes that compression and irritation of the nerve root does occur with aberrant motion or displacement of a joint from its normal position and that these changes can influence such neuron specific mechanisms as action potential propagation. (1-3,31,34,47-50) Further, with the implementation of an animal model that simulates spinal manipulation, downstream consequences of compression such as blood pressure changes have been documented. (37,90) The sensory insult hypothesis has received support from both animal studies and human studies. (62-68,71-73, 85-89) Specific evaluation of paraspinal muscle spindles and Golgi Tendon Organs suggest a proprioceptive consequence related to changes in vertebral movement and displacement along with application of a simulated or actual spinal adjustment. (62-64,71-72) While both the nerve compression and sensory insult hypotheses may contribute to changes in brain function, the sensory insult hypothesis has been the focus of research and chiropractic theories directly related to cortical function. (12-13)

Therefore, basic research outlining the neurophysiologic components is important to understanding the mechanism of action in chiropractic treatment.

Cortical level chiropractic neurophysiologic research:

Basic science research specifically focusing on changes in the activation patterns within the cerebral cortex (cortical) following a chiropractic adjustment has emerged in the last twenty years. (12-13,16) Previous neurophysiology research was focused on changes related to the nervous system at the joint level, meaning where the joint was manipulated or at the site of the subluxation. (85-90) This research provided a foundation for how the brain could be influenced by a chiropractic spinal manipulation. One example is the research conducted by Pickar and others related to the proprioceptive firing responses following application of a simulated thrust. (62-63,68) The proprioceptive system allows the brain to know where the body is in space, and if firing patterns are altered, this could be represented in altered body schema and changes in brain activation patterns. (12-13, 62-63,68)

Research regarding cortical consequence of the chiropractic adjustment have been conducted utilizing somatosensory evoked potentials (SEP) by Dr. Haavik and colleagues out of New Zealand. (9-11,16,18-20) Haavik and colleagues formalized a testable model, adapted from the sensory insult hypothesis. This model proposes that an area of spinal dysfunction produces altered afferent feedback, which when combined centrally with subsequent afferent feedback from the spine and limbs, a state of altered sensorimotor integration of the afferent input results. (12-13) This could be represented in slight clumsiness, for example. If an individual is not able to accurately perceive where he or she is in space, the resulting sensory integration and motor output will be inaccurate, potentially leading the individual to bump into objects more readily. It

is proposed that a chiropractic adjustment applied to the dysfunctional segment corrects the aberrant input, normalizing the sensorimotor integration. (12-13)

To test the model, Haavik and Murphy examined SEP responses following chiropractic cervical adjustments with and without motor training (typing task). (9-11,18-20) Using passive head rotation as the control, only participants receiving the chiropractic cervical adjustment demonstrated attenuation of the N20 and N30 SEP peaks. (9) The N20 SEP peak is thought to represent the receipt of contralateral afferent information from the receptor through the spinal cord, dorsal columns, and thalamus to the primary somatosensory cortex. (91-93) The frontal N30 SEP peak has been shown to reflect early sensorimotor integration, complex cortical and subcortical loops and underlying support for executive function and decision-making tasks. (91-95)

Given the observed attenuation of the N30 peak in previous chiropractic spinal manipulation studies and the multiple brain sites attributed to the N30 peak, a follow up SEP and EEG study utilized dipole source localization of the N30 peak post-manipulation. (11) This study sought to localize the source or sources generating the attenuated signal in patients with subclinical neck pain. This study initially proposed use of a five-dipole model as conducted in previous SEP and EEG research studies; however, given that the data acquisition was time-locked between 20 and 60 ms following SEP stimulus, one of the five dipoles did not fit within the acquisition and analysis protocols. (11) The insula had to be excluded, so the study was adapted to a four-dipole model. Using low-resolution brain electromagnetic tomography (LORETA) dipoles were placed in the following regions of interest: primary and secondary somatosensory cortices, cingulate and prefrontal cortex. (11,96-97) The pre and post chiropractic source localized strengths for each of the remaining regions of interest were evaluated

(ANOVA), and only the prefrontal cortex was found to be statistically significant. No changes were observed in the control condition. (11) This suggests that the prefrontal cortex may be the primary generator for the N30 peak attenuation observed following a chiropractic spinal manipulation. (11)

To affirm the influence of the chiropractic adjustment on early sensorimotor integration as demonstrated in the previously mentioned N30 SEP studies, a follow up study by Haavik examined early (EBP) and late (LBP) bereitschafts potentials in subclinical pain patients. (16) EBP begins up to 2 seconds prior to movement onset and similar to LBP are a measurement of movement related cortical potentials (MRCP), in this case from self-paced contraction of the tibialis anterior muscle in which EMG was used to control for force level. (16) Arising from the supplemental motor area, EBP have been shown to reflect motor preparatory activity. (16,98-100) LBP is recorded at 500 ms prior to muscle contraction and the contralateral primary motor cortex is considered the primary generator. (16,98) The amplitude of both EBP and LBP increased following a chiropractic adjustment. (16) As with the SEP N30 peak studies, this further suggests that the chiropractic adjustment alters early sensorimotor integration. (16) Additionally, unlike previous studies in which the participant was passive and not engaging in a motor activity during SEP assessment, in this study, the participants were performing repeated isometric contractions of the tibialis anterior muscle. (9,11,16) This may mean motor preparatory activity is influenced by the sensorimotor integration changes or there are independent and divergent changes following the adjustment. More research would be needed to determine which of the two scenarios occurs; relative to this study, it is important to note that brain changes have occurred. (9,11,16)

The same study by Haavik and colleagues examining EBP and LBP also utilized transcranial magnetic stimulation (TMS) to study corticospinal excitability. (16) TMS was used to examine motor evoked potential (MEP) amplitudes of the abductor pollicis brevis for a cervical manipulation and the tibialis anterior for full spine manipulation. (16) This allowed the investigators to evaluate changes in motor control through assessment of motor unit recruitment patterns. (16) Utilizing stimulus response curves to evaluate higher versus lower stimulus intensities and evaluate the MEPmax (maximum value of the motor evoked potential), a significant increase in the MEPmax following spinal manipulation was observed. (16) MEPmax has been shown to represent the plateau of the stimulus response curve, reflecting the balance between excitatory and inhibitory components of corticospinal excitability. (101) The results are supported by a previous TMS study that assessed motor evoked potentials (MEP), cortical silent periods (CSP), short-interval intracortical inhibition (SICI) and short-interval intracortical facilitation (SICF) of adjustment and control conditions. (102) While MEP was not observed to change in this earlier study (presumed to be due to the lower stimulus intensity), as expected opposite effects for the other measured values were observed for the abductor pollicis brevis compared to the extensor indicis proprios. (102) SICF and SICI reflect intracortical excitatory and inhibitory processes, respectively, whereas CSP is associated with both cortical and spinal inhibitory mechanisms. (16, 102-103) Pairing the results of both TMS studies with the previously discussed EBP and LBP research, this implies that the changes observed following chiropractic care are more a result of cortical as opposed to spinal level changes. (16, 98-100, 102)

Each of the studies listed above by the Haavik lab lend support to the hypothesis of a cortical consequence associated with the chiropractic adjustment, particularly in relation to

sensorimotor integration. The proposed model put forth by the Haavik lab suggests that altered afferent input, perhaps the result of abnormal joint position or movement, influences sensorimotor integration and the resulting efferent response. (12-13) According to the model a chiropractic adjustment can restore proper sensory input, normalizing the system. (12-13) Through her research and that of her colleagues, Dr. Haavik has been able to demonstrate brain changes following a chiropractic adjustment that are associated with the sensorimotor system and she has been able to demonstrate additional changes in motor response, more as a consequence of cortical changes as opposed to cord level changes. (9-11,16,18-20,102) Further, the changes observed in early sensorimotor response appear to be linked to the prefrontal cortex. (11) Given the observed changes, one topic still to be explored is the potential cognitive consequences of chiropractic care and potential sensorimotor related mechanisms through which the changes could occur?

Before proceeding, an additional consideration related to the mechanism leading to brain changes following chiropractic needs to be discussed. It has been proposed that the changes observed in the brain following a chiropractic adjustment are the result of the force applied to the dysfunctional joint, potentially restoring aberrant proprioceptive firing. (12-13) The control procedure used in the Haavik lab research studies accounts for similarity of movement through use of a protocol that takes the control participants through end range motion of the joints, similar to the chiropractic adjustment group; however, beyond the application of thrust, there is an additional difference between the active adjustment and control groups. (9,11,16) The researchers in the Haavik studies are mindful to not touch the spine in the control group. (9,11,16) This is important because touch, especially to the spine, has been shown to directly influence activation patterns in the brain such as the posterior cingulate, insular cortex,

amygdala, and inferior parietal lobe for C-tactile fiber related stimulation. (104-106) C-tactile fibers are non-myelinated fibers in the hairy skin such as the back or arm, and recent research suggests a relationship between C-tactile fibers and emotion. (104-105) Discriminant touch fibers, while also noted on the hairy skin are present on glabrous skin, such as the hand. (104-105) One study by Kida tested both hairy skin (forearm) and glabrous skin (palm of hand) with near-infrared spectroscopy (NIRS) to examine hemoglobin changes within the frontal polar cortex. (107) The study demonstrated increased oxy-hemoglobin concentration in the most anterior portion of the cortex when the palmar surface of the hand was stimulated, suggesting increased activation of the region. (107) The frontal polar cortex, the most anterior region, in particular, is suggested to perform meta-cognitive representations such as thinking and reflection about actions or values. (107-108) Interestingly, the increased activation only occurred with pleasant touch applied through use of a velvet fabric as opposed to the neutral stimulus applied through use of a piece of wood. (107) Considering the brain changes observed through touch both of the hairy skin and glabrous skin, it is reasonable to suspect that touch to the spine would also influence the brain. This is especially significant for regions of the body dense with C-tactile fibers. Based on studies of the C-tactile fiber related homunculus within the insula, the region attributed to the thoracic spine and scalp are considerably increased relative to other areas of the body. (104-105, 109) The touch component is typically not discussed relative to the chiropractic adjustment or other manual therapies. However, given the emerging research suggesting that touch can influence the brain and considering the dependence of the chiropractic adjustment on touch to the spine (either through the hand or from an instrument), it is suggested that in the future non-force related characteristics of the adjustment also be considered in the development of mechanism of action theories.

Cognitive outcomes of chiropractic care:

One topic the Haavik studies allude to, but do not directly address, are the cognitive consequences observed following chiropractic care. Cognitive changes have been observed in patients following both extended care and immediately pre-post adjustment, although many of the reports are anecdotal. (4-5,110) One immediate pre-post study assessed mental rotation reaction time and demonstrated significant results in participants receiving an upper cervical adjustment compared to those serving as a resting control. (5) In another study psychometric testing was performed on 157 learning disabled children aged six to thirteen before and after a series of chiropractic adjustments. (4) Children were accepted into the study if they had a history of learning, behavioral, performance impairment and/or reading difficulties. (4) This included children with attention deficit hyperactivity disorder (ADHD), dyslexia and other learning disabilities. (4) Eight standard psychometric tests assessing twenty areas of cognitive function were administered by a qualified speech-language pathologist to the children before and after standard Applied Kinesiology chiropractic care; the length of care and care plan were unique to each child. (4) Improvements were noted across all domains with greatest improvement in visual memory, memory load, visual discrimination, auditory perception, spatial orientation, and spatial organization. (4)

The studies listed above are interesting in that the physically applied intervention of chiropractic spinal adjustments resulted in cognitive performance changes, beyond sensorimotor muscle responses. Although it cannot be ruled out that improved motor performance aided in task response to some degree, the use of standard complex psychometric tests such as the Borel-Maisonny test (assesses phonological analysis and memorization) or the Oriented signs test (requires visual discrimination and visuospatial memory) would make it less likely. (4)

Conditions such as ADHD, while often multifactorial in etiology, have been associated with balance and postural distortion, of which proprioception and sensorimotor integration are key components. (111-115) In a study specifically designed to test proprioceptive responses with fine motor behavior in children with ADHD, 105 children (52 with ADHD and 53 healthy controls) were administered the Proprioceptive Diagnosis of Temperament and Character (DP-TC) computer-based assessment. The assessment uses line drawings and task performance to assess the relationship between motor behavior and performance based on proprioceptive information available to the participant in the absence of visual stimuli. (116) Children with ADHD demonstrated poorer fine motor task performance and precision than the healthy control participants. The ADHD participants also demonstrated increased rigidity in motor performance as represented by the decreased variability in line length drawing. (116) These finding suggest a potential proprioceptive discrepancy among children with ADHD, which may be a source of the balance and coordination challenges in this population. (116)

In addition to ADHD, acquired conditions such as post-concussion syndrome and whiplash syndrome have been shown to demonstrate balance and cervical proprioception disturbances along with cognitive challenges such as memory, spatial awareness, and executive function. (117-121) A study by Slobonov, for example, using motion tracking, force plate and 3D virtual reality technology on concussed (Grade 1-2) student athletes showed residual sensorimotor deficits up to thirty days post injury, even though patients were clinically asymptomatic and cleared for return to play by day ten. (117) The presence of diminished cognitive task performance in addition to balance and proprioception deficits, suggests that there may be a connection between the sensorimotor system and regions of the brain associated with higher level cognitive functions, such as memory and executive function.

Research performed by the Haavik lab using SEP and TMS demonstrates changes in early sensorimotor integration following chiropractic care and suggests alterations in the way the brain initially processes the sensory information. (9-11,16,18-20) The studies do not suggest how a chiropractic adjustment might influence processes not directly associated with sensorimotor activity, such as cognitive tasks like memory or executive function. A series of studies by the Haavik lab using dual somatosensory evoked potentials may provide insight into a potential relationship between chiropractic and changes in cognitive performance. (18-20)

The dual somatosensory evoked potentials (SEP) studies performed by Haavik and colleagues utilized dual SEP ratios to explore central interactions between afferent inputs of the median and ulnar nerves. (18-20) The central interactions between the two nerves relate to how the brain processes the two stimuli. It is important to know if the brain has to process both stimuli independently, or is there an efficiency mechanism built into the system that limits the amount of simultaneous information entering the brain? In the dual SEP assessment model, the afferent inputs of the two nerves reflects the degree to which excessive somatosensory afferent information is gated or filtered by the central nervous system and is important because the ability of the central nervous system to gate or filter incoming afferent information is relevant to the efficiency of the central nervous system. (20,122-124) For example, sensory gating occurs as a part of feedforward processing. (125) When the brain issues a motor command, an efference copy of the command generates a predicted sensory outcome. (125-127) When the motor action occurs, actual sensory afferents are compared to the predicted efference copy, providing an opportunity for sensory response modulation and to distinguish self-movements from non-self movements. (125-126,128) This model of efference copy, sensory comparison and response modulation is referred to as the forward model. (125-127) An accurate prediction cancels

ensuing sensation for the now recognized self-generated motion, improving cortical efficiency; therefore, improving response time or executive function related task performance. (129)

The forward model employs a sensory gating mechanism, in essence, providing a filter for extraneous information entering the nervous system, including signals related to self-movement. (125) The forward model provides for improved cortical efficiency and quick adaptation to the environment. (125) The more efficient the central nervous system becomes, the greater the availability of resources for other cognitive processes. (125) The inability to properly gate extraneous sensory information into the system can lead to increased cognitive burden.

An fMRI study by Blakemore demonstrates the close relationship of a forward model discrepancy (efference copy to actual sensory input mismatch) to a motor learning task and use of cognitive resources. (129) The study used the tickle test, which incorporates a time delay between the initiation of a self-tickle stimulation by the individual and the actual tickle stimulation experience felt by the participant. (126,129) This situation generates a mismatch in self-stimulus and self-perception. During time points causing a sensory mismatch, regions of the lateral cerebellum (margin of VI and Crus I) were activated (129); the same regions of the cerebellum activated during early and late phases of motor learning tasks. (126,130) While this is just one study, it suggests that early learning corresponds to the forward model's prediction and actual sensory outcomes, assisting with the learning of new internal models. (129) Essentially, this suggests that if a system is not gating properly and the sensory signal received from the body does not match the efference copy (sensory mismatch), then the brain may always be in a state of learning and therefore, less efficient. (129)

As more understanding is gained in relation to the effects of chiropractic on sensory gating abilities and cognitive efficiency, there may be implications related to the care of certain

pathologies. The inability to gate extraneous sensory information is present in a number of pathological conditions, including ADHD and schizophrenia. (131-133) In one study evaluating sensory gating deficits in ADHD and schizophrenia patients compared to healthy controls, the investigators used the Sensory Gating Inventory (SGI) and an auditory stimulation measure for sensory gating (P50 auditory evoked potential) as opposed to the somatosensory stimulation used in the Haavik studies. (132-133) The SGI is a validated self-report and the P50 auditory evoked potential presents as a positive peak approximately 50 seconds post-stimulus. (134-135) ADHD and schizophrenia participants in the study scored significantly higher on the SGI, indicating poorer ability to suppress incoming stimuli compared to the controls; there was also significantly lower suppression ability in the ADHD and schizophrenia participants compared to the controls as assessed by the P50 auditory evoked potential task. (132) The abnormal P50 suppression indicates that the participant is unable to properly gate stimuli coming into the brain through the auditory system. (132-133) The diminished sensory gating abilities for both ADHD and schizophrenia patients have been demonstrated in other studies, and a few studies also report changes in patients with Autism and post-concussive syndrome. (131,133,136-139)

In the Haavik Dual SEP procedure using SEP to test sensory gating abilities, the amplitude of the SEP peaks from simultaneous stimulation of the median and ulnar nerves (MU) were compared to the sum of the amplitudes for each nerve stimulated individually (M+U), as performed by Tinazzi in previous dystonia research. (18-20,140) In healthy individuals the afferent information from simultaneous stimulation is gated, resulting in a lower MU amplitude and lower MU/M+U ratio. (18-20,140) In individuals with motor discoordination conditions such as dystonia or Huntington's Chorea, dual stimulation leads to excessive afferent input and

higher dual SEP ratios, meaning the participants were exhibiting diminished ability to gate simultaneous stimuli coming from the median and ulnar nerves. (124,140)

Instead of a pathological condition such as dystonia, the Haavik lab compared healthy individuals to individuals with subclinical neck pain. (18-20) In individuals with subclinical neck pain excessive afferent input and higher dual SEP ratios were observed when compared to healthy controls. (18-20) Following a chiropractic adjustment the MU/M+U ratio decreased for the P22-N30 SEP peak, suggesting improvement in sensory gating ability for the subclinical population. The improved gating was observed immediately after a single session of chiropractic spinal manipulation and after a course of twelve weeks of chiropractic care. (18-20)

The dual SEP study demonstrated improved gating ability – decreased MU/M+U ratios – post-chiropractic care in a population of individuals with sub-clinical neck pain. (18-20) Subclinical neck pain patients have a history of neck pain without the complication of pain on the day of assessment. (18-20, 124-125) Studies comparing populations with subclinical neck pain to healthy controls demonstrated decreased joint position sense and mental rotation abilities in the subclinical population compared to healthy control participants with no history of neck pain, suggesting proprioceptive deficits and altered firing patterns within the muscle spindles and GTOs. (141-145) The presence of proprioceptive dysfunction in the subclinical neck pain population is of interest to chiropractic and cognition research because individuals with reported cognitive challenges such as those with ADHD and concussion also report sensory gating and proprioceptive deficits. (117-121, 132-133)

Using ADHD as an example, patients with ADHD demonstrate deficits in cognition, balance, proprioception, and sensory gating. (117-121, 132-133) Uniquely, sub-clinical neck pain patients exhibit improvement post-chiropractic care in cognition and sensory gating. (10-

20,110,142) While balance has not been measured directly for subclinical neck pain participants, a 2012 review of the literature examining balance changes following chiropractic did indicate support for chiropractic as a care modality for balance, although the authors acknowledged that the literature was limited. (143) Specific to the subclinical neck pain population, proprioceptive deficits have been demonstrated in this population. (141) One study compared healthy controls to individuals with subclinical neck pain. The study revealed significant baseline deficits in elbow joint proprioceptive responses for the subclinical neck pain participants when the cervical spine was placed in flexion, rotation, and neutral positions. Following an adjustment, the subclinical neck pain participants' proprioceptive responses improved, while the healthy control participant results degraded. (141) This suggests an inherent deficit, possibly proprioceptive, within the cervical spine of the subclinical neck pain population that can influence joint proprioceptive responses. (141) Relative to the brain, subclinical neck pain patients have also demonstrated changes in cortical function, such as that demonstrated through somatosensory evoked potential (SEP) N30 responses and movement related cortical potentials, both indicators of early sensorimotor integration changes. (9-11,16,18-20) Expanding on the use of ADHD as a condition with deficits similar to subclinical neck pain, i.e. proprioception and sensory gating, children and adults with ADHD also demonstrate changes in communication patterns between various networks of the brain. (144-146) Communication pattern differences in the subclinical neck pain population has yet to be conducted.

In one study, children with ADHD were compared to healthy age, sex and IQ matched controls. Resting state functional magnetic resonance imaging (R-fMRI) was performed on each of the participants: healthy controls (n = 31) and drug naïve ADHD (n = 46) children. (145) In order to examine differences in functional connectivity, Graph theory analysis was performed on

four resting state networks: the frontoparietal network (FPN), cingulo-opercular (CON) network, cerebellar network (CN) and the default mode network (DMN). The FPN and CON network were chosen by the investigators due to recent research suggesting the two networks are part of a dual-network model for human task control. (145,147-148) The CN and DMN were chosen because of the unique associations with the FPN and CON; the CN seems to be related to feedback or error signals with FPN and CON, and the DMN exhibits an anti-correlation with the FPN in the absence of neural stimuli. (145,149) The use of Graph theory analysis allowed the investigators to break down the represented regions into a series of nodes (anatomical brain regions) and edges (inter-nodal links) that could then be analyzed for connectivity and efficiency of the networks in relation to the individual networks or whole-brain. (145) Within the ADHD participants compared to the healthy controls, the study revealed fewer connection, lower network efficiency and significantly decreased functional connectivity within the DMN, FPN and among cross-network long-range connections within the ADHD children. (145) Another ADHD study of inattentive and combined subtypes compared to controls examined gray matter volume differences and network connectivity between the groups. (144) The ADHD subtypes demonstrated no change in brain volumetric differences between the groups; however, network connectivity disruption was present in both ADHD subtypes compared to the healthy controls. (144) These studies suggest that the interactions between the brain networks of the ADHD children function differently and experience diminished efficiency than the brain networks of the healthy control children. (144-145)

The altered connectivity patterns observed in ADHD children have also been observed in adults with ADHD. A study by Sidlauskaite used diffusion magnetic resonance imaging with graph theory analysis to assess structural (anatomic) connectivity of adults with ADHD (n = 18)

compared to healthy controls (n = 21). (146) Just as with the ADHD children, differences in local network organization and lower local efficiency was observed in the ADHD adults compared to the healthy controls. Although, where the children with ADHD exhibited altered long-range connections the adults' global connections did not vary from the healthy controls. (144-146) It is unknown what this means relative to potential developmental changes between children and adults. Of relevance to the present study are the implications related to alterations in cortical connectivity in the ADHD population, a population associated with sensory gating, proprioception and cognitive deficits similar to the subclinical neck pain population that demonstrated improvement in each domain following chiropractic care. It is proposed that the similarities in deficits of sensory gating, proprioception and cognition between the ADHD and subclinical neck pain population provide reasonable justification to suspect connectivity changes may occur following a chiropractic adjustment.

To date, only one study has explored the question of changes in connectivity following chiropractic spinal manipulation. (22) The purpose of the study was to examine the effects of chiropractic spinal manipulation, spinal mobilization and therapeutic touch on the pain processing network in individuals who were experiencing study induced pain. (22) Forty-eight hours following a study specific exercise protocol to induce pain in the participants, a baseline functional magnetic resonance imaging (fMRI) assessment was performed. The participants were then randomized to one of the three groups mentioned above, and following receipt of the therapy, the participants underwent a second fMRI. For clarity, the chiropractic spinal manipulation group (n = 6) received an HVLA thrust, the spinal mobilization group (n = 8) received a mobilizing force at a rate of 1 Hz for two minutes, followed by one-minute rest and a second 2 minutes of mobilizing force at 1 Hz, and the therapeutic touch (n = 10) participants

received a dual hand contact across the top of the pelvis with light pressure applied for 5 minutes. All three groups experienced functional connectivity changes between the posterior cingulate cortex (PCC) and the anterior insula (aINS), the posterior insula (pINS) and periaqueductal gray (PAG), and the left primary somatosensory cortex (SI) and the right pINS. For the chiropractic spinal manipulative therapy group, changes in connectivity were observed between the right hemisphere SI and aINS and the SI and PAG, with cross-hemisphere changes between the right aINS and left PCC. (22) While this study was specific to the pain processing network and in patients experiencing pain, it demonstrated that immediately post spinal manipulative therapy changes in connectivity between cortical regions in the brain can occur. (22)

Research regarding potential brain changes as a result of chiropractic has been conducted by Dr. Haavik and her team for the last eighteen years. Her lab aims to test the previously described sensorimotor hypothesis. (9-11,16,18-20) Through her research she has been able to demonstrate that spinal manipulative therapy can alter early sensorimotor integration. (9-11,16,18-20) While her research centers around sensorimotor integration, her sensory gating research when related to changes in cortical efficiency that occur during sensory mismatch comparisons, assists in understanding chiropractic's effects on cortical processes not directly sensorimotor in nature, such as cognition. (18-20) Further, Dr. Haavik's research using dual somatosensory evoked potentials (SEP) showed improvement in sensory gating abilities following chiropractic care. The studies compared subclinical neck pain patients to healthy controls. (18-20) The subclinical neck pain patients are relevant because of the similarity in deficits to diagnosed conditions such as ADHD. Both ADHD and subclinical neck pain patients exhibit deficits in proprioception, cognition and sensory gating. (4,9-11,16,18-20,111-121,132-

133,141-142) Further, ADHD patients show changes in brain connectivity patterns that reflect diminished efficiency. (144-146)

Given the sensory gating deficits and associated proprioceptive deficits, the forward model may provide a plausible explanation for the changes. The forward model proposes that whenever a motor command is issued, a copy of that motor command is compared to information received from the sensory system. (142-147) If the information matches, no further action is required. (142-147) However, if there is a mismatch between the incoming sensory information and the secondary signal, called a corollary discharge or efference copy, then the brain has to process the difference. (143-147) This sensory mismatch potentially places the brain into a learning mode. (126-130) Further, when an individual is unable to properly filter incoming information or there is a sensory mismatch, the individual may experience sensory gating deficits, such as in the subclinical population and ADHD population. (132-133) It is proposed that the diminished efficiency and increased cognitive demand as a result of sensory mismatch would be reflected in brain connectivity patterns following chiropractic care.

Although the present study is predominately focused on cortical changes that occur in the brain following an adjustment and how those pattern changes might lead to further understanding of clinically observed post-chiropractic cognitive performance changes, it should be noted that altered cortical activation patterns may not be the only region of the brain influencing cognitive performance. The cerebellum, for example, has been shown to influence cognitive task performance such as verbal memory, executive function, spatial processing, language, and working memory. (150-152) In a metanalysis by Stoodley a dichotomy began to emerge relative to cerebellar task performance; the anterior cerebellum seemed associated more with sensorimotor task performance and the posterior cerebellar regions seemed more associated with

cognitive and emotional domains. (152) Further, neuroanatomical research has shown a closed-loop with receiving and sending projections between the prefrontal cortex, Brodmann area 46 in particular, and cerebellar Crus I and Crus II that may underlie the changes observed in the frontal cortex following a chiropractic adjustment. (150) Acknowledging the role of the cerebellum in proprioception and motor performance, a few studies in the chiropractic neuroscience literature examined changes in cerebellar inhibition following a chiropractic adjustment. (153-154) Using a motor training performance task with transcranial magnetic stimulation (TMS) of the cerebellum just prior to motor cortex TMS stimulation, cerebellar inhibition was assessed through evaluation of motor evoked potentials. Participants with sub-clinical neck pain showed greater cerebellar inhibition following a motor performance task compared to healthy controls, but following spinal manipulation, the subclinical population instead exhibited facilitation of the motor evoked potentials following the motor performance task. (153-154) The results of the chiropractic cerebellar research paired with the cortical-cerebellar neuroanatomical interactions and the cognitive changes associated with the cerebellum, suggest that the cerebellum may contribute to the brain changes observed following a chiropractic adjustment, although more research is needed.

Notwithstanding other potential contributors to cognitive task performance such as the cerebellum or physiologic parameters, cortical changes – including connectivity in the pain network - have been observed following chiropractic. The connectivity study by Gay showed fMRI changes in a number of regions, but the patients were experiencing study induced pain during the fMRI scans, which may have influenced the results. (11,22) Given the communication changes observed in the fMRI spinal manipulation study, the proposed relationship between deficits in proprioception and sensory gating, and the potential consequences in brain efficiency

if a brain remains in a learning state, it is important to understand if the changes in brain efficiency and function would be reflected in regional and whole brain communication patterns in a healthy population. In addition, there is no current understanding related to a mechanism of action explaining the clinically observed changes in cognitive performance following a chiropractic adjustment. Therefore, the purpose of this study is to identify the effect of a single dose of chiropractic spinal manipulation on brain communication patterns of healthy individuals immediately after and one-week post spinal manipulation, and also to determine if the effects immediately after spinal manipulation are similar to the effects one-week post. To assess communication patterns, a secondary analysis of existing EEG data using Phase Slope Index (PSI) will be performed. The section below provides some background information on PSI, reasons for using PSI over the more commonly applied Granger Causality, and the time required for neuroplastic change, concluding with the study specific aims and hypotheses.

Phase Slope Index (PSI):

Through application of methods such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and electroencephalography (EEG) in the study of the brain, it is now understood that regions of the brain do not function in isolation. (23) Even a simple task such as recognizing an image on a page requires coordinated and patterned communication between a network of brain regions. (24) Essentially, the brain functions as a large network subserved by micro-level to large-scale sub-networks. (25) Using EEG technology, one way of examining the interactions between the micro-level and large-scale sub-networks is to apply Phase Slope Index (PSI) analysis to an EEG reading. PSI is a measure of effective connectivity. (21) Effective connectivity, which is one of three methods for examining brain connectivity, provides information on the direction and magnitude of communication

between the brain networks. The other two methods, structural and functional connectivity, provide a foundation for effective connectivity analysis. (21)

Structural research examining brain networks occurs along a spectrum from cadaveric studies to complex diffusion tensor imaging research. The focus is to identify the existence of neural tissue connections between brain regions. (21,155) The structural – anatomical – connections serve as the backbone for functional and effective connectivity. (156-157) Functional connectivity seeks to answer the question "are two or more brain regions coupled "– do they function together? (21,22) In electroencephalography (EEG) this can be assessed through coherence, which evaluates specific frequency bands (oscillations) to determine if there is a time difference (phase difference or phase angle difference) between two regions of the brain. (21,23) Effective connectivity analyzes additional aspects of the EEG frequency bands to understand the direction and magnitude of the connections. If using the example of individuals walking across the street, effective connectivity would provide information on the number of people walking and the direction they are walking in. (21, 158)

Although DTI and cadaver studies provide an understanding of the anatomic connections, research into the functional and effective connectivity is of importance. If the brain simply functioned from a linear sequencing of region to region connections, the complex activity and environmental responsiveness exhibited by the brain would not be possible. (158-159) Mechanisms have evolved to compensate for this time delay, expanding the efficiency of the cortical networks; interactions of brain oscillatory patterns are one proposed mechanism underlying dynamic coordination in the brain. (25,158-160) For instance, when two systems are in synchrony (phase locked) there is greater sensitivity to excitatory and inhibitory signals. This means that when the sending neuron pool wants to connect with the receiving neuronal pool, the

receiving neuronal pool is in a more receptive state. (159,161) Effective connectivity, such as PSI, allows us to determine which area of the brain is sending the information and to what degree. (21,162-164)

Two primary mechanisms of effective connectivity analysis are Granger Causality and PSI. (158,162-163) Of the two, Granger Causality has been in use for a longer period of time - first applied to the frequency domain in 1982 - and is more commonly used. (158) PSI is still a relatively new development, but is experiencing increasing use, including adaptation to fMRI analysis. (158,162-163,165-166) Granger Causality is a comparison of time series data using autoregressive modeling; past values in the time series are used to model future values for the time series. (158-159) The challenge with this analysis, however, are the significant false detections in the presence of independent noise, such as volume conduction. (163) This means that the accuracy of Granger Causality suffers in an electrically noisy environment. (163)

Independent noise and volume conduction can occur naturally in the background and within the brain. (21,158, 162-163,167-168) Volume conduction, in particular, can be produced from multiple sources within the human body. This can include membranes, skin and other tissue, leading to the spread of electrical potentials across the scalp. (167-168) Therefore, the resulting wave of electrical impulse demonstrates a near zero phase lag between any two points, and if not accounted for, the model can result in false positives such as inaccurate directionality of the connectivity results. (162-163,167,169)

Nolte, in investigating Phase Slope Index as a viable measure of effective connectivity tested the model against Granger Causality using simulated and real EEG data. (162-63) In simulated clean data without the addition of random noise, Phase Slope Index detected the correct direction of information flow as well as Granger Causality. (162). In simulated data with

a mixture of noise, Granger Causality detected erroneous relationships – as high as 50% in higher noise levels – between two points, Phase Slope Index was robust against noise interference with rare false detections. (162) Similar results were obtained in follow up studies by Nolte (real and simulated data) and Haufe (simulated data). (162-163, 169) Phase Slope Index provides reliable data with improved accuracy in noisy systems. (161-163,169)

As with Granger Causality, Phase Slope Index presumes that the driver of neural activity occurs earlier than the recipient. (162-163,170) Nolte noticed that when calculating the imaginary part of complex coherency of a multivariate time series, the imaginary part of the coherency did not change with increased noise. (162,171) The imaginary part of the coherency is how far away the summed phase vector deviates from the x-axis. (158,170) Essentially, the imaginary part of coherency overcame the challenge with zero-lag (no time lag) coherence – often the result of volume conduction. (170-171) PSI evaluates the slope of the phase of cross-spectra between two time series, using Fourier-transformed cross-spectrum, complex coherency and the imaginary part of coherency. (162-163, 170) In simplified terms, this means that PSI uses the phase differences (coherency) plotted over different frequencies to fit a linear regression line of the phase difference. (161-163) Then, taking the slope of the line multiplied by the coherence, you get the PSI over a particular bandwidth. (161-163) This provides the direction of the communication between two regions of the brain and the magnitude or level of communication between the two regions. (161-163)

The goals of Phase Slope Index are to define an average phase slope that accomplishes the following: 1.) properly represents the relative time delays of the two time series 2.) be robust to signals that do not actually interact, but that may superimpose the signals (e.g. volume

conduction) 3.) correctly weight various frequency regions according to statistical relevance. (140-142) Additional details on the calculation of PSI are provided in the methods section.

Understanding connectivity patterns through analysis protocols such as PSI may help in the development of therapies that could serve to enhance performance or overcome cognitive pathologies. In neurofeedback, for example, the patient's brain patterns are compared to a normative database, then using operant conditioning the patient is rewarded through visual or auditory cues when his or her brain waves move away from a pathological direction towards normal. (172-173) Neurofeedback to change brain wave patterns has been used successfully in a number of conditions, including ADHD. (172-173) Relative to chiropractic, perhaps the cognitive changes observed clinically, are a result of underlying brain changes; however, until the brain changes that occur following chiropractic care are understood, the use of chiropractic as a therapy for conditions such as ADHD is limited.

In addition to potential use as a therapeutic modality for pathology, chiropractic may also assist in improving cortical efficiency. According to the dual SEP studies assessing sensory gating abilities pre and post chiropractic, chiropractic improves the ability of the brain to filter (gate) extraneous information. (18-20) This diminished ability to gate sensory information may be a consequence of sensory mismatch, as discussed previously in relation to the forward model. (108-113) The consequence of the sensory mismatch may be diminished cortical efficiency that could be reflected in brain connectivity patterns. (125-130)

Intelligence quotient (IQ) effective connectivity research is one example that demonstrates how changes in the underlying connectivity is reflected in cognitive performance. (21) Using Phase Slope Index, a study by Thatcher of 371 children aged 5 to 17.6 years of age demonstrated that greater efficiency directly correlated with higher IQ. (21) While information

flow occurred in all participants, the results showed that the higher IQ participants demonstrated more efficient local processing, reducing the need for communication with distant neural resources. The lower IQ participants exhibited greater communication with distant neural resources. (21) This suggests that when local networks (hubs) are inefficient, compensatory hubs send information to the weak hubs to improve function of the network as a whole. (21) This theory is supported by the homeostatic neuroplasticity model of intelligence, which proposes that optimally functioning local (small-world) networks minimize the need for long distance information processing, maximizing the efficiency of the network resources. (21,174) As in the Thatcher IQ study, this altered efficiency can be reflected in cognitive performance. (21)

Improvement in information processing, particularly with respect to reduction of long distance activation patterns and improvement of small-world (local) systems seems fundamental to the optimization of brain function, resulting in reduced demand for the more biologically expensive long-distance connections. (175-177) It is proposed that chiropractic may influence brain connectivity patterns, and the feedforward system may be one mechanism allowing for the change. If that is the case it might be reasonable for chiropractic adjustments to differentially impact the magnitude and direction of information flow within the brain. Therefore, as stated earlier, the purpose of this investigation is to identify the effect of a single dose of chiropractic spinal manipulation on brain communication patterns of healthy individuals immediately after and one-week post spinal manipulation, and also to determine if the effects immediately after spinal manipulation are similar to the effects one-week post.

There are two unique aspects to this study. First is the one-week follow up assessment. Previous chiropractic neurophysiology research indicated that changes following chiropractic care lasted up to thirty minutes. (9,178) Given that the participants in these previous studies were

limited in their movement due to continued neurophysiologic monitoring post-adjustment, it is proposed that their brains were not allowed time for neuroplastic adaptation to the new sensory signals that may be entering the brain from the muscle spindles and GTOs that were restored to proper lengths following the spinal manipulation. (9,178) Early neuroplasticity research showing changes in cortical activation patterns over time lends support to this proposed need for additional time to accommodate plastic change. (14-15) Following peripheral nerve transection the cortical somatotopic maps served by a transected nerve began shrinking within twenty-four hours and continued to change over the next several weeks. (14) In a primate study by Merzenich complete disappearance of the median nerve associated somatotopic map in monkeys who underwent median nerve transection occurred in as little as one week. (15) Although the change in afferent input from the median nerve transection research is considerably more drastic than the suggested proprioceptive changes that occur following an adjustment, it is suggested that full adaptation to the new sensory firing patterns will take time. For this reason, PSI for the post-chiropractic and sham EEG reading will be compared to the one-week post values in this study – in addition to the pre-post chiropractic PSI assessments.

The second unique aspect of the study is the selection of brain regions. Previous studies by Haavic, Lelic and Gay focused predominately on areas associated with somatosensory integration and pain, respectively. (11-13, 22) The Haavic and Lelic studies examined regions of the brain that were associated with the somatosensory evoked N30 peak. These included the primary and secondary somatosensory cortices, insula, cingulate, and prefrontal cortex. (11) The study by Gay focused specifically on regions of the brain that process and modulate pain, which included the somatosensory cortex, secondary somatosensory cortex, thalamus, anterior and posterior cingulate cortices, anterior and posterior insula and periaqueductal gray. (22) While the

current study will examine effective connectivity among regions identified in the previous chiropractic studies, this study will also examine regions associated with cognitive performance, specifically mental rotation. Since mental rotation performance has been shown to improve in patients post-chiropractic adjustment and in those with subclinical neck pain, (5) the neural correlates of mental rotation task performance will be evaluated as a secondary outcome for the current study. Several fMRI studies have defined the neural correlates for mental rotation; these include: superior and inferior parietal lobules (BA 7,40), medial frontal gyrus (BA 6), dorsal lateral medial frontal cortex (BA 46) and the visual association cortex (BA 18). (179-183) While additional areas such as the cerebellum, thalamus, and superior temporal gyrus have also been implicated in mental rotation task performance, the five selected areas listed previously showed activation patterns consistent across studies and are accessible with the LORETA PSI software being used in this study. (179-183) Given that a mechanism has yet to be proposed that describes how clinically observed changes in cognitive task performance post-chiropractic may occur, evaluation of brain changes associated with areas known to participate in mental rotation task performance may provide some insight into the unknown mechanism. (4-5)

The research is focused on the following specific aims, and seeks to test the associated null-hypotheses:

Study Aims: The specific aims of this study are

- **Aim 1**: To determine if a single dose of chiropractic manipulative therapy will modify brain communication patterns as assessed by calculation of phase slope index in healthy individuals immediately post-manipulation.
    - **Hypothesis 1**: We hypothesize that a single dose of chiropractic manipulative therapy as opposed to a single sham dose of manipulative therapy will significantly change the direction

and magnitude of communication patterns among Brodmann areas 1, 2, 3, 9, 13, 23, 29, 30, and 31 within the brain immediately post manipulation in healthy individuals.

  - **Hypothesis 2**: We hypothesize that a single dose of chiropractic manipulative therapy as opposed to a single sham dose of manipulative therapy will significantly change the direction and magnitude of communication patterns among Brodmann areas 6, 7, 18, 40, and 46 that are associated with mental rotation in healthy individuals immediately post manipulation.

- **Aim 2**: To determine if a single dose of chiropractic manipulative therapy will modify brain communication patterns as measured by phase slope index at baseline and one-week post manipulation in healthy individuals.
  - **Hypothesis 3**: We hypothesize that a single dose of chiropractic manipulative therapy as opposed to a single sham dose of manipulative therapy or a no dose control will significantly change the direction and magnitude of communication patterns among Brodmann areas 1, 2, 3, 9, 13, 23, 29, 30, and 31 within the brain one-week post manipulation in healthy individuals.
  - **Hypothesis 4**: We hypothesize that a single dose of chiropractic manipulative therapy as opposed to a single sham dose of manipulative therapy or a no dose control will significantly change the direction and magnitude of communication patterns among Brodmann areas 6, 7, 18, 40, and 46 within the brain that are associated with mental rotation in healthy individuals one-week post manipulation.
- **Aim 3:** To determine if brain communication patterns as measured by phase slope index observed immediately post chiropractic manipulative therapy will be sustained one-week post manipulation.
  - **Hypothesis 5** We hypothesize that following a single dose of chiropractic manipulative therapy as opposed to a single sham dose of manipulative therapy the direction and magnitude of communication patterns among Brodmann areas 1, 2, 3, 9, 13, 23, 29, 30, and 31 within the brain one-week post manipulation in healthy individuals will significantly change.

- **Hypothesis 6**: We hypothesize that a single dose of chiropractic manipulative therapy as opposed to a single sham dose of manipulative therapy will significantly change the direction and magnitude of communication patterns among Brodmann areas 6, 7, 18, 40, and 46 within the brain that are associated with mental rotation in healthy individuals one-week post manipulation.

CHAPTER 3

METHODS

The present proposed study represents a secondary analysis of data collected as part of a previous randomized clinical trial (NCT01953614). The trial was conducted in the Life University Center for Chiropractic research in collaboration with a student researcher (PI), statistician and practicing chiropractor who administered the adjustments. Dr. Sullivan was actively engaged in the project, provided study oversight and served as the lead mentor for the research.

The primary aim of the original study was to document regional electroencephalographic (EEG) changes in absolute power (micro volts) associated with chiropractic adjustments. Unknown are the region-to-region communication changes that may occur within the brain. Therefore, this study seeks to perform a secondary analysis of the data using Phase Slope Index (PSI) to determine if region-to-region communication patterns change before and after application of a single dose of chiropractic manipulation. The following outlines the procedures performed during the original study and the subsequent secondary analysis specific to the proposed study.

Participants:

Thirty-seven healthy, neurologically intact individuals over the age of eighteen were recruited from the Life University community through word of mouth and Life University electronic newsletters. To limit contamination from previous chiropractic care, the participants were required to be either naïve to chiropractic or have abstained from receipt of an adjustment

for thirty days prior to participation in the study. This was in alignment with previous chiropractic cross-over studies that utilized a four-week washout period. (10, 184-185)

Exclusion Criteria: Due to potential risks associated with chiropractic care, the attending chiropractor was allowed the freedom to exclude participants based on physical exam and health history. Exclusion criteria were also based on risk factors to chiropractic care such as fractures, surgeries, or trauma to the spine within the past six months. (186-188) Additional exclusionary risk factors included inability to attend all study sessions, untreated diagnosed osteoporosis, and articular instability such as atlanto-axial instability present as a result of congenital anomaly or progressive rheumatoid arthritis. (186-188)

Given that EEG values can be influenced by medication, participants were asked to disclose medications used during the two months prior to the study and between study related data collection time points. Participants were automatically excluded from participation in the study if they had taken Benzodiazepine class medications, cannabis, or nasal decongestants within what would be five half-lives of the respective medication, as these medications have a known contamination effect on the EEG. (189-195) All other medications were evaluated on an individual basis by the study EEG technician with ten years of experience.

Of the thirty-seven participants recruited, seven participants were excluded due to non-compliance with scheduled follow-up or use of excluded substances. Thirty individuals completed the study, with ten participants in each of the study groups.

Study groups:

Using computerized randomization, participants were assigned to one of three groups (ten in each group): chiropractic adjustment, sham (placebo) adjustment, or control.

Chiropractic adjustment: The chiropractic adjustment group participants received a health history review, physical exam and adjustment by a Georgia licensed chiropractor with over twenty years of experience. Analysis and adjustment were provided according to chiropractic Sacral Occipital Technique (SOT®). SOT® is a system of analysis and gentle adjusting that utilizes high velocity low amplitude (HVLA) adjustments to the spine and pelvis in addition to blocking (prolonged static forces applied to the pelvis in specific directions according to the analysis- DeJarnette blocks - Sacro-Occipital Research Society International, Idaho Falls, ID, USA) for correction of specific pelvic and lumbar dysfunctions. (196) For the HVLA adjustments a hand-held instrument (Activator® II - Activator Methods International, Phoenix, AZ USA) was used for force application as opposed to hand manipulation. This served to limit movement of the participant and avoid disturbance of EEG cap placement.

The clinician evaluated the participants utilizing muscle testing, static palpation, leg length discrepancy and motion palpation, all standard procedures for location of subluxations and to define SOT categorical dysfunction: category I, II or III. (196) Category I participants demonstrated restricted motion of the sacral auricular boot (n = 2), a condition theorized to impede cerebral spinal fluid flow. (196) Category II participants showed aberrant ability of the sacrum to function in gravity (n = 8) which is associated with ligamentous stretching or strain. (196-197) No participants in the chiropractic adjustment group exhibited a category III dysfunction, considered to be a form of lumbar disc dysfunction. (196) All participants received either DeJarnette blocks (n = 8) or an Activator thrust to the sacroiliac region (n = 2), and one participant received both DeJarnette blocks and an Activator thrust to the 5th lumbar segment.

Sham adjustment: As with the chiropractic group, sham participants underwent a health history review, physical exam and SOT analysis. However, instead of having their spinal and sacroiliac

segments adjusted as dictated by the analysis, the participants received a set sham protocol. The sham adjustment was delivered by the hand-held instrument set at the zero-force setting. This resulted in an audible click with no application of force. Set regions receiving the sham intervention were: left posterior inferior ischial tuberosity, right vertebral facet eighth thoracic vertebra, right vertebral facet seventh thoracic vertebra.

Control condition: The control participants only underwent a review of their health history. No other procedures beyond study outcome assessments (EEG and Adult Self Report) were performed.

Initial Study Protocol:

Participants interested in participating in the study were scheduled for an initial phone or face-to-face interview to review medication and study participation criteria. If participants did not exhibit exclusion criteria, they were scheduled for their initial analysis and intervention session. Upon presentation to the Research Lab at Life University, participants were provided information about the study and allowed time to read and sign the informed consent. As previously stated, participants in the chiropractic and sham groups received a health history review and physical exam. Control participants received only a brief review of their health history with no physical exam. Participants were then placed in a quiet room with table and chair to complete the written Adult Self Report (ASR) portion of the Achenbach System of Empirically Based Assessment (ASEBA). The ASR provides a standardized measure of overall mental health and functioning, asking questions related to behavior, psychological problems and substance abuse. (198) The ASR is a validated instrument commonly used in research and clinical care environments that allows for pre-post evaluation in addition to comparison to an age-matched normative database. (198-200)

Upon completion of the ASR, EEG set up and recording were conducted. Participants were asked to report caffeine consumption and hours of sleep, as both can affect EEG recordings. (1201-203) The EEG recording was performed in a quiet room with minimal electrical interference. Electrode placement sites lateral to the eyes, clavicles, and ears were cleaned with alcohol and slightly abraded with NuPrep gel to improve electrode conduction. A 19-channel Electro-Cap (Electro-Cap International, Inc. Eaton, OH, USA) was then placed on the participant's head to provide consistent electrode placement in accordance with the international 10/20 system of EEG. (204-205) The participant's head was measured to ensure that the proper Electro-Cap size was used. Following proper cap placement conductive gel was applied to the electrode sites on the scalp, ears, clavicles and lateral eyes, then monitored to ensure that impedance was below 5 kilo-Ohms.

Baseline eyes-open and eyes-closed EEG recordings were performed in a seated position using a Cadwell Easy II amplifier (Cadwell Laboratories Inc, Kennewick, WA, USA) with linked ears as the reference and 60 Hz filter. During recording, participants were instructed to relax, slightly open their mouth to relax their jaw, either keep eyes open or closed based on instruction from the technician and if they needed to move, make the movement exaggerated. The exaggerated movement assists in later artifact removal from the EEG. To ensure collection of at least sixty seconds of artifact free data (i.e., no muscle movements, blinking or other related EEG contamination) five to six minutes each of recording time was performed for eyes open and eyes closed. Following baseline assessment and keeping the Electro-Cap on, the participants in the chiropractic group received a chiropractic adjustment, while the sham group received a sham adjustment. The patient then was returned to a seated position and a second session of EEG data was recorded; impedance was checked prior to recording and the electrodes were adjusted as

necessary to maintain a value of less than 5 kilo-Ohms. Upon completion of the second EEG recording session (first for control participants), the Electro-Cap was removed from the participant and gel removed from hair and scalp with the technician's assistance. The participant was then scheduled for a one-week follow-up evaluation and asked to maintain similar sleep times and caffeine consumption prior to the follow-up session.

Participants returned to the research lab after one week for follow-up assessments. The participants were asked to disclose any changes in medication, sleep or caffeine consumption. Following the initial questions, the participant was again placed in a quiet room with table and chair to complete the ASR. After ASR completion, the procedures for placement of the Electro-Cap and recording of the baseline EEG were repeated. Following the EEG recording session, the participants were again cleaned of the cap and electrode gel, then thanked for their time. This concluded participation in the study.

Artifacting:

The raw EEG data were imported into NeuroGuide™ software (Applied Neuroscience, Inc., Largo, FL, USA) for manual artifact removal by a trained EEG technician with ten years of experience. To assist in the process, signals recorded from cardiac and lateral eye electrodes allowed for eye movement and cardiovascular comparison with EEG signals to identify artifacts. Notes that were made by the technician during recording sessions to mark any unusual movements that may have influenced the EEG were also utilized in the artifacting process. Additionally, apparent muscle bursts, sleep waves and electrode problems were also removed from the data. As a further means of assuring clean EEG signals, split-half (ratio of variance between the even and odd seconds of a selected EEG time series) and test re-test (ratio of variance between the first and second halves of a selected EEG time series) reliability tests were

performed and deemed satisfactory when a value above 0.90 was achieved. Split-half and test-retest reliability tests set at above 0.90 was done in accordance with previous research by Thatcher, using the same software application. (21,206) The artifacting process was continued until at least one minute of clean eyes closed data was retrieved per EEG session (Baseline, post and one-week post). (206-208).

Secondary analysis:

The following provides information on the procedures that were performed for the secondary analysis of the artifacted data collected as part of the previously described study.

Power Spectral analysis:

To prepare for power spectral analysis, the cleaned, artifacted data was subdivided into one Hertz (Hz) frequency bands from one Hz to thirty Hz for all 19 scalp locations, digitized at 100 Hz, and up-sampled to 128 Hz, according to standard protocol for the software. (21) The Power spectral analysis was performed on each segment of the eyes closed artifacted data for each study condition (adjustment, sham and control) and for each time-point (baseline, post and one-week post). Note, no immediate post session was recorded for the control condition, only baseline and one-week post. A Fast-Fourier transform (FFT) auto-spectral and cross-spectral analysis was computed on two second epochs. As performed by Thatcher in a previous PSI research study and as part of the recommended NeuroGuide software protocol, a sample rate of 128 samples/sec will be used which will yield 256 digital time points per 2 sec epoch. This resulted in 0.5 second frequency resolution, from zero to forty Hz. (21) Essentially, by breaking signals down into sine waves of different amplitudes and frequencies, the FFT shows how often a given intensity occurs. (209-210)

Because the segmenting of the signal into two second epochs leads to sharp changes between the epochs, the FFT process produces a window artifact that decreases the reliability and validity of quantitative EEG analysis. (211) Therefore, the 75% sliding window method of Kaiser and Sternman was used for the FFT spectral analysis. (211) In this method two-second epochs (256 points) were overlapped by a sixty-four-point sliding window protocol for the entire artifacted EEG record. (211) This protocol assisted in minimizing the effects of the FFT window artifact. (21,211)

Low Resolution Electromagnetic Tomography (LORETA):

The processed data for each of the three groups underwent standard procedures for the computation of LORETA (NeuroGuide Software version X. (212-216) LORETA computation provides a non-invasive localization of neuronal signal generators measured at the scalp surface with EEG. Using electric currents as a model for neural activity, LORETA works backwards from scalp potentials that would result from hypothetical current distributions – forward problem – and the actual measured EEG data at specific positions in order to estimate the sources fitting the measurements – inverse problem. (206,208,214,217) This allows for a three-dimensional (3D) estimation – inverse solution - of the source of the electrical generators within the brain.

LORETA procedures have been in use for over twenty years with implementation of quantitative neuroanatomy in 1999 based on the Talairach atlas provided by the Brain Imaging Centre, Montreal Neurological Institute. While challenges to the computation exist in the deeper current source densities (deeper in the brain), as a result of the high accuracy of the LORETA based solution to the inverse problem LORETA compares favorably to PET and fMRI technologies, especially given the high temporal resolution of EEG (213-214,218-219) For the present study, the 3D data (x, y and z coordinates) were referenced to the Talairach Atlas of the

Montreal Neurological Institute, thus linking the data to the standard anatomical 7 x 7 x 7 mm voxels corresponding to a distinct Talairach Atlas Coordinate. (206, 208,214) The NeuroGuide software used for the study defines Brodmann area classifications through application of groups of voxels to clear anatomical landmarks based on the Talairach Atlas. (206,208) In fourteen Brodmann areas the time series of current source vectors in the x, y and z directions were computed at the center voxel for each of the specified left and right Brodmann areas. (206,208) Further transformation of the data using the Hilbert Transform equation – modifies the real-valued signal to provide analytic representation - was conducted between each pair of the Brodmann area time series in order to compute the instantaneous coherence, which provided for calculation of the Phase Slope Index(PSI). (206,208,220) LORETA coherence was calculated for each of fourteen Brodmann areas (left and right) at eight different frequency bands (Delta = 1.0-4.0 Hz; theta = 4.0-8.0 Hz; alpha1 = 8-10 Hz; Alpha-2 = 10-12 Hz; Beta1 = 12-15 Hz; Beta2 = 15-18 Hz; Beta3 = 18-25 Hz; Hi-Beta = 25-30 Hz). An additional benefit to LORETA is that no a priori constraints are required regarding the number and location of sources. (213) This allowed for Phase Slope Index comparisons of study specific region of interest areas in relation to each region of interest, both within and across hemispheres.

Phase Slope Index:

Phase Slope Index (PSI) is a measure of effective connectivity, which provides information on the direction and magnitude of information flow between two signals. (21) The direction of information flow is estimated according to the assumption of a driver-responder relationship – based on temporal order - between two regions of the brain. (162) In the representation $\Psi_{ij} > 0$, signal "i" occurs before signal "j" and "i" is the driver and "j" is the responder. For PSI calculation as specified by Nolte in his original 2008 paper, coherence is

calculated, but the absolute value of coherence is not taken; this maintains directionality for the calculation and is referred to as coherency. (161-162) Coherency was calculated between each of the fourteen Brodmann areas.

The NeuroGuide PSI analysis, developed by Robert Thatcher, is based on Nolte's original formula published in 2008. (162-163) While PSI is still a relatively new measure of effective connectivity, it was designed to overcome the challenges associated with volume conduction present in the commonly used Granger Causality method. (162-163) PSI has been found to be a robust measure of effective connectivity in both real and simulated data. (162-163,169,221) The NeuroGuide software uses the FFT power spectra and LORETA coherency to derive the PSI changes between each specified Brodmann area.

The following formula for PSI was applied to the data:

$$\psi_{ij} = \Im\left(\sum_{f\epsilon F} C_{ij}^{*}(f)\, C_{ij}(f+\delta f)\right)$$

Psi (Ψ_{ij}) is the coherency function between channel i and j, δf is the frequency resolution. In this study the frequency resolution was 0.5 Hz. Imaginary coherency was represented by $\Im$. Volume conduction may be indicated if the imaginary part of coherency approximates zero for any channel pair, and if imaginary coherency was greater than zero (positive), signal *i* was considered to have occurred before signal *j,* suggesting signal *i* is the driver. If the value for imaginary part of coherency was below zero (negative), then *j* is considered to be the driver among the two channel pairs and *i* was considered to be the responder. (21, 162-163,221) PSI will be calculated for each of the 0.5 Hz frequencies, then averaged according to the following standard band definitions: Delta = 1.0-4.0 Hz; theta = 4.0-8.0 Hz; alpha1 = 8-10 Hz; Alpha-2 = 10-12 Hz; Beta1 = 12-15 Hz; Beta2 = 15-18 Hz; Beta3 = 18-25 Hz; Hi-Beta = 25-30 Hz).

Statistical analysis:

Descriptive statistics for age, gender, handedness, medicine use and epoch length were calculated for each study group. One-way ANOVAs were conducted to determine if significant differences existed between group age and epoch length differences, post-hoc t-tests were performed as needed. Fisher's exact tests were used to determine if significant differences existed between gender, handedness and medicine use among the groups.

LORETA PSI has the capacity to calculate Brodmann area combinations between each of 44 Brodmann areas, which includes left, right and interhemispheric combinations. Additional calculations can be provided for each of eight different spectral bands. However, similar to the spinal manipulation study evaluating changes in functional connectivity within the pain processing network and studies such as those evaluating connectivity for ADHD children, the number of paired comparisons was narrowed for the present study through a priori region of interest selection. (22,144-145) Based on previous source localization and functional connectivity research showing changes in cortical activation patterns following a single dose of chiropractic, this study examined PSI connections for the following nine cortical regions: prefrontal cortex (BA9), primary somatosensory cortex (BA1,2,3), anterior insula (BA13), and posterior cingulate cortex (BA23, 29, 30,31). (11,21-22)

The regions of interest were selected based on previous research by Lelic and Gay that indicated changes in the areas post-chiropractic spinal manipulation. (11,22) The prefrontal cortex was implicated as the primary generator of the SEP N30 peak attenuation in the dipole source localization study by Lelic. (11) The remaining regions of interest demonstrated changes in functional connectivity following spinal manipulation in an fMRI pain study by Gay and colleagues. In addition to the cingulate cortex, anterior insula, and primary somatosensory cortex

assessed in the present study, the posterior insula and periaqueductal gray also demonstrated connectivity changes in the study by Gay. (22) Functional connectivity in the Gay study was measured using fMRI, which allows for analysis of deeper structures, unfortunately, using EEG based LORETA, the equivalent Brodmann areas were not available.

As stated previously, a secondary outcome examining effective connectivity changes in five regions attributed to mental rotation task performance were also conducted. Given that no mechanism of action has been identified to explain the clinical changes in cognitive task performance observed following chiropractic care, this additional outcome for the current study sought to aid in future mechanism of action development. Mental rotation, which is important for object recognition, spatial navigation, and movement planning was chosen for two reasons. (179-183,222) First, previous chiropractic research using a rotated letters paradigm demonstrated improved reaction time (14.9%) following a single chiropractic adjustment. (5) Impairment in mental rotation ability at baseline and after four weeks was also observed in patients who experienced subclinical neck pain compared to healthy controls. (222) Based on previous research, impairment in the subclinical population suggests proprioception may be a factor, and as has been discussed previously, chiropractic manipulations have been shown to change proprioceptive firing patterns and improve clinical assessments of proprioceptive associated performance. (63, 12-13)

The second reason for choosing to examine the neural correlates of mental rotation was the support in the literature relative to locations in the brain associated with mental rotation task performance. (179-183) An fMRI study by Cohen demonstrated changes in brain activation patterns during mental rotation of an image of a pair of objects. The rotated pair was compared to presentation of a pair of objects requiring no rotation and a simple cross-hatch presentation. The

authors, who used the Talaraich Atlas and Brodmann area classifications similar to the current EEG analysis, observed changes in the superior and inferior parietal lobules (BA 7,40), medial frontal gyrus (BA 6), dorsal lateral medial frontal cortex (BA 46) and the visual association cortex (BA 18). (179) A few additional areas were reported, such as the middle frontal Gyrus (BA 8) and the extrastriate cortex (BA 39 and 19); however, the five main areas reported above were chosen because each area was also commonly reported in other mental rotation research studies. (179-183) Although a few of the Brodmann areas being analyzed as a result of the Lelic and Gay studies - Brodmann areas 1, 2, 3, and 9 - demonstrated activation in the Cohen study, the areas in the Lelic and Gay study have been associated with early sensorimotor activation and pain. (11,22, 179) Specifically analyzing regions associated with the cognitive task of mental rotation provided additional insight relative to informing future research examining neural mechanisms associated with the chiropractic adjustment and cognitive task performance.

To examine effective connectivity for the proposed fourteen Brodmann areas, NeuroGuide software (v 2.9.3.5) was used to perform LORETA PSI analysis between each of the selected Brodmann areas. One limitation of the software was the use of a global transform for normalization of the PSI data as opposed to the Jacknife method recommended in the original Nolte article. (21,162-163) To overcome this limitation the current study used PSI normalized through application of a validated normative database. The normative database uses 678 individuals from age ranges two months to eighty-two years and has been validated, published and used in a number of research studies. (223-227) Also, the normative database being used in this study is similar to the Jacknife method used by Nolte in that both methods use standard deviations of the data and apply leave-one-out procedures. (223-224)

Use of a normative database was similar to a study conducted by Prichep who applied a normative database to evaluate activation patterns within the pain network. To statistically analyze the differences between the groups, Prichep conduced t-tests between the groups and then applied permutation tests to protect against Type I error, especially given that Prichep was examining thirteen regions of interest. (228) One reason for the normalization of the PSI data in the Nolte article was to eliminate PSI values demonstrating less than a 95% confidence interval, represented by any value less than two. (162-163, 229-230) Similar to the procedure used by Prichep, in the current study t-tests with applied permutation procedures for each of the compared Brodmann areas were conducted and assisted in narrowing the number of Brodmann area pairs and limited false positive responses. (228) The permutation tests in this study were conducted in R (www.R-project.org, Vienna, Austria), resampling the data 1200 times to generate a revised p-value. The use of t-tests to narrow false positive PSI values was previously adopted by Thatcher in his study comparing effective connectivity in high versus low IQ children. (21) While Thatcher used a 0.05 alpha in his first step, this study chose the more conservative 0.01 as used by Hohlefield in his PSI study of subthalamic local field potentials in Parkinson's disease patients. (21, 231)

To assess for differences between the chiropractic, sham, and control groups, a second series of analyses using two-way mixed Analysis of Variance (ANOVA) were performed (SPSS v.25. IBM Corporation, Armonk, New York). This two-step process of narrowing the data and limiting the number of false positives was used by Tsuchimoto in an fMRI and EEG study examining resting state fluctuations in the sensorimotor rhythm and by Butler in a study assessing differences in mental rotation processing between men and women. (181,232) Specific

to PSI, the two-step process was also used in a series of studies by Veldman and in the Thatcher PSI and IQ study discussed previously. (223-224, 229-230)

While the first level of assessment narrowed the number of data available for analysis, the second level of comparison assessed the between group differences using two-way mixed ANOVA; the within-subjects factor being time and the between-subjects factor being intervention group. Since the permutation test was used as a method to control for false positives in the first step of the analyses, no additional correction beyond alpha set at 0.05 as in the Tsuchimoto , Butler and Veldman research was applied to the 2-way mixed ANOVAs. (181,229-230,232) Post-hoc Tukeys and simple main effects for group and time were reviewed for significant two-way mixed ANOVA results.

A limitation of the source data for the current study was the lack of a middle time-point for the control group. For this reason, the time points assessed using the two-way ANOVA were baseline and immediate post assessment, baseline and one-week post intervention or baseline and one-week post baseline for the control, and immediate post intervention and one-week post intervention. The immediate post and one-week post provided an opportunity to determine if changes following chiropractic adjustment were sustained at one-week. Sample size and use of ANOVA was similar to previous studies used to determine regions of interest for the current study and evaluation of SEP changes post-chiropractic care. (9-11,16,22) Although many of the previous chiropractic studies used a repeated measures ANOVA, this study utilized a two-way mixed ANOVA given that both a between-subjects (group) and within-subjects (time) interaction were being examined.

CHAPTER 4

RESULTS

Group characteristics:

Participant age and mean epoch length for each time point were compared across the three groups receiving different interventions (chiropractic adjustment, chiropractic sham adjustment and control) using one-way ANOVAs, with the exception of the one-week post epoch length. The one-week post epoch length violated the assumption of normality, so a Kruskal-Wallis non-parametric test was performed. Epoch length represents the length in seconds of the artifacted electroencephalography recording (EEG) analyzed between two Brodmann areas for Phase Slope Index. There were no significant differences in age between the chiropractic adjustment (chiropractic) group ($M = 27.9$, $SD = 6.17$), the chiropractic sham (sham) group ($M = 33.7$, $SD = 15.33$), and the control group ($M = 34.0$, $SD = 16.23$), $F(2,27) = .661$, $p < .524$, $\eta^2 = .047$. Mean epoch length was compared for each of the three time points, and no significant differences were found between groups for baseline ($F(2,27) = 1.736$, $p < .195$, $\eta^2 = .114$), immediate post (post) intervention ($F(1,18) = .167$, $p < .688$, $\eta^2 = .009$), or for one-week post (one-week) intervention ($p < .396$) Mean epoch lengths for each participant group and time point are provided in Table 1, with the exception of the control group. EEG data was only recorded at two time points for the control group: baseline and one-week after initial recording.

Fisher's exact tests were performed for comparison of gender, medication use, and handedness between participant groups. Fisher's exact test was used instead of the Chi^2 test because three expected cell counts in each of the assessed characteristics (gender, medication

use, and handedness) were less than five. Each intervention group consisted of ten participants. The proportion of females to males for the chiropractic group (5:5), sham group (4:6), and control groups (7:3) were not statistically significant, $p < .384$. Non-statistically significant differences in proportions were also evident for medication use ($p = 1.0$) and handedness ($p < .224$). Each intervention group had one participant on medication and the ratio of right to left handedness is reported in Table 1.

Data Analyses:

The participant characteristics data analyzed and listed in Table 1 and the Phase Slope Index (PSI) values used in the two-way mixed ANOVA assessment of Brodmann Area (BA) connectivity were all screened for presence of outliers, normality and homogeneity of variances. To assess for outliers, boxplots of the dependent variables were inspected. If outliers greater than +/- 3 SD were present, the assessment was repeated without the presence of the outlier. Outliers were present in two sets of data, age ($n = 2$) and PSI Beta one for left Brodmann area (BA) pair 18 and 31 ($n = 1$). For age, no change to significance status was noted upon removal of the outliers, so the outliers were left within the data set. For BA pair 18 - 31, the outlier was removed and the group * time interaction was no longer present. To verify assumption of normality, Shapiro-Wilk's test, histograms and normal Q-Q plot results were reviewed. Only the one-week post epoch length data violated the assumption of normality. Transformation of the data set was performed using reflection and inverse transformation; however, the violation of normality was still present. In order to account for the violated assumption of normality the non-parametric Kruskal-Wallis test was performed. The data are represented in Table 1. Levene's test was used to assess for equality of variances. Log 10 transformations were performed on the data violating

the assumption of equality of variances (n = 2); however, to retain PSI directionality, the mean and standard deviation for the non-transformed data are reported.

Using a two-step process, data analysis was conducted on the normalized PSI scores between fourteen study-specific Brodmann areas across eight different frequency bands (Delta = 1.0-4.0 Hz; theta = 4.0-8.0 Hz; alpha1 = 8-10 Hz; Alpha-2 = 10-12 Hz; Beta1 = 12-15 Hz; Beta2 = 15-18 Hz; Beta3 = 18-25 Hz; Hi-Beta = 25-30 Hz) and three different time points for each group, exempting the control group with only two time points. Table 2 provides a list of the study specific Brodmann areas paired with the associated brain region. The PSI timepoint comparisons were baseline recording to immediate post intervention (post), baseline recording to one-week post (one-week) intervention and post to one-week. First, within-subject t-tests were performed on the 5,824 different BA pair, group, and time point combinations. For each of the student t-tests found to be significant, a permutation test was performed. Permutation tests used a randomized number sampling technique (repeated 1200 times) for each of the data sets and were performed to assist in controlling for false positive results (Type I errors) that may have occurred as a result of the multiple comparisons. Using an alpha of 0.01, forty-one significant BA pairs remained and are listed in Tables 3 and 4. Tables 3 and 4 provide the mean, standard deviation, and permuted p-values for each of the remaining BA pairs and time points. Figure 1 provides a cross-representation of BA pair interactions related to band and time point and Figures 2 through 4 illustrate changes in mean PSI across time.

For the second step of the data analysis process and to assess between-group differences for hypothesis testing, a two-way mixed ANOVA (group * time) for each of the remaining BA pairs and time points was performed with post hoc Tukeys and univariate analyses to assess for simple main effects of group and time. Given the rigor of the permutation test in limiting Type I

error and the use of an alpha of 0.01 in the first step of the analysis process, alpha for the second step of the analysis was set at 0. 05 as discussed in the methods section. The lack of change in the control group following the two-way mixed ANOVA suggests reliability of data for the baseline to one-week post assessment.

Specific Aim one:

The first Specific Aim sought to determine if a single dose of chiropractic manipulative therapy would modify brain communication patterns as assessed by calculation of PSI in healthy individuals immediately post chiropractic manipulation. Two hypotheses were to be tested:

- **Hypothesis 1**: That a single dose of chiropractic manipulative therapy as opposed to a single sham dose of manipulative therapy would significantly change the direction and magnitude of communication patterns among Brodmann areas 1, 2, 3, 9, 13, 23, 29, 30, and 31 within the brain immediately post chiropractic manipulation in healthy individuals.
- **Hypothesis 2**: That a single dose of chiropractic manipulative therapy as opposed to a single sham dose of manipulative therapy would significantly change the direction and magnitude of communication patterns among Brodmann areas 6, 7, 18, 40, and 46 that are associated with mental rotation in healthy individuals immediately post chiropractic manipulation.

To assess the between group differences for each of the Brodmann Area (BA) pairs, two-way mixed ANOVAs were conducted between the baseline PSI values and the immediate post (post) PSI values following either a chiropractic adjustment or a sham chiropractic adjustment for each of the fourteen Brodmann areas being assessed in this study.

Following the first step of permutation, the PSI for the following BA combinations demonstrated within-subject changes from baseline to post (R = right hemisphere; L = Left hemisphere): R1 – 13, R9 – 31, L 6 – 13, L9 – 13, and L9 – 29. PSI mean and standard deviations for each of the BA pairs are represented in Tables 3 and 4. Only BA pair L6 – 13 (medial frontal gyrus and anterior cingulate) in the Beta one band was significant for group * time effects for baseline chiropractic (M = -.071, SD = .865) and sham (M = .573, SD = .995) compared to post chiropractic (M = -.129, SD = .947) and sham (M = -.891, SD = .603) with F (1,18) = 10.512, $p < .005$, $\eta^2 = .369$. Results for mean, standard deviation and p-value for all two-way mixed ANOVA analyses are presented in Table 5, and Figures 5 through 13 provide PSI mean values at time points one, two, and three. For simple main effects, there was a statistically significant difference in PSI between interventions at the post recording time point, F (1,9) = 4.618, $p < .045$, $\eta^2 = .204$, but no significant difference at the baseline timepoint. For simple main effect of time, there was a statistically significant effect of time on PSI for the sham group, F (1,9) = 18.505, $p < .003$, $\eta^2 = .673$, no significant effect for the chiropractic group. Simple main effects for group and time are represented in Tables 6 and 7.

For convention, the BA pairs associated with the nine Brodmann areas in hypothesis one will be referred to as the chiropractic related Brodmann areas. These areas have demonstrated changes in source localization and connectivity in previous chiropractic research literature. (11,22) The five Brodmann areas associated with hypothesis two will be referred to as the mental rotation Brodmann areas, as previous research has associated each of the areas with mental rotation task performance (179-183) Given that hypothesis one specifically sought to examine interactions between chiropractic related BA pairs and hypothesis two specifically sought to assess BA pair interactions among five mental rotation Brodmann areas, as stated, hypothesis

one and two were rejected for baseline to post intervention. No interactions among the chiropractic related BA pairs were significant for group*time effects. Similarly, no interaction among the mental rotation related BA pairs were significant for group*time effects. However, between the two collections of Brodmann areas (chiropractic related and mental rotation) a significant baseline to post group * time effect was demonstrated in the left hemisphere between BA six and BA thirteen. Relative to PSI directionality, the first number in the BA pair is considered a driver if the value is positive and a responder if the PSI value is negative. This also means that the second BA in the pair is the opposite. For Specific Aim One the significant simple main effect for the sham group, BA six shifted from being a driver (M = .573) - meaning communication between the brain regions was driven by the BA – to being a responder (M = -.891) - meaning communication between the brain regions was towards the BA. Figures 14 through 17 provide direction of flow for each significant simple main effect for time.

Specific Aim Two:

The second Specific Aim sought to determine if a single dose of chiropractic manipulative therapy would modify brain communication patterns as assessed by calculation of PSI in healthy individuals at baseline and one-week post chiropractic manipulation, and two hypotheses were to be tested:

- **Hypothesis 3**: That a single dose of chiropractic manipulative therapy as opposed to a single sham dose of manipulative therapy or a no dose control would significantly change the direction and magnitude of communication patterns among Brodmann areas 1, 2, 3, 9, 13, 23, 29, 30, and 31 within the brain one-week post manipulation in healthy individuals.

- **Hypothesis 4**: That a single dose of chiropractic manipulative therapy as opposed to a single sham dose of manipulative therapy or a no dose control would significantly change the direction and magnitude of communication patterns among Brodmann areas 6, 7, 18, 40, and 46 within the brain that are associated with mental rotation in healthy individuals one-week post manipulation.

To assess the between group differences for each of the BA pairs, two-way mixed ANOVAs were conducted between the baseline PSI values and PSI values recorded one-week post the initial assessment for the control group and one-week post either a chiropractic adjustment or sham chiropractic adjustment for each of the fourteen Brodmann areas being assessed in this study.

Following the first step of permutation, the PSI for the following BA pairs demonstrated within-subject changes from baseline to one-week post: R 1 – 18, R9 – 13, R9 – 46, R 13 – 31, R 18 – 23, R 23 – 46, R 31 – 46, L 1 -18, L 3 – 18, L6 – 23, L 9 – 18, L 9 – 31, L 31 – 46. PSI mean and standard deviations for each of the BA pairs are represented in Table 2. The BA pairs listed above represent thirteen of the forty-one BA pairs remaining following step-one permutation. Of the thirteen BA pairs, only four pairs were significant for group * time interaction effects: R 18 – 23 ($F(2,27) = 5.421$, $p < .010$, $\eta^2 = .287$) for the alpha one band and R 23 – 46 ($F(2,27) = 7.277$, $p < .003$, $\eta^2 = .350$P), R 31 – 46 ($F(2,27) = 5.499$, $p < .01$, $\eta^2 = .289$), and L 9 – 31 ($F(2,27) = 4.148$, $p < .027$, $\eta^2 = .235$) for the alpha two band. Simple main effects for group were only observed for R 18 -23 at baseline, $F(1,9) = 5.567$, $p < .009$, $\eta^2 = .292$, and for L 9 – 31 at one-week post, $F(1,9) = 8.223$, $p < .002$, $\eta^2 = .379$. Significant simple main effects for time on PSI were observed for the sham group, $F(1,9) = 11.552$, $p < .008$, $\eta^2 = .562$, on BA pair R 18 – 23. The remaining three BA pairs demonstrated significant simple main

effects for the chiropractic group: R 23 – 46 ($F(1,9) = 15.499$, $p < .003$, $\eta^2 = .004$), R 31 – 46 ($F(1,9) = 11.042$, $p < .009$, $\eta^2 = .551$), and L 9 – 31 ($F(1,9) = 32.885$, $p < .000$, $\eta^2 = .785$).

The brain regions associated with the BA pairs demonstrating significant changes were the visual association cortex (BA 18) and the posterior cingulate cortex (BA 23, 29, 30 and 31) for the group showing simple main effects on time for the sham group. Cortical regions associated with BA pair changes in simple main effects for the chiropractic group also included the cingulate cortex (BA 23, 29, 30 and 31). Additionally, the prefrontal cortex (BA 9) and the dorsal lateral prefrontal cortex (BA 46) were represented in the pairs demonstrating simple main effect for chiropractic. For BA pair 18 – 23, BA 18 went from being a driver (M = 1.09) to a responder (M = -.034) in the sham group, the direction of information flow for the chiropractic group remained the same (M = .379 to M = .362), and BA 18 in the control group went from being to a responder (M = -.172) to driver (M = .104). For the remaining BA pairs, the posterior cingulate cortex Brodmann areas went from being the driver to the responder for the chiropractic group: R 23 – 46 (M = .360 to M = -.715), R 31 – 46 (M = .321 to M = -.741), and L9 – 31 (M = -.298 to M = .645). The results were mixed for the sham and control groups and are reported in Table 5.

As with the hypotheses in Specific Aim one, each hypothesis for Specific Aim two was restricted to either the chiropractic related BA pairs for hypothesis three or the mental rotation associated BA pairs for hypothesis four. Support for hypothesis three has been provided by the significant group*time result for BA pair L9 – 31, the simple main effect on time for the chiropractic group, and the change in directionality for Brodmann area nine from a responder to a driver of information flow. However, since the remaining BA pairs involve the posterior cingulate cortex (BA 23 and BA 31) from the chiropractic associated regions paired with the

dorsal lateral prefrontal cortex (BA 46) or visual association area (BA 18), hypothesis four related to changes among regions associated with mental rotation must be rejected.

Specific Aim three:

The third Specific Aim sought to determine if brain communication patterns as measured by phase slope index observed immediately post chiropractic manipulative therapy would be sustained one-week post manipulation. The following two hypotheses were to be tested.

- **Hypothesis 5**: That following a single dose of chiropractic manipulative therapy as opposed to a single sham dose of manipulative therapy the direction and magnitude of communication patterns among Brodmann areas 1, 2, 3, 9, 13, 23, 29, 30, and 31 within the brain one-week post manipulation in healthy individuals will significantly change.
- **Hypothesis 6**: That following a single dose of chiropractic manipulative therapy as opposed to a single sham dose of manipulative therapy the direction and magnitude of communication patterns among Brodmann areas 6, 7, 18, 40, and 46 within the brain that are associated with mental rotation in healthy individuals one-week post manipulation will significantly change.

To assess the between group differences for each of the Brodmann Area (BA) pairs, two-way mixed ANOVAs were conducted between the immediate post PSI values and PSI values recorded one-week after either a chiropractic adjustment or sham chiropractic adjustment for each of the fourteen BA being assessed in this study.

Following the first step of permutation, the PSI for the following BA combinations demonstrated within-subject changes from baseline to one-week post: R 1 – 46, R 2 – 18 (2), R 3 – 18 (2), R 9 – 13 (2), R 9 – 46, R 23 – 40, R 31 – 40, R 31 – 46, L 2 – 13, L3 – 13, L 6 – 13, L6

– 23, L 6 – 46 (2), L 7 – 40, L 9 – 13, L 9 – 31, L 18 - 31. PSI mean and standard deviations for each of the BA pairs are represented in Tables 3 and 4. The BA pairs listed above represent twenty-one of the forty-one BA pairs remaining following step-one permutation. Of the twenty-one BA pairs, seven pairs were significant for group * time interaction effects. In the delta band R 23 – 40 was significant at $F(1,18) = 22.843$, $p < .001$, $\eta^2 = .717$. The simple main effects for group were only significant for the immediately post, $F(1,9) = 5.897$, $p < .026$, $\eta^2 = .247$, and for time the sham group demonstrated significant values, $F(1,9) = 22.843$, $p < .001$, $\eta^2 = .717$. For directionality, while the chiropractic group did not change (M = .408 to M = .357), BA R23 in the sham group went from being a responder to a driver (M = -.571 to M = .318). There were three BA pairs in the theta band: R2 – 18 ($F(1,18) = 5.995$, $p < .025$, $\eta^2 = .250$), R 3 – 18 ($F(1, 18) = 5.430$, $p < .033$, $\eta^2 = .229$), and L 6 – 46 ($F(1,18) = 5.412$, $p < .032$, $\eta^2 = .231$. For group simple main effects, significant results were only observed in the R2 – 18 ($F(1,9) = 3.566$, $p < .042$, $\eta^2 = .209$) one-week post and in the L 6 - 46 ($F(1,9) = 6.282$, $p < .022$, $\eta^2 = .259$) immediate post. Across all three theta band BA pairs, the simple main effects for time were significant for the sham group and not the chiropractic group: R 2 – 18 ($F(1,9) = 8.244$, $p < .018$, $\eta^2 = .478$), R 3 – 18 ($F(1,9) = 8.329$, $p < .018$, $\eta^2 = .481$), and L 6 – 46 ($F(1,9) = 12.739$, $p < .006$, $\eta^2 = .586$). For directionality, the somatosensory cortex BA areas (R 2 and R 3) in the sham group started as drivers relative to the visual association area (R 18) but following one-week the somatosensory mean PSI direction switched to being responder: R 2 – 18 (M = .522 to M = -.704) and R 3 – 18 (M = .480 to M = -.670). The chiropractic directionality was the opposite: R 2 – 18 (M = -.105 to M = .302) and R 3 – 18 (M = -.071 to M = .249). The medial frontal gyrus (BA 6) remained a driver for the chiropractic group relative to the dorsal lateral prefrontal cortex

(BA 46) at M = .309 to M = .180; however, in the sham group the BA 6 went from being a responder (M = -.553) to a driver (M = .597) relative to BA 46.

The alpha one band results for R 2 – 18 and R 3 – 18 were similar to the theta band results for group*time, simple main effects and directionality. The significant group*time results for R 2 -18 in the alpha one band were $F(1,18) = 7.418$, $p < .014$, $\eta^2 = .292$ and for R 3 – 18 the results were $F(1,18) = 7.919$, $p < .011$, $\eta^2 = .306$. Relative to simple main effects for group both BA pairs were significant for group on the one-week mean PSI: R 2 – 18 ($F(1,9) = 4.010$, $p < .030$, $\eta^2 = .229$) and R 3 – 18 ($F(1,9) = 4.225$, $p < .025$, $\eta^2 = .238$). For time, simple main effects, only the sham mean PSI values were significant for R 2 – 18 ($F(1,9) = 10.827$, $p < .009$, $\eta^2 = .546$) and R 3 – 18 ($F(1,9) = 14.523$, $p < .004$, $\eta^2 = .617$) and not the chiropractic group. The directionality was the same as the theta band results for the chiropractic and sham groups, with the somatosensory regions becoming drivers as opposed to responders for BA 2 (M = -.081 to M = 267) and BA 3 (M = -.124 to M = 216) in the chiropractic group and the opposite in the sham group: BA 2 (M = .550 to M = -.771) and BA 3 (M = .545 to M = -.783). The last of the BA pairs to demonstrate a significant group*time effect was R 1 – 46 in the Beta one band, $F(1,18) = 7.953$, $p < .011$, $\eta^2 = .306$. The simple main effect for group was observed in the immediate post mean PSI, $F(1,9) = 4.672$, $p < .044$, $\eta^2 = .206$, and the simple main effect for time was in the chiropractic group, $F(1,9) = 8.285$, $p < .018$, $\eta^2 = .479$. As with the previously discussed BA pairs involving the dorsal lateral prefrontal cortex (BA 46) in the alpha two band for baseline one-week, the directionality shifted for the chiropractic group, resulting in BA 46 being a driver of information as opposed to the primary somatosensory cortex (BA 1) being the driver (M = .310 to M = -.721).

Although BA pair changes occurred between the chiropractic related Brodmann areas and the mental rotation related Brodmann areas, based on the above described results, hypothesis five concerning changes in PSI from immediate post to one-week post for the chiropractic related BA pairs, must be rejected. The changes demonstrated in the PSI values for six of the significant pairs contain one BA from the chiropractic related group and one from the mental rotation related group. Hypothesis six concerning changes in PSI from immediate post to one-week post for the mental rotation related BA pairs must also be rejected. While changes in L 6 – 46 were evident and within the mental rotation Brodmann areas, the directionality for the chiropractic group did not change and the significant main effects were observed in the sham as opposed to the chiropractic group.

Table 1: Mean age and epoch length and gender, medication, and handedness ratios across participant groups

	Sham participants (n = 10)	Adjustment participants (n = 10)	Control participants (n = 10)	Test statistic
Age mean yrs. (SD)	33.7 (15.33)	27.9 (6.17)	34.0 (16.23)	$F(2,27) = .661$, $p < .524$, $\eta^2 = .047$
Gender (F:M)	5:5	4:6	7:3	Fisher's exact test, $p < .384$
Medication (Y:N)	1:9	1:9	1:9	Fisher's exact test, $p = 1.0$
Handedness (R:L)	8:2	9:1	10:0	Fisher's exact test, $p < .224$
Epoch length (Baseline)	107.5/19.603	106.30/24.413	123.40/24.382	$F(2,27) = 1.736$, $p < .195$, $\eta^2 = .114$
Epoch length (Post)	100.70/26.183	96.60/17.964		$F(1,18) = .167$, $p < .688$, $\eta^2 = .009$
Epoch length (One- week)	90.20/26.084	110.7/19.120	105.00/22.930	Kruskal-Wallis, $p < .396$

SD = Standard deviation; F = Female; M = Male; Y = Yes; N = No; R = Right; L = Left;
Post = Immediate post intervention; One-week = One-week post intervention

Table 2: Study specific Brodmann areas by brain region

Brain region	Brodmann area
Primary somatosensory cortex	1
	2
	3
Prefrontal cortex	9
Anterior insula	13
Posterior cingulate cortex	23
	29
	30
	31
Medial frontal gyrus	6
Superior parietal lobule	7
Visual association cortex	18
Inferior parietal lobule	40
Dorsal lateral prefrontal cortex	46

Table 3: Right hemisphere significant within-subjects t-tests results with permutation, ($p < .01$)

BA area pairs	Grp	Band	Baseline (B)			Immediate Post (P)			One-week post (W)			Time	p-value (Perm)
			Sham	Chiro	Control	Sham	Chiro	Control	Sham	Chiro	Control		
			M S/D	M S/D	M S/D	M S/D	M S/D	M S/D	M S/D	M S/D	M S/D		
R 1 – 13	Chiro	Beta 2		0.46/0.41			-0.28/0.73					BP	.008
R 1 – 18	Sham	Alpha 1	0.02/0.89						-1.14/0.82			BW	.009
R 1 – 46	Chiro	Beta 1					0.31/0.92			-0.72/0.73		PW	.009
R 2 – 18	Sham	Theta				0.52/0.80			-0.70/0.81			PW	.006
	Sham	Alpha 1				0.55/0.82			-0.77/0.81			PW	.003
R 3 – 18	Sham	Theta				0.48/0.71			-0.67/0.93			PW	.006
	Sham	Alpha 1				0.55/0.75			-0.78/0.78			PW	.003
R 9 – 13	Con	Beta 1			-0.91/0.64						-0.10/0.64	BW	.008
	Chiro	Beta 1					0.78/0.63			-0.46/0.69		PW	.000
	Chiro	Beta 2					0.59/0.69			-0.55/0.85		PW	.008
R 9 – 31	Chiro	Alpha 1		-0.27/1.05			0.76/0.40					BP	.009
R 9 – 46	Sham	Alpha 1	0.47/0.97						-0.66/0.83			BW	.008
	Sham	Theta				0.82/1.23			-0.76/0.76			PW	.004
R 13 – 31	Chiro	Delta		0.32/0.67						-0.45/0.56		BW	.009
R 18 - 23	Sham	Alpha 1	1.09/0.64						-0.03/0.83			BW	.005
R 23 – 40	Sham	Delta				-0.57/0.49			0.32/0.56			PW	.003
R 23 – 46	Chiro	Alpha 2		0.36/0.81						-0.72/0.46		BW	.002
R 31 – 40	Sham	Delta				-0.67/0.32			0.09/0.61			PW	.000
R 31 – 46	Chiro	Alpha 2		0.32/0.85						-0.74/0.44		BW	.003
	Chiro	Alpha 2					0.07/0.70			-0.74/0.44		PW	.007

BA = Brodmann areas; perm = permutation; Sham = chiropractic sham manipulation; Chiro = Chiropractic adjustment
Time: BP = Baseline to immediate post; BW = Baseline to one-week post; PW = Immediate post to one-week post
R = Right

Table 4. Left hemisphere significant within-subjects t-tests results with permutation, ($p < .01$)

BA area pairs	Grp	Band	Baseline (B)			Immediate Post (P)			One-week post (W)			Time	p-value (Perm)
			Sham	Chiro	Control	Sham	Chiro	Control	Sham	Chiro	Control		
			M S/D	M S/D	M S/D	M S/D	M S/D	M S/D	M S/D	M S/D	M S/D		
L 1 – 18	Chiro	Alpha 2		-0.11/0.62						-0.58/0.56		BW	.006
L 2 – 13	Chiro	Delta					0.56/0.61			-0.80/0.92		PW	.003
L 3 – 13	Chiro	Delta					0.37/0.62			-0.66/0.91		PW	.008
L 3 – 18	Chiro	Alpha 2		-0.58/0.56						0.29/0.73		BW	.006
L 6 – 13	Sham	Alpha 2				-0.81/0.68			0.37/1.09			PW	.006
	Sham	Alpha 2	0.30/0.88			-0.81/0.68						BP	.006
	Sham	Beta 1	0.57/0.99			-0.89/0.60						BP	.000
L 6 – 23	Sham	Beta 1	0.02/0.88						-0.97/0.67			BW	.009
	Sham	Beta 1				-0.01/0.70			-0.97/0.67			PW	.009
L 6 – 46	Sham	Theta				-0.55/0.65			0.60/1.01			PW	.008
	Sham	Alpha 1				-0.44/0.72			0.80/1.03			PW	.009
L 7 – 13	Chiro	Delta		-0.54/0.49						-0.44/0.60		BW	.008
L 7 – 40	Chiro	Beta 3					0.40/0.79			-0.42/0.49		PW	.009
L 9 – 13	Sham	Theta	0.40/0.68			-0.56/0.72						BP	.008
	Chiro	Alpha 1					-0.01/0.73			0.59/0.75		PW	.004
L 9 – 18	Chiro	Alpha 2		-0.17/0.60						0.63/0.60		BW	.009
L 9 – 29	Sham	Beta 2	-0.50/0.58			0.51/0.76						BP	.003
L 9 – 31	Chiro	Alpha 2		-0.30/0.73						0.65/0.48		BW	.003
	Chiro	Alpha 2					-0.21/0.79			0.65/0.48		PW	.009
L 18 – 31	Sham	Beta 1				1.26/0.61			0.43/0.64			PW	.008
L 31 – 46	Chiro	Delta		-0.49/0.74						-0.46/0.93		BW	.010

BA = Brodmann areas; perm = permutation; Sham = chiropractic sham manipulation; Chiro = Chiropractic adjustment
Time: BP = Baseline to immediate post; BW = Baseline to one-week post; PW = Immediate post to one-week post
L = Left

Table 5: Phase Slope Index significant results of two-way mixed ANOVA, ($p < 0.05$)

		Baseline (B)						Immediate Post (P)						One-week post (W)						Time	P-Value	F-stat	η^2
Brodmann area pairs	Band	Sham		Chiro		Control		Sham		Chiro		Control		Sham		Chiro		Control					
		M	S/D	M	S/D	M	S/D	M	S/D	M	S/D	M	S/D	M	S/D	M	S/D	M	S/D				
R 1 – 46	Beta 1							-.578/.918		.310/.919				-.444/.670		-.721/.727				PW	.011	7.952	.306
R 2 – 18	Theta							.522/.802		-.105/.683				-.704/.810		.302/1.20				PW	.025	5.996	.250
	Alpha 1							.550/.818		-.081/.610				-.771/.814		.267/1.21				PW	.014	7.416	.292
R 3 – 18	Theta							.480/.706		-.071/.673				-.670/.926		.249/1.20				PW	.033	5.430	.229
	Alpha 1							.545/.750		-.124/.744				-.783/.785		.216/1.19				PW	.011	7.919	.306
R 18 – 23	Alpha 1	1.09/.638		.379/.686		-.172/1.13								-.034/.826		.362/.575		.104/1.01		BW	.010	5.421	.287
R 23 – 40	Delta							-.571/.491		.408/1.26				.318/.561		.357/.841				PW	.001	22.84	.717
R 23 – 46	Alpha 2	-.027/.899		.360/.814		-.411/.732								.034/1.18		-.715/.460		.095/.998		BW	.003	7.277	.350
R 31 – 46	Alpha 2	-.166/.803		.321/.851		-.400/.666								-.061/1.265		-.741/.437		.008/.971		BW	.024	4.279	.024
L 6 – 13	Beta 1	.573/.995		-.071/.865				-.891/.603		-.129/.947										BP	.005	10.51	.369
L 6 – 46	Theta							-.553/.648		.309/.874				.597/1.006		.180/1.15				PW	.032	5.412	.231
L 9 – 31	Alpha 2	-.143/.863		-.298/.727		-.092/.581								.418/.866		.645/.476		-.520/.646		BW	.027	4.148	.235

L = Left; R = Right; Sham = chiropractic sham manipulation; Chiro = Chiropractic adjustment;
Time: BP = Baseline to immediate post; BW = Baseline to one-week post; PW = Immediate post to one-week post

Table 6: Phase Slope Index simple main effects of time for two-way mixed ANOVA

Brodmann area	Band	Group	F-stat	p-value	η^2
R 1 – 46	Beta one	Sham	.425	.531	.045
		Chiro	8.285	**.018**	.479
R 2 – 18	Theta	Sham	8.244	**.018**	.478
		Chiro	.631	.447	.066
	Alpha 1	Sham	10.827	**.009**	.546
		Chiro	.566	.471	.059
R 3 – 18	Theta	Sham	8.329	**.018**	.481
		Chiro	.417	.535	.044
	Alpha 1	Sham	14.523	**.004**	.617
		Chiro	.504	.496	.053
R 18 – 23	Alpha 1	Sham	11.552	**.008**	.562
		Chiro	.006	.942	.001
		Control	.530	.485	.056
R 23 – 40	Delta	Sham	22.843	**.001**	.717
		Chiro	.019	.894	.002
R 23 – 46	Alpha 2	Sham	.036	.854	.004
		Chiro	15.499	**.003**	.633
		Control	2.603	.141	.224
R 31 – 46	Alpha 2	Sham	.060	.812	.007
		Chiro	11.042	**.009**	.551
		Control	1.303	.283	.126
L 6 – 13	Beta 1	Sham	18.505	**.003**	.673
		Chiro	.047	.833	.005
L 6 – 46	Theta	Sham	12.739	**.006**	.586
		Chiro	.085	.778	.009
L 9 – 31	Alpha 2	Sham	1.225	.286	.125
		Chiro	32.885	**.000**	.785
		Control	2.030	.188	.184

Significant results designated by bold lettering, $p < .05$

R = Right; L = Left; Sham = chiropractic sham manipulation; Chiro = Chiropractic adjustment

Table 7: Phase Slope Index simple main effects of group for two-way mixed ANOVA

Brodmann area	Band	Time	F-stat	p-value	η^2
R 1 – 46	Beta one	Post	4.672	**.044**	.206
		One-week	.540	.589	.038
R 2 – 18	Theta	Post	3.539	.076	.164
		One-week	3.566	**.042**	.209
	Alpha 1	Post	3.837	.066	.176
		One-week	4.010	**.030**	.229
R 3 – 18	Theta	Post	3.191	.091	.151
		One-week	3.292	.053	.196
	Alpha 1	Post	4.021	.060	.183
		One-week	4.225	**.025**	.238
R 18 – 23	Alpha 1	Baseline	5.567	**.009**	.292
		One-week	.599	.557	.042
R 23 – 40	Delta	Post	5.897	**.026**	.247
		One-week	.060	.942	.004
R 23 – 46	Alpha 2	Baseline	2.221	.128	.141
		One-week	2.350	.115	.148
R 31 – 46	Alpha 2	Baseline	1.755	.192	.115
		One-week	1.257	.301	.085
L 6 – 13	Beta 1	Baseline	2.116	.140	.136
		Post	4.618	**.045**	.204
L 6 – 46	Theta	Post	6.282	**.022**	.259
		One-week	2.272	.122	.144
L 9 – 31	Alpha 2	Baseline	.213	.809	.016
		One-week	8.223	**.002**	.379

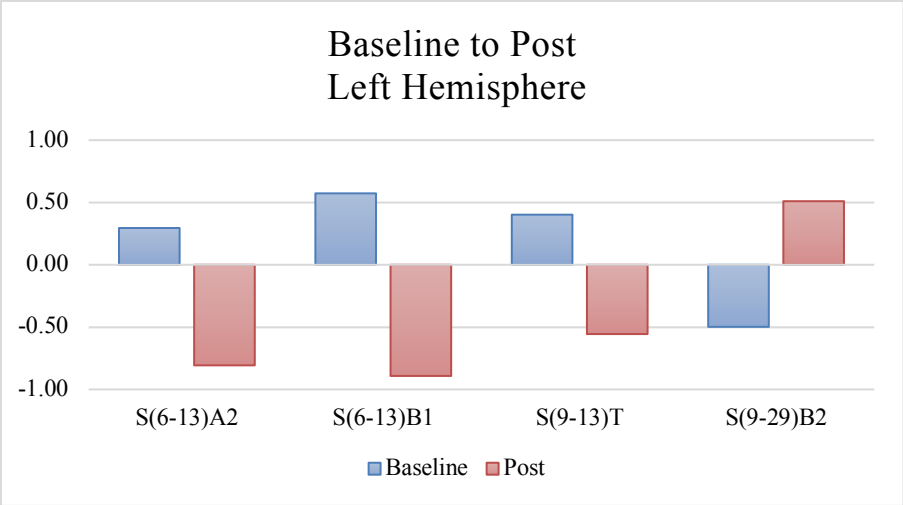
Significant results designated by bold lettering, $p < .05$

R = Right; L = Left; Sham = chiropractic sham manipulation; Chiro = Chiropractic adjustment

Brodmann area (Left hemisphere)	*13*	*18*	*23*	*29*	*30*	*31*	*40*	*46*
1		BW: AA2						
2	PW: AD							
3	PW: AD	BW: AA2						
6	BP: SA2 BP: SB1; PW: SA2		BW: SB1 PW: SB1					PW: ST PW: SA1
7	BW: AD						PW: AB3	
9	BP: ST PW: AA1	BW: AA2		BP: SB2		BW: AA2 PW: AA2		
13								
18						PW: AB1		
23								
29								
30								
31								BP: AD

Brodmann area (Right hemisphere)	*13*	*18*	*23*	*29*	*30*	*31*	*40*	*46*
1	BP: AB2	BW: SA1						PW: AB1
2		PW: ST PW: SA1						
3		PW: ST PW: SA1						
6								
7								
9	BW: CB1 PW: AB1 PW: AB2					BP: AA1		BW: SA1 PW: ST
13						BW: AD		
18			BW: SA1					
23							PW: SD	BW: AA2
29								
30								
31							PW: SD	BW: AA2 PW: AA2

Figure 1: Brodmann Area pairs significant for within-subjects t-tests following permutation, ($p < 0.01$)
Time: BP = Baseline to immediate post; BW = Baseline to one-week post; PW = Immediate post to one-week post; S = Sham adjustment; A = Chiropractic adjustment; C = Control; D = Delta; T = Theta; A1 = Alpha one; A2 = Alpha two; B1 = Beta one; B2 = Beta two; B3 = Beta three;
Color: pink = sham adjustment only; green = chiropractic adjustment only; yellow = control only; gray = mixed groups



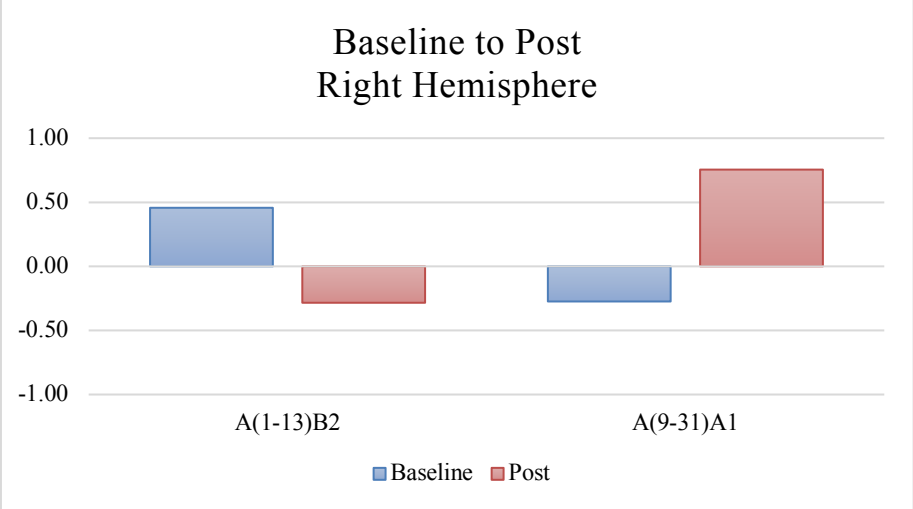
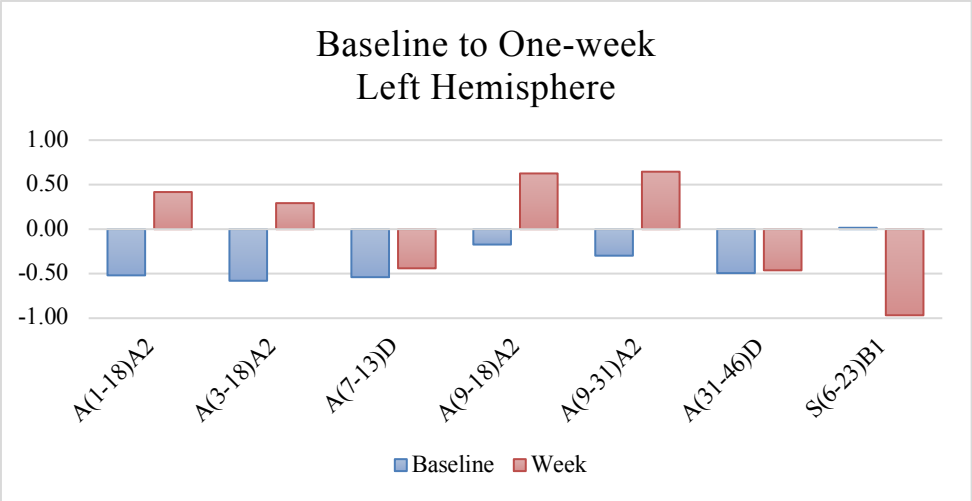


Figure 2: Changes baseline to immediate post (Post) intervention for significant mean Phase Slope Index within-subjects t-tests following permutation, ($p < 0.01$)

A = Chiropractic adjustment; S = Sham adjustment; C = Control; T = Theta; D = Delta; A1 = Alpha one; A2 = Alpha two; B1 = Beta one; B2 = Beta two; B3 = Beta three; Post = immediate post intervention; Week = one-week post intervention



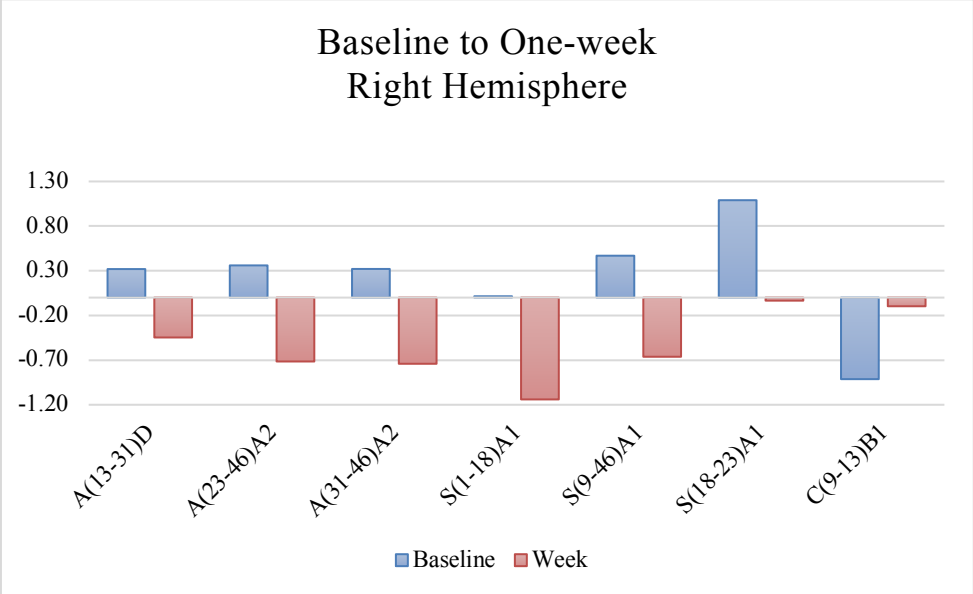
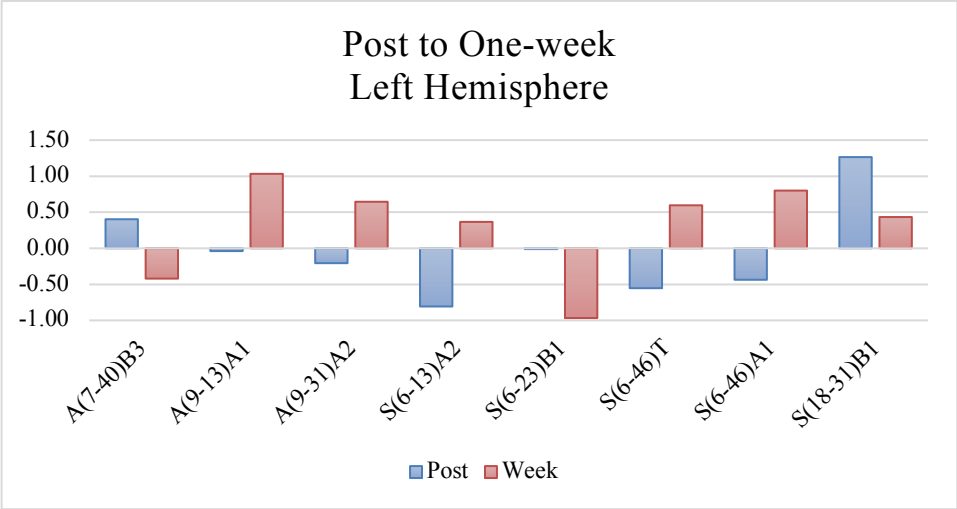


Figure 3: Changes baseline to one-week post (One-week) intervention for significant mean Phase Slope Index within-subjects t-tests following permutation, ($p < 0.01$)

A = Chiropractic adjustment; S = Sham adjustment; C = Control; T = Theta; D = Delta; A1 = Alpha one; A2 = Alpha two; B1 = Beta one; B2 = Beta two; B3 = Beta three; Post = immediate post intervention; Week = one-week post intervention



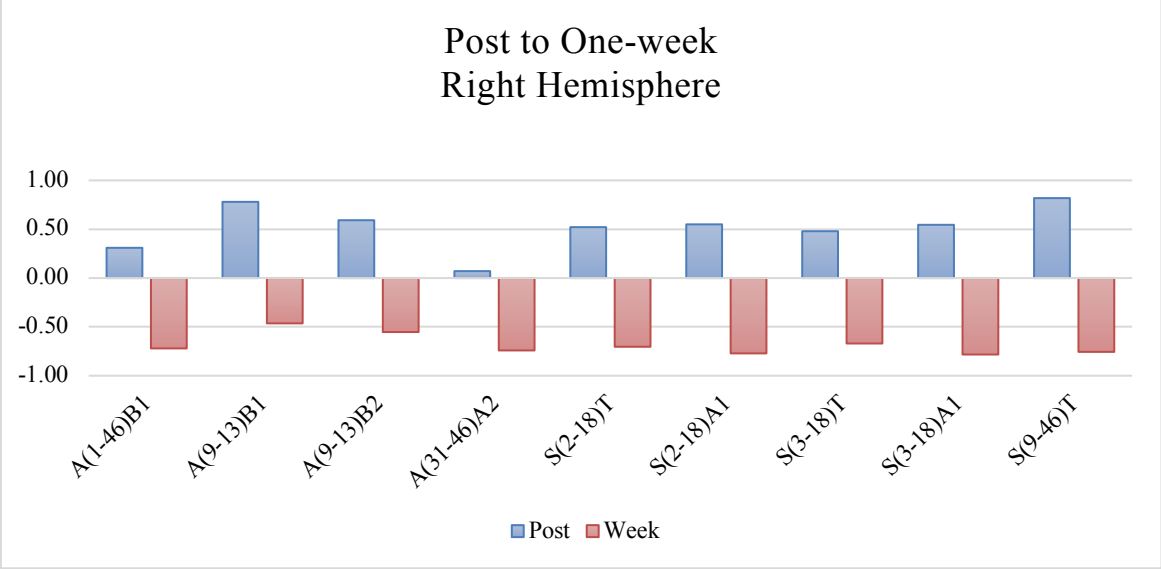


Figure 4: Changes post to one-week intervention for significant mean Phase Slope Index within-subjects t-tests following permutation, ($p < 0.01$)

A = Chiropractic adjustment; S = Sham adjustment; C = Control; T = Theta; D = Delta; A1 = Alpha one; A2 = Alpha two; B1 = Beta one; B2 = Beta two; B3 = Beta three; Post = immediate post intervention; Week = one-week post intervention

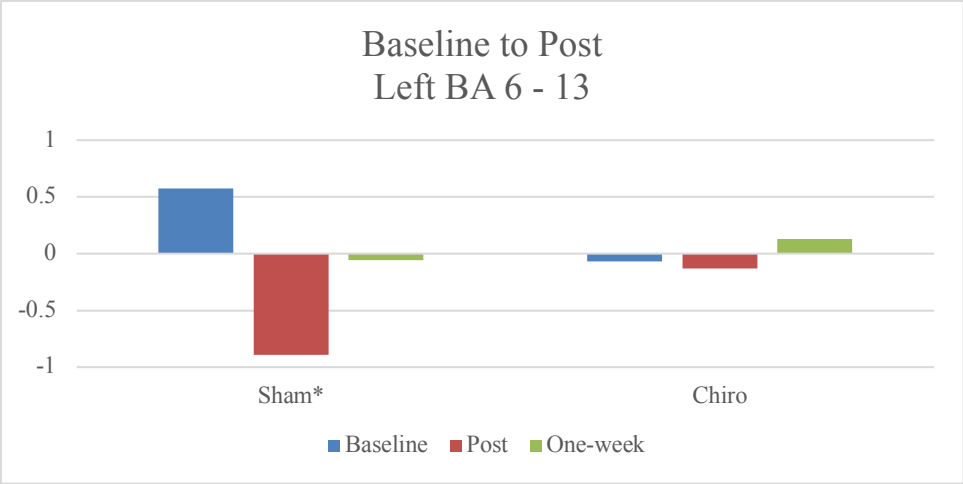


Figure 5: Baseline, immediate post, one-week post for Phase Slope Index two-way mixed ANOVA results for left Brodmann Area (BA) 6 to BA 13

* designates significant simple main effect for time
Sham = Sham chiropractic adjustment; Chiro = Chiropractic adjustment

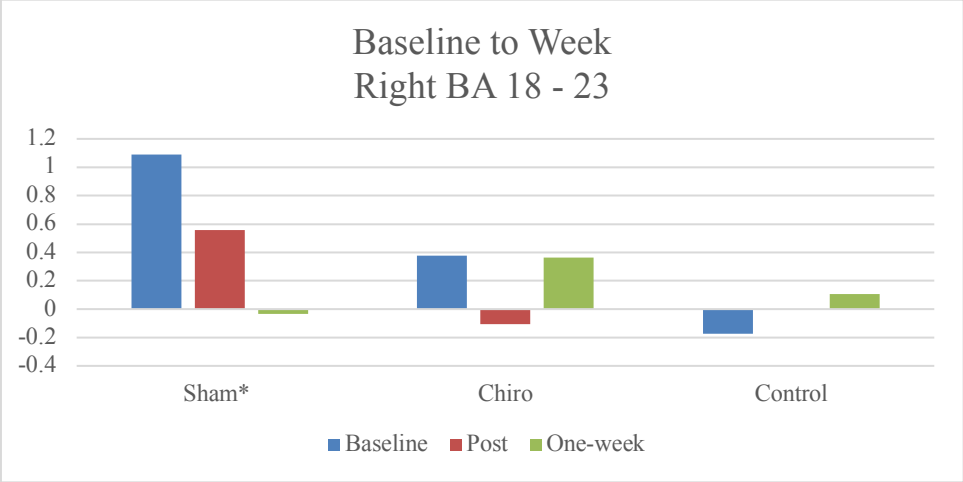


Figure 6: Baseline, immediate post, one-week post for Phase Slope Index two-way mixed ANOVA results for the right BA 18 to BA 23

* designates significant simple main effect for time
Sham = Sham chiropractic adjustment; Chiro = Chiropractic adjustment

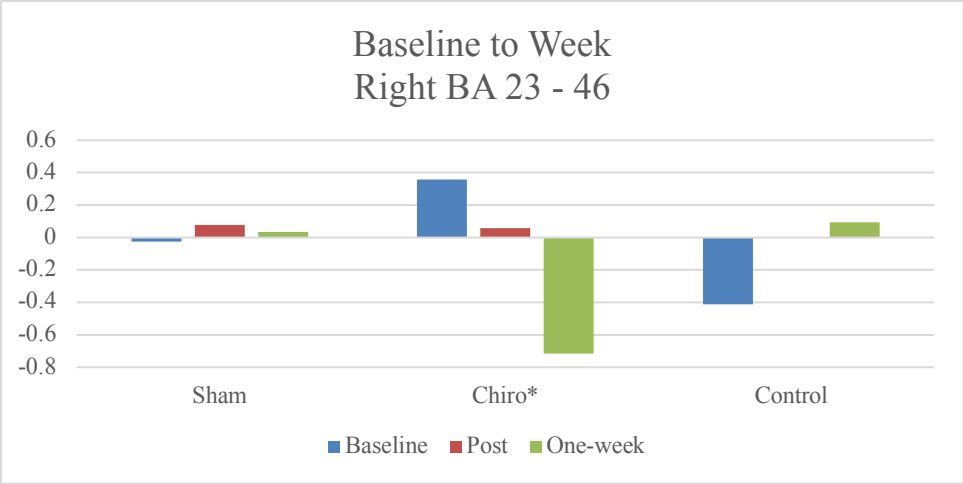


Figure 7: Baseline, immediate post, one-week post for Phase Slope Index two-way mixed ANOVA results for the right BA 23 to BA 46

* designates significant simple main effect for time
Sham = Sham chiropractic adjustment; Chiro = Chiropractic adjustment

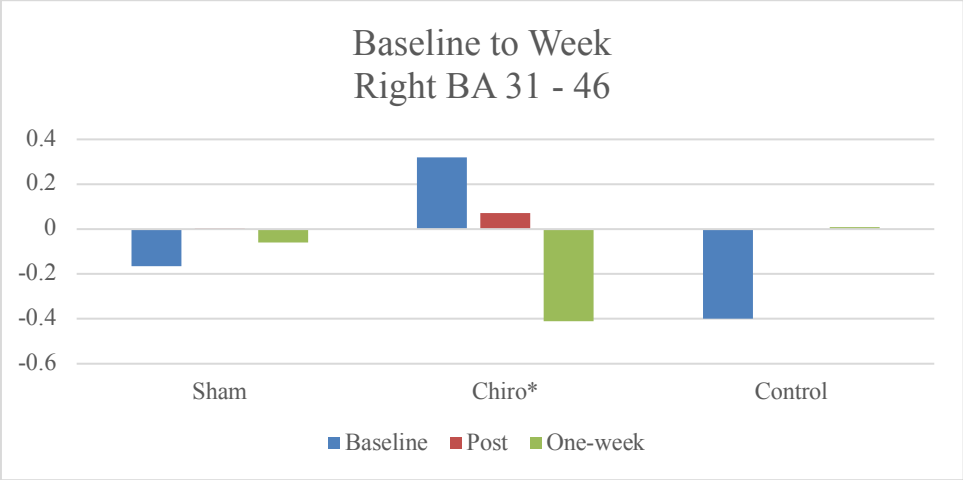


Figure 8: Baseline, immediate post, one-week post for Phase Slope Index two-way mixed ANOVA results for the right BA 31 to BA 46

* designates significant simple main effect for time
Sham = Sham chiropractic adjustment; Chiro = Chiropractic adjustment

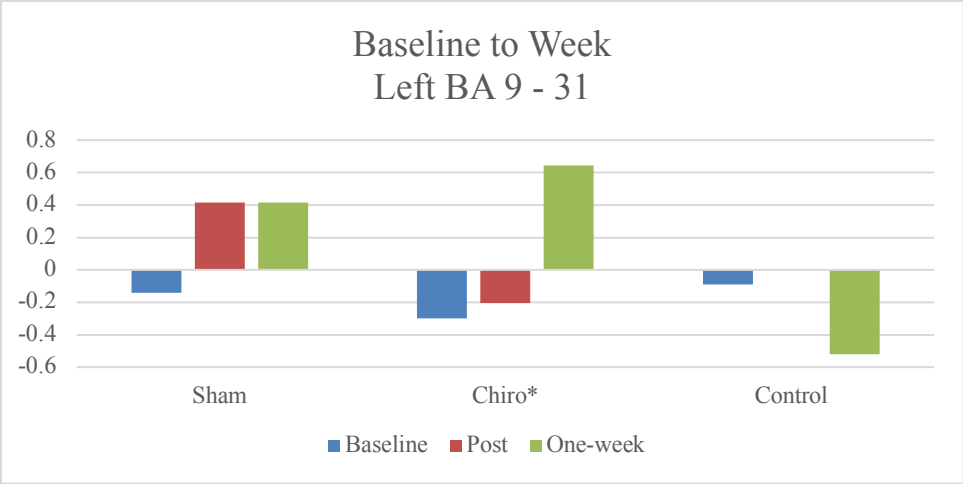


Figure 9: Baseline, immediate post, one-week post for Phase Slope Index two-way mixed ANOVA results for the left BA 9 to BA 31

* designates significant simple main effect for time
Sham = Sham chiropractic adjustment; Chiro = Chiropractic adjustment

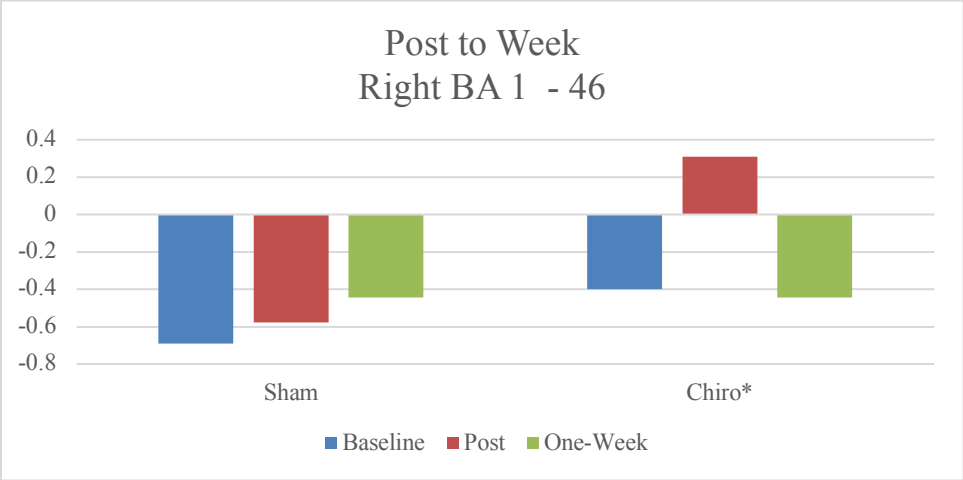


Figure 10: Baseline, immediate post, one-week post for Phase Slope Index two-way mixed ANOVA results for the right BA 1 to BA 46

* designates significant simple main effect for time
Sham = Sham chiropractic adjustment; Chiro = Chiropractic adjustment

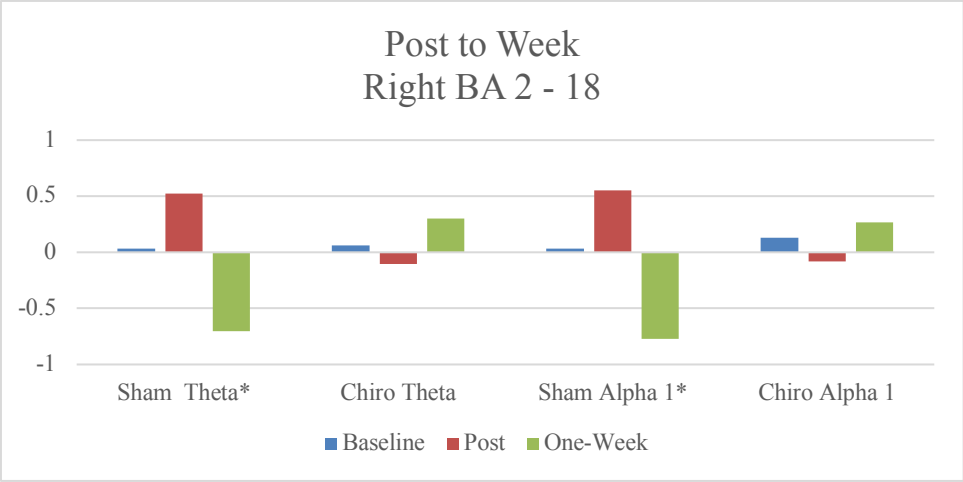


Figure 11: Baseline, immediate post, one-week post for Phase Slope Index two-way mixed ANOVA results for the right BA 2 to BA 18 (Theta and Alpha one)

* designates significant simple main effect for time
Sham = Sham chiropractic adjustment; Chiro = Chiropractic adjustment

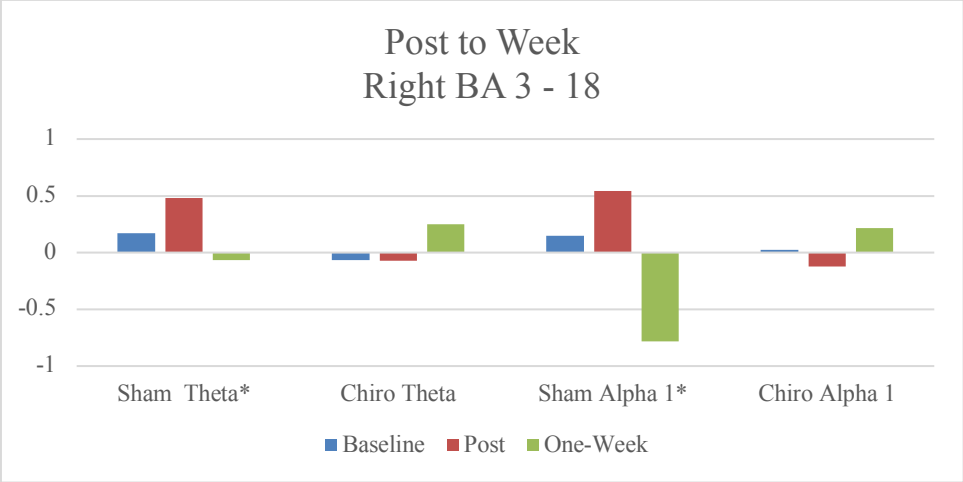


Figure 12: Baseline, immediate post, one-week post for Phase Slope Index two-way mixed ANOVA results for the right BA 3 to BA 18 (Theta and Alpha one)

* designates significant simple main effect for time
Sham = Sham chiropractic adjustment; Chiro = Chiropractic adjustment

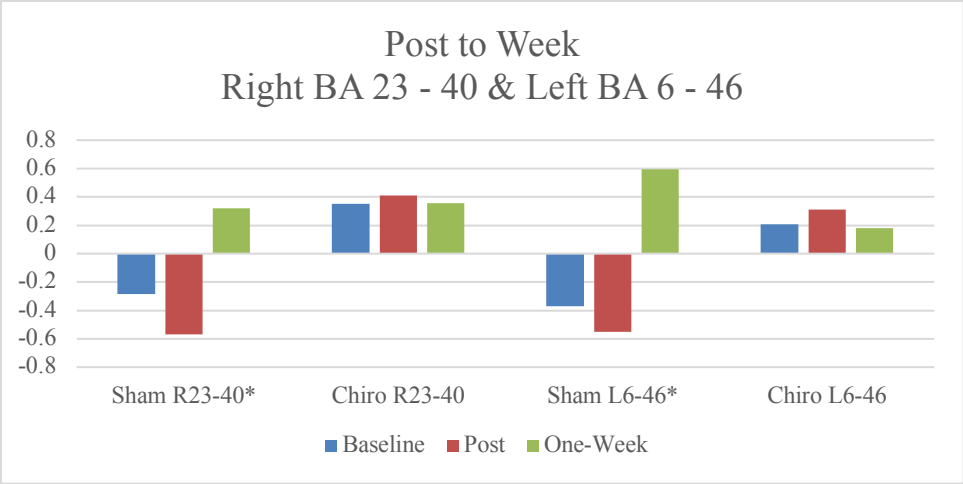


Figure 13: Baseline, immediate post, one-week post for Phase Slope Index two-way mixed ANOVA results for the right BA 23 to BA 40 and Left BA 6 to BA 46

* designates significant simple main effect for time
Sham = Sham chiropractic adjustment; Chiro = Chiropractic adjustment

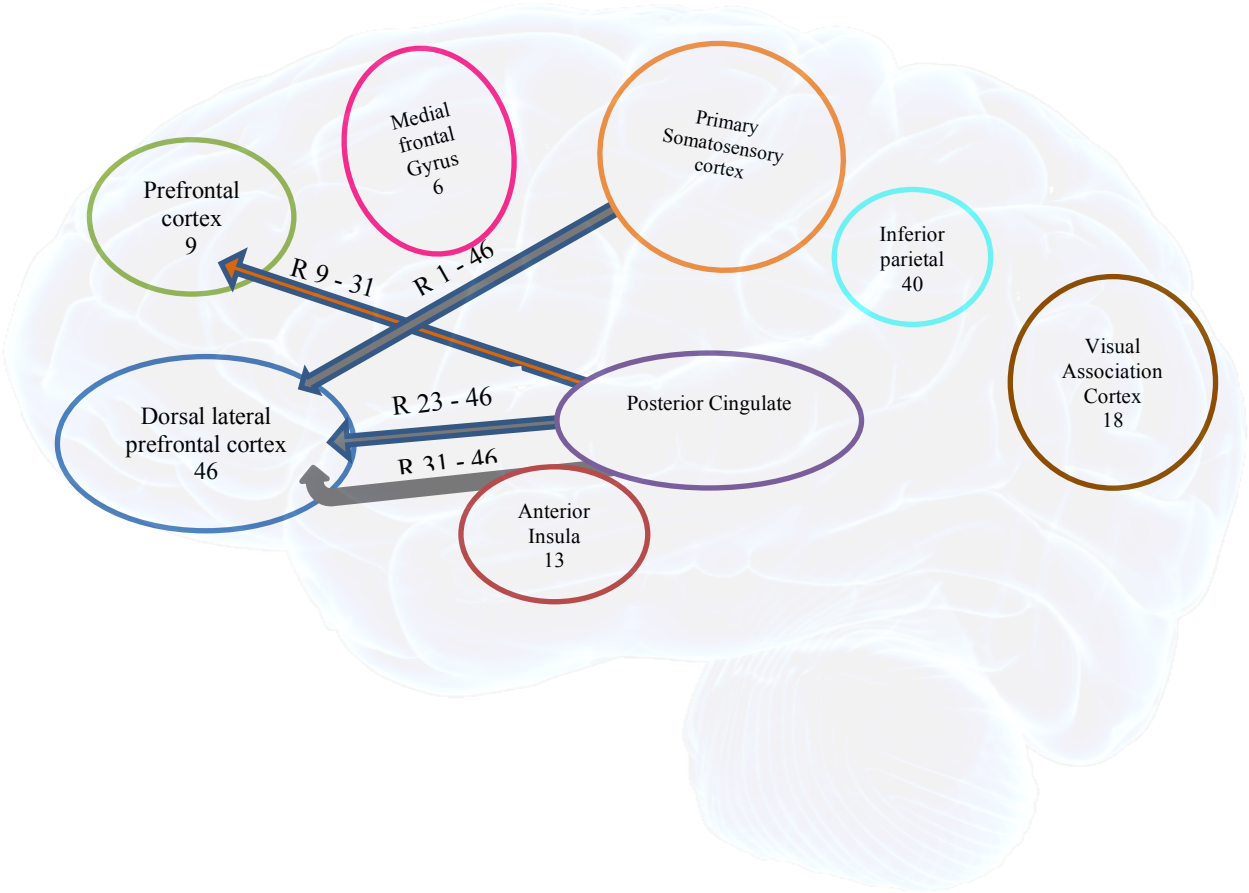


Figure 14: Direction of Phase Slope Index two-way mixed ANOVA significant simple main effects for chiropractic adjustment at baseline or immediate post intervention (time point one)

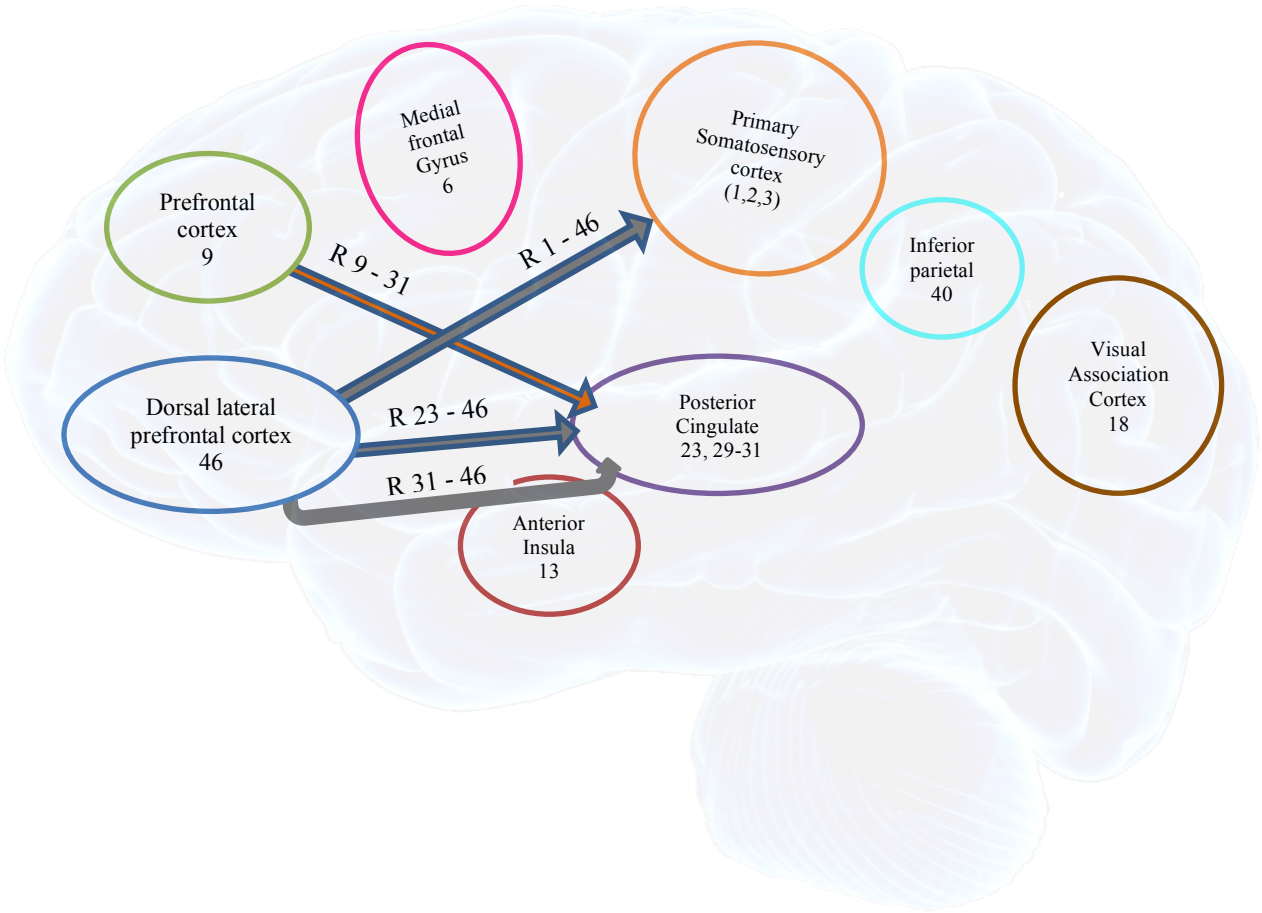


Figure 15: Direction of Phase Slope Index two-way mixed ANOVA significant simple main effects for chiropractic adjustment at immediate post intervention or one-week post intervention (time point two)

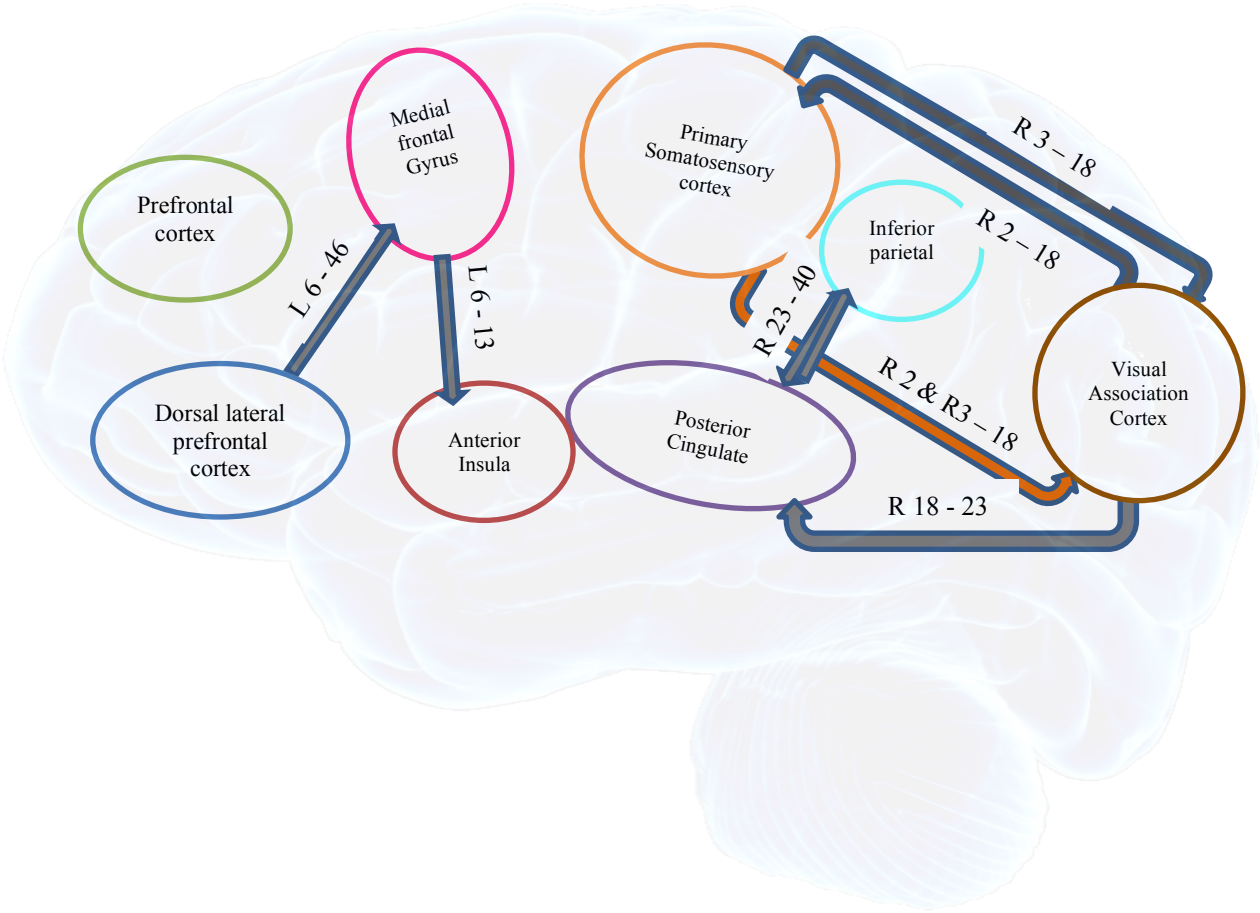


Figure 16: Direction of Phase Slope Index two-way mixed ANOVA significant simple main effects for sham adjustment at baseline or immediate post intervention (time point one)

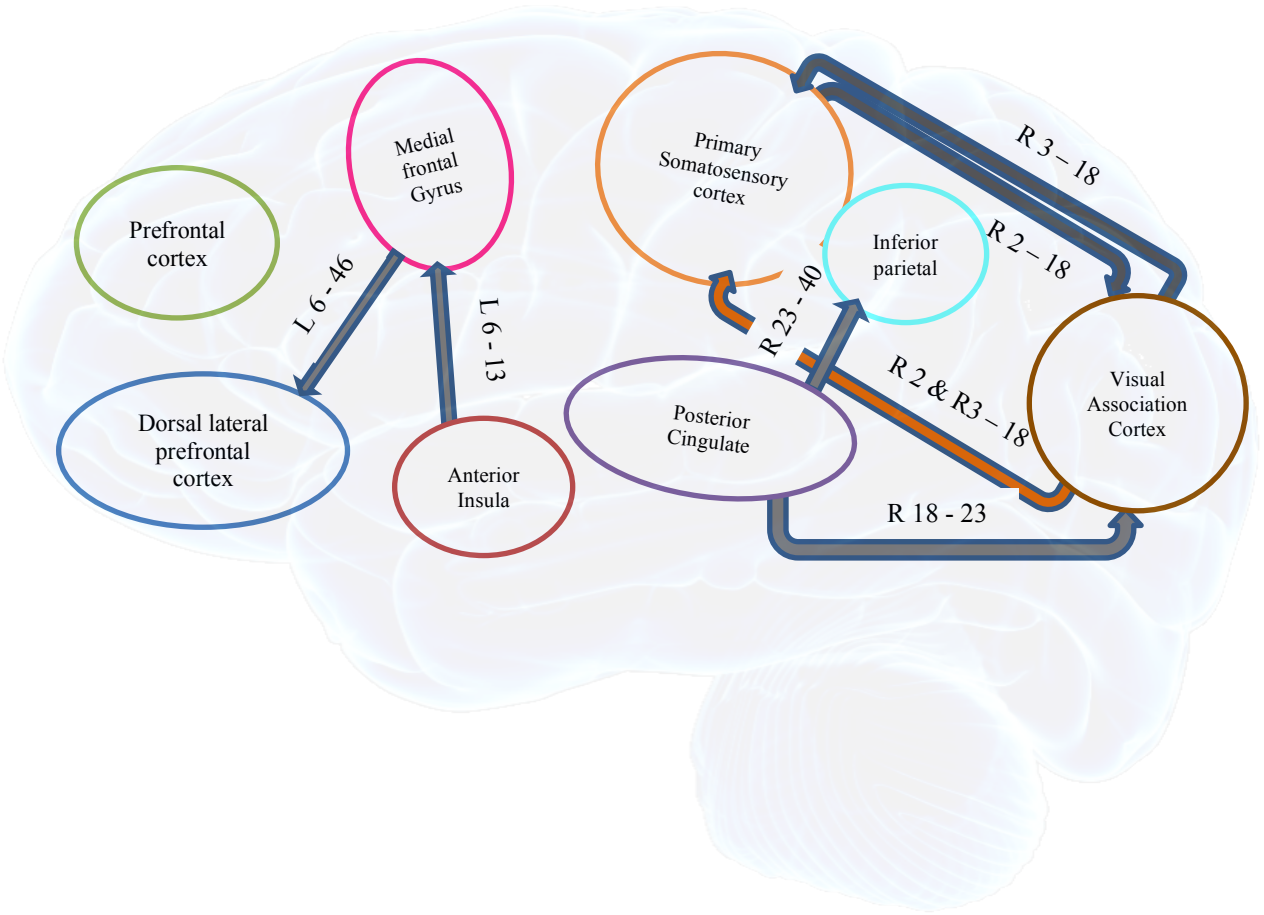


Figure 17: Direction of Phase Slope Index two-way mixed ANOVA significant simple main effects for sham adjustment at immediate post intervention or one-week post intervention (time point two)

CHAPTER 5

DISCUSSION

The current study was designed to explore the possible effects of a single session of chiropractic intervention on the electrical connectivity between particular sites (Brodmann Areas) in the brain. To isolate possible short-term effects, connectivity measurements were made at baseline, immediately post intervention (post), and one-week post intervention (one-week) to determine if changes had occurred. To establish whether any observed effects were due to the chiropractic intervention only, three participant groups (n = 10 each) were utilized for comparison. The chiropractic group received the chiropractic intervention (adjustment); the sham group received a 'sham' intervention (sham) while the control group received no intervention.

The technique used to measure connectivity was Phase Slope Index (PSI). PSI is a measure of effective connectivity, which reflects both the magnitude and direction of information transmission (i.e. connectivity) between pairs of Brodmann areas (BAs). (162-163) In the present work, two different groupings of BA pairs were examined. The first group included areas that had previously been shown to exhibit changes in neural activation patterns following a chiropractic adjustment. (11-13,22) The second group included BA pairs specifically associated with cognitive performance of mental rotation tasks. This second group of BA pairs were relevant to this study because mental rotation reaction time improvements have been observed following a single session of chiropractic manipulation. (5, 179-183)

Before examining in detail the BA pair changes observed following the adjustment, it is meaningful to examine the results within the context of time. Most research in the field of

chiropractic neuroscience only examine changes in the brain immediately following the chiropractic adjustment; therefore, comparing changes in the brain at each of the three time points examined in this study (baseline to post, baseline to one-week, and post to one-week post) was important. (12-13) For example, when all three time points were examined together, two regions that showed significant simple main effects for time between post and either the baseline or one-week time point demonstrated a return towards baseline. The mean PSI changes for each assessment time point are represented in Figures 5 to 13. This return towards baseline PSI value was observed for the adjustment group in the BA pair between the right somatosensory cortex (BA 1,2,3) and the dorsal lateral prefrontal cortex (BA 46) and in the sham group between the left medial frontal gyrus (BA 6) and the anterior insula (BA 13). If the present study had been similar to past chiropractic neurophysiology research, which does not include a one-week post assessment, the return towards baseline would not have been observed. (9-13) One challenge with the limited time frames examined in previous baseline to post chiropractic studies is the applicability to the practice of chiropractic. While some studies demonstrate a relationship between increased chiropractic dose and decreased pain following adjustments spaced out over weeks, others such as Laframboise showed improved results in myofascial pain pressure sensitivity when two chiropractic adjustments are applied just thirty minutes apart. (233-235) Without understanding how long changes are sustained following a chiropractic adjustment, establishment of ideal dose related practice guidelines is hampered. Research regarding how long a chiropractic adjustment is sustained could aid in maximizing the potential benefits of care and improving cost efficiency.

Uniquely, the present study only demonstrated significant between group baseline to post change for BA 6 – 13. All other significant changes for group*time were observed for either

baseline to post or baseline to one-week time points. Given that the simple main effects were significant for the sham group for BA 6 - 13, with no significant change attributed to the adjustment group, this result is contrary to previous chiropractic research. (9,11,22, 236) One case series (n = 10) by Sparks using functional magnetic resonance imaging (fMRI) to study changes in induced pain following a chiropractic adjustment showed changes baseline to post in regions similar to those observed in the present study sham group; however, as a case series no comparison groups were used, and the regions described in that study were more diffuse, not limited to specific BAs. (236) Plus, only the insular cortex was significant baseline to post. The region closely associated with BA 6 was not significant. In light of the return towards baseline value mentioned previously and the lack of significant baseline to post results within the present study compared to previous chiropractic brain research, critical evaluation of the present study design elements, such as the use of PSI, the selected chiropractic technique, or sham protocol should be evaluated prior to use in future studies.

Examining the between baseline and one-week timepoint, significant group differences were observed between four different BA pairs: Right (R) 23 – 46, R 31 – 46, Left (L) 9 – 31, and R 18 – 23. The BAs represent the posterior cingulate (BA 23, 29, 30, 31), the dorsal lateral prefrontal cortex (BA 46), the prefrontal cortex (BA 9), and the visual association area (BA 18). Of the four regions, all but R 18 – 23 showed significant simple main effects for chiropractic, which was instead significant for the sham. The within-subjects t-tests for R 31 – 46 and L 9 – 31 were also both significant for changes between the post assessment and the one-week assessment. This suggests, at least for the two BA pairs, changes in the chiropractic group continued to occur up to one week after the adjustment. This is in alignment with previous

research demonstrating that brain neuroplastic change continues to occur over time. (14-15, 237, 238)

Although neuroplastic change has been observed within minutes following interventions such as TMS stimulation, the brain continues to change in response to physical alterations within the body. Neuroplasticity research suggests that there are fast and slow neuroplastic adaptations to learning, such as what occurs following altered sensory stimulation. (14, 237,239-241) The fast phase occurs within minutes to hours following stimulation or change. (240-241) In motor performance task research, this fast phase often reflects goal directed learning. (240-241) Following the fast phase, the slow phase of learning involves procedural based, potentially structural modifications. (14-15, 237, 239-241) Sleep is another factor that needs to be considered relative to slow or longer-term learning. For motor learning, sleep is important for consolidating, stabilizing, and enhancing a motor representation. (238,241-242) During sleep, memory systems integrate new representations with past experience and may erase previous memory representations. (238,241-249) Adaptation to amputation, which is an extreme case of altered sensory input, shows changes occur within the first 24 hours, with considerable gains at one week to ten days. (14-15, 243). Neuroplastic changes over time indicate a potential limitation of previous chiropractic research studies that only examined baseline and post adjustment brain changes. Further, due to continued neurophysiologic monitoring post-adjustment (wires and EEG or EMG electrodes), a participant is restricted in his or her normal movement patterns. It is proposed that this limits neuroplastic adaptation to new sensory signals potentially generated as a result of the adjustment. This is of particular relevance given that one of the main mechanism of action theories related to the role of the chiropractic adjustment in changing brain activation patterns is that the chiropractic adjustment alters proprioceptive

afferent information, which is then suggested to lead to altered sensorimotor integration in the brain. (12-13, 62-64,) Research showing changes in cortical activation patterns over time and with sleep lends support to the proposed need for additional time to accommodate plastic change. (14-15,237-238) This suggests that in the design of future chiropractic studies, it would be advisable to add additional assessment time points following an accommodation period.

In the current study the sham group showed a number of significant changes, especially from post to one-week in simple main effects for time. Interestingly, the activated regions were similar to those activated in the study by Charles Gay: the primary somatosensory cortex (SSI) (BA 1,2,3) and the posterior cingulate (PCC). (22) These regions were represented in five of the six significant sham BA pairs between post and one-week. When added to the results previously discussed, the presence of significant between group changes within both the adjustment and sham groups, but not the control group, raises the question about whether or not the zero-force Activator protocol was actually a sham protocol or a placebo effect. During the sham protocol, the Activator came in contact with the spine, and it has been argued that touch has an influence on the brain. (104-106,109) Recent research of non-myelinated C-tactile afferents have been shown to activate areas of the brain related to emotion, such as the insular (medial and dorsal) cortex along with regions such as the PCC, inferior parietal lobe, and inferior frontal gyrus (104-106,109,244) In a previous study examining brain connectivity following C-tactile fiber stimulation, changes were noted between the PCC and inferior parietal lobe and the PCC and inferior frontal gyrus. (244) C-tactile fibers respond to low indentation forces in addition to soft stroking motions, and as suggested by the size of the C-tactile fiber homunculus within the posterior insula, greater fiber density has been indicated for the thoracic spine. (104-105,109) Signals from both C-tactile fibers and Aβ discriminant fibers (sensory discriminant touch fibers

for pressure, vibration and slip) ultimately interact with the primary somatosensory cortex. (104-105) Uniquely, however, the C-fibers produced a significant deactivation of the somatosensory cortex upon stimulation as observed by fMRI. (245-246) C-tactile fiber stimulation has even been shown to decrease heart rate, blood pressure and change cortisol release. (109) Given all of the research noting physiologic and brain changes with touch, a recent report by McGlone et. al. proposed that touch be considered a sub-modality of the somatosensory system, and as such is "likely to play a direct and significant role in the efficacy of manual therapies." (105) The results of the present study support McGlone's conclusion, in that for both the adjustment and sham groups BA pair changes occurred within the PCC, inferior parietal lobe, and/or somatosensory cortex, although the BA pair interactions were unique for each group. While it seems self-evident that touch would influence both the adjustment and sham group, evaluation of the differences between the two results may provide insight into the effects of force versus touch, and accounting for touch as a neurophysiological influencing factor could improve design of future chiropractic studies.

In addition to light pressure and touch transmitted by C-tactile fibers, other forms of unmyelinated C-fibers are responsible for pain response. (247-250) Myelinated Aδ fibers are associated with the initial fast pain response and the unmyelinated C fibers are associated with a slower second pain response. (250) This slower second pain response has been associated with sustained central hyperalgesic responses - persistent pain. (248-250) Interestingly, C fiber neural activation patterns noted in previous induced pain research studies were similar to regions demonstrating increased activation in the current study. For example, a series of studies by Staud examining fMRI changes following pain related C fiber stimulation showed activation of the insula, thalamus, primary somatosensory cortex and secondary somatosensory cortex, with one

of the studies showing changes in the prefrontal cortex and anterior insula specifically. (248-249) Although pain free, the present study sham and chiropractic groups did show change in the primary somatosensory cortex, and individually, the chiropractic and sham groups showed changes in the prefrontal cortex and anterior insula, respectively. Persistent pain fiber activation is relevant to the chiropractic profession because the dominant reason patients seek chiropractic care is for the relief of pain, low back and neck pain in particular. (8) Low back pain, for example, is a global burden and the number one cause of disability. (251-252) As future research is conducted in the chiropractic profession that investigates the touch versus force components of a chiropractic adjustment, the presence or absence of pain in the study population should be accounted for.

Considering future study designs, more brain regions associated with C-tactile fiber stimulation were noted in the present study for the sham group compared to the adjustment group. This may have been the result of the difference between the sham protocol and where the participants were adjusted. For the sham, the Activator instrument was placed at two different locations on the thoracic spine and on the ischial tuberosity. The participants in the chiropractic group only received chiropractic adjustments with the Activator and /or sacral blocking (placement of triangular shaped blocks under specific regions of the pelvis) within the sacroiliac region, with the exception of one participant who was adjusted at the 5th lumbar. Beyond the 5th lumbar, no regions along the spine were adjusted in the chiropractic group. This is significant because of suggestions that greater C-tactile fiber density is present in the thoracic region compared to the lumbar and sacral regions. Touch is one component of the therapeutic effect of chiropractic that has yet to be studied independent of the actual force effects. A future study design might include a pseudo random design, where one participant receives a chiropractic

adjustment with the Activator and the following participant receives a sham Activator adjustment in the exact same locations as the previous active chiropractic participant, but the Activator is set at zero. The addition of a no touch group that follows the same motions (including placement on the adjusting table) and a resting control might also be advisable. While the role of touch as part of the therapeutic effect of the chiropractic adjustment still needs to be understood, in the present study there were unique differences between regions of the brain that responded to the chiropractic adjustment compared to the sham.

Using PSI, the present study examined changes in communication patterns (direction and magnitude) for fourteen different BAs, representing nine different functional brain regions. As stated earlier, one group of BAs demonstrated changes in previous chiropractic research (SSI, prefrontal cortex (PFC), anterior insula, and PCC) and the BAs in second group had been shown to activate during mental rotation task performance (medial frontal gyrus, superior parietal lobule, visual association cortex, inferior parietal lobule and dorsal lateral prefrontal cortex (DLPC). The present study demonstrated twelve significant between group BA pair results. Nine were significant for simple main effects over time for the sham and four were significant for the adjustment group. Interestingly, the BA pair interactions for the sham were mostly in the posterior aspect of the brain and the adjustment group changes were mostly in the anterior portion of the brain. Four of the sham BA pair interactions were between the SSI (BA 1,2,3) and the visual association area (BA 18). When directionality of information flow between the two Brodmann areas was considered, three of the four sham results for the post sham reading have the SSI being the driver and the visual association cortex (BA 18) being the responder. At one-week this relationship is switched, and BA 18 is the driver. This phenomenon may be due to the body's natural suppression of the visual areas, including the visual association areas, during

attention to a touch stimulus. (253) Further, this cross-modal suppression could have been compounded by the auditory click produced by the Activator instrument, which has also been shown to suppress touch sensation. (253-254)

In addition to the SSI cortex and visual association areas, two PCC BA pairs were observed in the sham group: the PCC and visual association area and the PCC and inferior parietal lobe. While the PCC and visual association area may be a result of touch-based attention shifting as suggested in the previous paragraph, the PCC and inferior parietal lobe interaction was also observed in two research studies assessing changes in the brain following touch related stimulation. (244,255) One study by Cerritelli showed connectivity changes specifically between the PCC and inferior parietal lobe following C-tactile fiber stimulation; in a second study by Mansour examining neural correlates of pressure applied to the spine, the inferior parietal lobule was shown to increase in activation following application of pressure. (244,255) The results of the present study compared to previous touch related research, further reinforce the need to be mindful of touch related factors in study design and interpretation.

Although most of the sham results in the present study were represented in the posterior aspect of the brain, two BA pairs were present anteriorly. These were between the DLPC and medial frontal gyrus and the medial frontal gyrus and anterior insula. As mentioned previously, in the medial frontal gyrus (BA 6) to anterior insula pair, it appears as if the one-week post is moving back towards baseline, so this result may be an artifact of an immediate post recording; it does not appear as if the change was sustained. For the medial frontal gyrus and DLPC pair, the magnitude changed immediately after the sham. Then, at one-week post the direction shifted to the medial frontal gyrus being the driver as opposed to the responder. While no conclusions can be drawn in this study relative to behavior, decreased metabolism in the medial frontal gyrus has

been associated with patients exhibiting symptoms of psychological adjustment disorder, and may be a result of C-tactile fiber connections with the affective centers of the brain. (104-106,109,256) With the exception of the DLPC and medial frontal gyrus BA pair in the present study, the remaining BA pairs for the sham group represent results similar to those observed by Gay in the therapeutic touch group (PCC and anterior insula) and chiropractic adjustment group (SSI) and Cerritelli in the touch-based C-tactile fiber research (PCC and inferior parietal lobe). (22, 244) These results again illustrate the need for more research related to chiropractic study design that accounts for the effects of touch.

Interestingly, for the present study, between group PSI differences that showed simple main effects for the adjustment group were predominately in the anterior aspect of the brain in relation to the PCC. This is excluding the one result between the somatosensory cortex and the DLPC that essentially went back to baseline one-week post adjustment. The remaining areas reflect changes between the PCC and regions commonly attributed to executive function: the DLPC and the PFC. (257-258) These results are similar to what has been observed in the chiropractic neuroscience literature. (9-11) Using somatosensory evoked potentials, early research showed changes within the N30 frontal peak and the N20 parietal peak following a chiropractic adjustment compared to a control, and the N30 peak, in particular, continued to demonstrate consistent changes. (9-11) The N30 peak is thought to represent early sensorimotor integration, complex cortical and subcortical loops and underlying support for executive function and decision-making tasks. (11, 96-97,257) In a follow-up low resolution electromagnetic tomography (LORETA) study designed to examine which of the N30 peak associated brain regions may be the generator for the changes observed following a chiropractic adjustment, significant changes were only observed in the PFC. (11) Also of note are the reciprocal closed-

loop connections between the DLPC and the cerebellum. (150) The cerebellum has been shown to play a role in cognitive task performance, such as executive function. A few recent studies showed facilitation of typically inhibited motor evoked potential performance following a chiropractic adjustment; in addition to potential direct cortical changes, the cerebellum may contribute to the brain changes observed in this study. (150-154) The results of the present study support the previous research showing changes in areas of the brain associated with executive function performance. This may indicate a potential mechanism through which chiropractic has been shown to influence clinically observed cognitive task performance.

Another interesting finding for the present study was the change in PSI directionality for the PCC related BA pairs of the adjustment group. In each PCC and DLPC or PFC pair, the baseline readings showed the PCC as the driver with a decreased magnitude following the adjustment; however, at one-week, the PCC became the responder and either the DLPC or PFC became the driver of information flow. There are many potential implications for this change. Although this study was not designed to evaluate the meaning of the changes, since the PCC has been shown to coordinate incoming spatially related sensory information and chiropractic has been shown to improve the brain's ability to gate sensory information, future research examining the relationship between such direction related changes, sensory gating, and cognitive efficiency would be beneficial, especially given the changes noted in the present study and previous research showing changes in regions associated with executive function performance. (255,259)

In conjunction with observed brain changes in the locations of most of the BA pairs demonstrating significant differences (sham-posterior, chiropractic-anterior), each pair included one BA from a chiropractic related Brodmann areas and one from the mental rotation related BAs. The one exception was the BA pair between left BA6 and BA 46 (DLPC), which were both

related to mental rotation. (179-183) The connections between the two BA groups is significant because it demonstrates a link between previously researched brain regions shown to change following a chiropractic adjustment and cognitive task performance-based regions that have yet to be studied. Currently, in the chiropractic profession there does not exist a mechanism of action theory that relates clinically observed cognitive task performance results, such as those observed in mental rotation, to a mechanism of action for the profession. While much work needs to be done in this area, this study contributes information on both the direction and magnitude of interactions between brain regions and information on the differences demonstrated between a chiropractic adjustment, a sham adjustment and a control. Although the control did not demonstrate any significant simple main effects between the groups over time, the sham intervention used in this study did, suggesting the additional need for investigation into an ideal sham procedure for chiropractic research.

The sham intervention used in this study utilized an Activator instrument placed on the skin at set locations (two thoracic and one on the ischial tuberosity). The Activator was clicked, but the force application was set at zero. This was an adapted sham protocol from previous chiropractic research. (260-263) In the Lelic study that used LORETA to examine the neural generator of the N30 somatosensory evoked potential peak, the control condition consisted of a non-chiropractor passively moving the participants head and body, being mindful of not touching the spine. (11) This form of passive movement for the control condition without touching the spine was only designed to mimic the motions used by the chiropractor, not simulate a chiropractic adjustment. (9,11,16) This method has been used in several studies by the Haavik lab, which has performed the bulk of chiropractic neurophysiology research to date. (9,11,16) Additionally, in a study by Chaibi specifically designed to validate a sham (placebo) chiropractic

adjustment, the investigators also intentionally avoided the spine. (264) Although sham procedures such as those used in the Haavik lab and in the Chaibi study may not account for additional adjustment related factors such as spine related touch, the studies do provide an opportunity to account for the placebo effect. (9-11, 264) In fact, in the Chaibi study over 80% of the patients felt they received the active intervention regardless of the assigned group, meaning many of the placebo patients believed they had received the actual adjustment. (264) The placebo effect has long been known to influence therapeutic consequences, and some even attribute the placebo effect to much of the successes provided by early medicine. (265-266) Although now considered a challenge to research study design, the placebo effect historically was used intentionally by medical physicians to benefit the mind of the patient. Now recognized as a phenomenon that can influence clinical outcome, researchers need to be mindful of the placebo effect in study design practices. (266) Interestingly, touch has been used as both a therapy and a placebo treatment. (22, 267) The differences in types of sham procedures used, especially related to on or off the spine, paired with research showing that touch changes the brain - as an actual neurophysiologic phenomenon or placebo effect - highlights some of the unique challenges present in manual therapy studies such as chiropractic. The present study demonstrated unique brain changes within the adjustment and sham groups, so being mindful of the non-force related aspects of the adjustment that may have contributed to the results may help in the design of future research studies.

In summary, the direction and magnitude of communication patterns between different brain regions related to the chiropractic adjustment and mental rotation do appear to change following the application of a chiropractic adjustment and the sham adjustment selected for this research. Among the regional changes observed, the chiropractic related changes were observed

more anterior in the brain and the sham related adjustment changes were more posterior. Furthermore, touch may be a key factor contributing to the effects observed in this study, so additional research designed to study the touch and thrust components of the adjustment would be of benefit to future chiropractic research. Also based on the results of the current study, the addition of a one-week post evaluation beyond the immediate post and baseline assessments is recommended for future studies. The results were limited in the baseline to immediate post assessments; however, the use of all three assessments provided a clearer picture of changes that were only temporary.

Limitations:

This study was a secondary analysis of data obtained in previous research, so only artifacted data with minimal participant information was transferred to the investigators for the research. The sample size of ten in each group was a limitation; although, the data could be used to design a follow up research study. The lack of a second time point for the control group (i.e. one that would have corresponded to the post time point for the adjustment and sham groups) was also a limitation. This hampered the analysis and study conclusions. For future studies, one potential alteration to control for the effect of body position on the EEG would be to have the control participant lie on the table for a time period similar in length to the sham and adjustment interventions, then have the participant sit up for a second time point assessment.

Additional limitations regarding the participants included no debriefing post-conclusion of the study. For instance, it was not known how the participants perceived the sham adjustment and if they assumed it was an actual chiropractic adjustment. It is possible that both would have a placebo component. A survey at the conclusion of the study asking their opinion, noting any changes post- intervention would be beneficial in future studies. Also, since a chiropractic

analysis was not performed on the sham and control groups, the presence or absence of chiropractic subluxations was not known. Although the participants in this study were healthy individuals, the previous research done by the Haavik lab worked with individuals who had a history of neck or back pain, just no pain on the day of the assessment and adjustment. (9-13) Thus, comparing the results of the present study to those observed by the Haavik lab may have limitations. Each of the above participant related limitations could easily be improved upon and incorporated into future studies.

Finally, the software package used for the PSI analysis did not apply the same jackknife method of normalizing the data that was recommended by Nolte in his original PSI article. (142) To overcome this challenge, the data in this study was normalized to a validated and published database consisting of 678 individuals from age ranges two months to eighty-two years. (223-224) Then, to limit Type I errors (false positives) a permutation test was applied to the data that had yielded significant within subjects t-tests results. While each of the analysis procedures used in this study were used in previous research, it would be interesting to compare the results of this study to an analysis performed using the original procedure applied by Nolte. (162-163)

In spite of the limitations listed above, the results of this study demonstrated unique changes in the chiropractic adjustment group and the sham group. This study provided valuable insight into the sham procedure utilized in the study and provided a foundation for future research related to touch. Also, this study reinforced the need for inclusion of assessment time periods beyond that of baseline and immediate post.

CHAPTER 6

CONCLUSION

Chiropractic from its early beginnings as a profession in 1895 was based on the belief that the chiropractic adjustment of the articulations of the spine influenced the function of the nervous system. (1,2) While the application of a manual thrust to the spine to restore function is not exclusive to chiropractic, the premise that correction of abnormal joint position and motion restores proper function to the nervous system is unique to the profession. (1-3,26-29) The challenge is that over the past 120 years very little research has been done to advance this concept, especially relative to the brain. Clinically, chiropractic research has documented changes in such symptoms as attention, memory, reaction time, spatial cognition, mental rotation, and executive function. (4-7) In one study a chiropractic manipulation, also referred to as an adjustment, was applied only to the cervical spine. Following the adjustment, mental rotation reaction time was significantly improved in the chiropractic population compared to the resting control population. (5) The challenge is that there is no currently accepted mechanism of action to explain the clinical changes observed following an adjustment. Therefore, it is important to expand the chiropractic neuroscience research literature.

This study explored two aspects of chiropractic related neuroscience research. First, it expanded the timeline of post assessment to one week after the intervention; second, it examined changes in brain communication patterns assessing both magnitude and direction of information flow. The first objective related to timing was designed to overcome some of the challenges present in much of the current chiropractic neuroscience research, which is the limitation of time. (9-13) Typically, chiropractic studies have only been designed to assess baseline and immediate

post responses. (9-13) Based on previous neuroplasticity research, this may limit the true understanding of the effects of chiropractic. Studies by Merzenich and colleagues suggest that changes in the brain occur from twenty-four hours to one-week post intervention. (15) Without a one-week post assessment, it may be that only reflexive information is being perceived and application of the research in determining dose response is limited. The second focus of the study was to examine where and to what degree changes in the brain occurred. This was accomplished through use of a measure called Phase Slope Index (PSI). Uniquely, PSI determines the magnitude and direction of communication patterns between two regions of the brain. (162-163) In this study the communication patterns between fourteen different Brodmann areas were evaluated. These regions included areas of the brain previously shown to change following chiropractic, and to assist in the development of a model that relates changes following chiropractic care to clinically observed cognitive outcomes, regions associated with mental rotation were also studied.

The overall results of the study indicated that the direction and magnitude of communication patterns changed over the course of one week and the changes were unique for individuals who experienced the chiropractic adjustment compared to the sham adjustment. Relative to timing, only one Brodmann area pair demonstrated a change from baseline to immediately after the intervention, with simple main effects attributed to the sham adjustment group. When compared across all three time points, the results for the baseline to immediate post were not sustained, and the PSI for the two Brodmann areas returned towards baseline. This return to baseline was also observed in one of the Brodmann area pairs significant for the chiropractic group. The immediate post intervention compared to one-week post time point demonstrated significance; however, when the baseline timepoint was also observed, it was evident that the one-week PSI value was

simply a return to baseline. When the baseline or immediate post time points were compared to the one-week post, a more robust picture of the presence or absence of sustained changes emerged. In the Brodmann area pairs that exhibited a simple main effect for the sham, most of the interactions were in the posterior part of the brain (Posterior Cingulate, visual association area and somatosensory cortex). The sham used for the current study involved two touch points on the spine and one touch point on the pelvis, plus an audible sound. Given the recent research on the connection between touch and the influence on the brain, the emotional centers in particular, it makes sense that changes would be observed. (104-106,244) For the chiropractic group, the regions in the brain that changed were more anterior (prefrontal cortex, dorsal lateral prefrontal cortex and posterior cingulate cortex). Further, the directionality of the communication between the brain regions shifted between baseline and one-week post for all but one of the four Brodmann area pairs; the fourth returned to baseline. Originally, the posterior cingulate was the driver, but one week after the adjustment the direction shifted and the prefrontal cortex and dorsal lateral prefrontal cortex – both executive control centers - became the drivers. This reflects previous chiropractic research that showed the prefrontal cortex as a driver of attenuation of the N30 somatosensory evoked potential peak. (11) The results for both the sham and chiropractic groups also reflected changes, although slightly different, that were observed in a previous connectivity study examining changes across three different manual therapy techniques: chiropractic adjustment, mobilization, and therapeutic touch. (22) In brief, while this study did contribute to the limited chiropractic neuroscience research and brain changes were observed following intervention, the knowledge gained relative to the need for extended assessment time periods and a study design that tests the components of touch and thrust in the chiropractic adjustment may help improve the design of future studies.

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APPENDIX A

PARTIAL SAMPLE PHASE SLOPE INDEX DATA FILE DELTA THROUGH BETA TWO:

CONTROL PARTICIPANT

Subject ID:
Epoch Length
(sec): 121.63
LORETA Phase Slope Index
Left Hemisphere Phase Slope Index values from a
single control participant one-week post baseline

Brodmann Areas	Delta	Theta	Alpha 1	Alpha 2	Beta 1	Beta 2
1 L - 2 L	0.786849	0.539357	0.608807	-0.52367	-1.3804	-1.61742
1 L - 3 L	0.050786	0.309959	0.208672	0.112783	-0.30131	-0.71751
1 L - 6 L	2.34966	2.005545	1.179524	0.134636	-0.11824	-0.29844
1 L - 7 L	1.16961	2.085792	1.950312	1.152489	1.019069	0.06716
1 L - 9 L	0.659576	0.657256	0.190183	-0.7582	-0.68158	-0.85992
1 L - 13 L	-0.94725	-0.3865	-0.53704	-0.3762	-0.61222	-0.80363
1 L - 18 L	4.321495	2.219911	1.638989	0.906423	-0.03826	-0.23458
1 L - 23 L	0.975238	0.960743	0.439592	0.99399	0.040543	-0.53198
1 L - 29 L	2.728383	3.21083	2.576904	1.955046	0.595775	0.115061
1 L - 30 L	1.770269	0.616442	-0.12833	0.260666	-1.32646	-1.69098
1 L - 31 L	0.615754	2.024451	0.981998	0.94292	-0.31035	-0.38401
1 L - 40 L	-2.25415	-1.73745	-1.35444	0.041309	0.381578	0.888402
1 L - 46 L	2.670901	1.062826	0.854524	0.142222	0.359782	0.392048
2 L - 3 L	0.333203	0.169042	0.111568	0.158235	0.153229	0.416942
2 L - 6 L	2.632048	2.303457	1.346781	-0.2589	-0.74896	-0.65514
2 L - 9 L	1.302401	0.632162	-0.05016	-0.96286	-0.49613	0.229928
2 L - 13 L	-1.88029	-1.27225	-0.84805	0.220288	-0.30779	-0.31803
2 L - 18 L	2.151426	1.38751	1.197699	-0.29196	-1.30094	-1.53625
2 L - 23 L	2.776685	2.190772	1.469237	0.889806	-0.22495	-0.8863
2 L - 29 L	2.679545	2.617768	2.083183	1.744922	0.167031	-0.3963
2 L - 30 L	2.0372	2.008991	0.605021	-0.18217	-1.37448	-1.89149
2 L - 31 L	2.54724	1.993745	0.877701	0.882616	-0.40246	-0.88142
2 L - 40 L	-6.69922	-3.87986	-2.44842	1.255854	2.303357	2.352435
2 L - 46 L	2.034577	0.740957	0.105509	-0.76712	0.469494	0.73535
3 L - 6 L	1.993842	1.91392	1.001188	0.188921	-0.89329	-0.42866

3 L - 7 L	1.563633	1.480346	1.328271	0.753418	-0.12368	-0.56224
3 L - 9 L	1.503702	0.549981	-0.28995	-0.7311	-0.23843	-0.3278
3 L - 18 L	3.690061	2.288428	1.44317	0.260711	-1.14421	-1.21848
3 L - 23 L	2.163756	1.967636	1.081069	1.126422	0.018002	-0.83187
3 L - 29 L	2.488979	2.615043	2.287286	1.691798	0.667784	-0.26328
3 L - 30 L	2.973579	1.863531	1.065271	0.060051	-1.65161	-2.01552
3 L - 31 L	2.123011	1.661661	0.977312	0.922261	-0.23258	-0.88892
3 L - 40 L	-4.4063	-3.00739	-2.46346	0.226595	1.215316	1.326749
3 L - 46 L	2.683035	1.208518	0.732204	0.09191	0.885474	0.64314
6 L - 7 L	-1.75118	-1.16635	-0.68312	-0.53165	-0.1391	0.108438
6 L - 9 L	0.677199	-0.4797	-0.51827	-0.39202	-0.25567	0.202906
6 L - 18 L	1.317675	1.137236	0.558125	0.092899	0.412304	0.276671
6 L - 23 L	-0.40244	-0.5162	-0.24346	-0.43491	0.262368	0.221341
6 L - 29 L	-1.22161	-0.80609	-0.55129	-0.01218	0.323121	0.759413
6 L - 30 L	-1.44891	-0.5874	-0.04459	-0.08021	0.855414	1.415895
6 L - 31 L	0.639336	0.145868	-0.00598	-0.08615	0.475936	0.346583
6 L - 40 L	-2.4308	-1.81445	-1.3903	-0.37148	0.234513	0.112557
6 L - 46 L	-0.50215	-0.26524	-0.43381	-0.55319	-0.22037	0.006759
7 L - 9 L	1.638528	0.530106	0.431543	-0.75674	-0.55304	-0.10249
7 L - 18 L	1.225312	0.781231	0.470637	-0.62504	-0.40426	-0.2061
7 L - 23 L	-2.75045	-1.18161	-0.53629	1.620223	2.220246	1.526717
7 L - 29 L	-2.2646	-0.30831	-0.27879	1.388243	1.465854	1.062322
7 L - 30 L	-1.16975	-0.80868	-0.52481	1.154289	1.264898	0.906642
7 L - 31 L	-3.14357	-1.62065	-0.42173	1.557394	2.142792	1.612439
7 L - 40 L	-1.73878	-2.23022	-1.6145	-1.41226	-1.19921	-0.31713
7 L - 46 L	0.395733	-0.66197	-0.45351	-1.0176	-0.78311	-0.45057
9 L - 13 L	3.136634	1.952848	1.053245	-0.32053	-0.86976	-0.39129
9 L - 18 L	3.009317	1.584084	0.78293	-0.35493	-0.61766	-0.74147
9 L - 29 L	0.219843	0.113751	0.190504	0.754818	0.145143	-0.1376
9 L - 30 L	1.023481	0.942441	0.225711	0.026436	-1.15323	-0.91768
9 L - 31 L	-0.40083	-0.10759	-0.43751	0.016618	-0.12374	-0.55563
9 L - 40 L	-1.44513	0.098944	0.311286	0.273186	0.374914	0.59117
9 L - 46 L	1.426126	0.457491	0.043756	0.389752	-0.16011	-0.13476
13 L - 18 L	-0.16896	0.916265	1.219102	1.960355	1.752146	1.524624
13 L - 23 L	0.229008	0.758278	0.236792	1.10525	0.367229	0.306584
13 L - 29 L	-0.28845	0.1274	0.273881	1.055128	-0.18301	-0.1652
13 L - 30 L	2.136039	1.372572	1.007818	1.558546	0.712774	0.761737
13 L - 31 L	0.854863	1.121616	0.733065	0.67101	0.273083	-0.05907
13 L - 40 L	2.066558	1.357232	0.366544	0.417927	-0.09528	0.379289
13 L - 46 L	-1.5896	-0.46814	0.870686	1.006948	0.935676	0.721794

18 L - 23 L	1.598147	0.573406	0.699399	0.609145	-0.4769	-0.96871
18 L - 29 L	0.136855	-0.47402	-0.06876	0.197857	-0.88816	-0.72215
18 L - 30 L	3.271318	0.756121	0.480021	-0.61189	-1.81677	-1.34306
18 L - 31 L	1.142656	0.089638	0.360515	0.297603	-0.74825	-1.1308
18 L - 40 L	-2.48775	-1.09665	-0.44916	-0.63552	-0.62336	0.025187
23 L - 29 L	1.555001	0.602476	0.440794	-1.46922	-2.0195	-1.52253
23 L - 30 L	-2.0503	-1.29967	-0.88829	0.406912	0.983841	0.946945
23 L - 31 L	1.122212	0.707264	0.347369	-0.30515	-0.30106	-0.26498
23 L - 40 L	0.124179	-0.36632	-0.45278	-0.86223	0.146889	0.577781
29 L - 30 L	-3.1077	-1.56296	-0.66632	1.427666	2.423404	1.834005
29 L - 31 L	-1.4996	-0.75712	-0.34987	1.186418	1.601624	1.33994
29 L - 32 L	-0.05454	-0.50102	0.090945	0.359074	0.604795	0.674489
29 L - 40 L	-2.52198	-2.67351	-2.20877	-1.79988	-0.68584	-0.31887
29 L - 46 L	0.501392	0.11461	0.202608	-0.6655	-0.25664	-0.14768
30 L - 31 L	3.264285	1.966022	1.027695	-1.12751	-1.90602	-1.49758
30 L - 40 L	-2.62906	-1.41861	-0.39646	0.444991	1.13421	1.503417
30 L - 46 L	-1.4694	-0.6447	-0.52292	-0.16393	1.002158	0.87324
31 L - 40 L	-0.92079	-1.0364	-0.67747	-1.28089	0.177356	0.384937
31 L - 46 L	0.834404	0.413981	0.586945	-0.10453	-0.00726	0.050072
40 L - 46 L	0.092976	0.348617	0.251329	0.23499	0.459017	0.384572

APPENDIX B

PARTIAL SAMPLE PHASE SLOPE INDEX DATA FILE DELTA THROUGH BETA TWO:

SHAM ADJUSTMENT PARTICIPANT

Subject ID:
Epoch Length
(sec): 79.75
LORETA Phase Slope Index
Left Hemisphere Phase Slope Index values from a single sham adjustment participant one-week post baseline

Brodmann Areas	Delta	Theta	Alpha 1	Alpha 2	Beta 1	Beta 2
1 L - 2 L	-2.09114	-0.9	-0.09443	0.389813	1.368358	2.186571
1 L - 3 L	-1.55455	-0.31442	0.296392	0.34369	1.546499	1.959574
1 L - 6 L	2.514189	1.793056	1.836111	1.54485	0.834561	0.976874
1 L - 7 L	-0.45852	-0.77034	-0.3683	-0.76947	-0.99305	-0.39052
1 L - 9 L	-0.55503	-0.09236	-0.36737	-0.30604	0.964332	1.418046
1 L - 13 L	1.443283	1.513207	0.505504	0.416515	-0.58828	-1.06807
1 L - 18 L	4.623192	3.654237	3.285366	1.039666	0.125542	-0.07337
1 L - 23 L	3.785482	1.862496	0.87986	-0.74314	-1.69492	-1.38434
1 L - 29 L	0.130956	-1.03538	-0.94815	-1.67984	-1.5728	-1.12403
1 L - 30 L	3.004479	1.17596	0.397053	-1.50619	-2.18022	-2.07156
1 L - 31 L	3.610742	1.935674	0.953087	-1.70771	-2.26078	-1.85363
1 L - 40 L	-1.41494	-1.73891	-1.49184	-0.30963	-0.58213	-0.61825
1 L - 46 L	1.983705	2.08065	1.931131	0.183508	0.990189	1.653576
2 L - 3 L	0.607443	0.260872	0.046437	-0.15582	-0.64465	-0.99891
2 L - 6 L	1.119112	0.698261	0.354687	0.4751	0.042346	0.150167
2 L - 7 L	1.929281	1.246377	0.52169	-0.40949	-1.14471	-0.60575
2 L - 9 L	-0.82733	-1.27204	-0.83431	-0.95549	0.907568	0.731898
2 L - 13 L	0.69863	-0.14893	-0.59145	0.551738	0.483954	-0.04832
2 L - 18 L	3.080422	2.45127	2.210276	0.618218	0.011239	-0.82486
2 L - 23 L	3.09524	2.341851	1.470455	-0.76147	-1.43956	-1.54342
2 L - 29 L	0.948722	0.094202	0.265137	-1.17815	-1.35651	-1.26318
2 L - 30 L	1.800919	1.35012	0.872226	-0.63627	-0.90133	-0.88924
2 L - 31 L	4.37198	2.879974	1.521954	-0.75787	-1.17398	-1.25166
2 L - 40 L	0.366308	-0.22574	-0.78609	-0.42417	-1.37179	-1.80619

2 L - 46 L	-0.32117	-0.08033	-0.01241	-0.85322	0.904005	0.026196
3 L - 6 L	0.771746	0.969034	1.412659	0.659532	-0.0302	0.438003
3 L - 7 L	1.570482	1.132835	0.033423	-0.35874	-0.63944	-0.52766
3 L - 9 L	-1.13599	-0.95897	-1.40019	-1.15496	0.827021	1.044734
3 L - 13 L	0.87277	0.104076	-0.81766	0.174802	0.206196	-0.53292
3 L - 18 L	3.883315	2.625472	2.193008	0.788046	0.087148	-0.67578
3 L - 23 L	3.119906	1.830783	1.073692	-1.08609	-1.50014	-1.40792
3 L - 29 L	0.716616	0.341747	-0.07489	-1.55773	-1.34968	-1.35762
3 L - 30 L	2.410509	1.377831	0.838733	-0.99947	-1.25334	-1.28969
3 L - 31 L	3.720497	2.679547	1.232414	-1.3479	-1.62893	-1.58361
3 L - 40 L	-0.22389	-0.77819	-1.30355	-0.43751	-1.69791	-1.82734
3 L - 46 L	0.512248	0.59685	0.463847	-0.74087	1.022364	0.77737
6 L - 7 L	0.410106	0.850933	0.742188	0.584092	0.478846	0.03339
6 L - 9 L	1.403064	0.583758	0.646826	-0.16043	-0.50973	-0.40704
6 L - 13 L	-1.70329	-1.15183	-1.00813	0.236581	0.205554	0.569778
6 L - 18 L	1.352753	1.692654	1.559608	0.16634	-0.10225	0.300958
6 L - 23 L	1.087948	0.922638	0.915013	0.001582	-0.39524	0.044316
6 L - 29 L	0.185528	0.872323	0.032902	0.673401	0.879209	0.391432
6 L - 30 L	-0.11931	-0.17243	-0.31892	-0.88526	-0.4464	0.247609
6 L - 31 L	1.595984	1.038923	0.80327	-0.46955	-0.55606	-0.25395
6 L - 40 L	-1.16568	-1.06705	-1.238	-1.66509	-1.18532	-0.84656
6 L - 46 L	1.139584	-0.35975	0.532602	-0.14461	-0.25521	0.318581
7 L - 9 L	-4.98317	-2.97934	-2.21146	0.230791	0.229065	-0.23418
7 L - 13 L	-1.95663	-1.59802	-1.51559	-0.68376	0.120729	0.028661
7 L - 18 L	0.013722	0.471198	-0.16681	0.112908	-1.20552	-1.32866
7 L - 23 L	-5.85675	-5.05098	-3.60254	-1.21208	-0.1158	0.849712
7 L - 29 L	3.671969	1.087935	0.147731	-1.26519	-0.48618	0.028512
7 L - 30 L	-0.49354	-1.38792	-1.24814	-1.01791	-1.54219	-0.14451
7 L - 31 L	-5.37171	-3.90283	-3.20526	-1.45584	-0.59483	0.790884
7 L - 40 L	1.924353	1.315062	1.451246	1.005687	0.468075	0.176358
7 L - 46 L	-4.9831	-3.20161	-2.55723	-0.14263	0.980839	0.682867
9 L - 13 L	-1.75165	-1.34491	-1.35764	0.445459	0.794616	1.441808
9 L - 18 L	2.029359	0.976651	0.222255	0.000699	0.610084	0.135476
9 L - 23 L	1.614633	1.389879	1.36929	1.04235	0.050604	0.094428
9 L - 29 L	3.514894	2.613115	2.063997	0.385613	-0.03179	-0.15779
9 L - 30 L	-0.48657	-1.2045	-0.09977	0.276569	-0.12009	0.134374
9 L - 31 L	2.111593	1.740127	1.170314	0.472621	-0.26471	-0.11565
9 L - 40 L	-1.49687	-0.67464	-0.71894	-0.04349	-1.36452	-1.20858
9 L - 46 L	-0.16725	-1.00818	-0.33814	-0.2802	0.221797	0.127474
13 L - 18 L	3.242103	1.682911	1.363833	0.869346	0.902796	0.752241

13 L - 23 L	0.46681	0.407361	1.019014	0.595671	1.35039	1.062433
13 L - 29 L	-0.93695	0.254154	0.413534	0.105928	0.678563	0.627559
13 L - 30 L	-0.48095	-0.38247	0.109135	-0.13859	0.897666	0.95456
13 L - 31 L	0.603114	0.893446	0.951865	0.782413	1.150627	0.837502
13 L - 40 L	-2.51473	-2.54515	-1.40547	-0.4695	0.364106	0.301972
13 L - 46 L	1.112359	0.796251	0.441501	-0.5247	-1.06109	-1.57702
18 L - 23 L	-0.99471	-0.90003	-1.09158	-1.16919	0.761631	0.981427
18 L - 29 L	-0.56835	-0.97401	-1.23037	-0.16059	0.324114	0.762799
18 L - 30 L	-0.0256	-0.94819	-1.42654	-0.82859	-0.19133	0.557156
18 L - 31 L	-0.86867	-0.86482	-1.28383	-0.76401	0.446624	1.018012
18 L - 40 L	-2.99041	-2.94666	-3.03484	-1.34971	0.04542	0.264498
18 L - 46 L	-2.54124	-1.91215	-0.42974	-0.5723	-0.50934	-0.16221
23 L - 29 L	2.872911	1.970931	1.287269	0.747283	0.105019	-0.77113
23 L - 30 L	2.461349	1.860307	1.562141	-0.08931	-1.68434	-2.23551
23 L - 31 L	2.250519	1.597158	1.245114	0.325336	-0.35953	-0.93319
23 L - 40 L	-3.27231	-1.84718	-0.53816	0.558616	1.502704	1.08793
23 L - 46 L	-0.84344	-1.25112	-0.2021	-0.72717	0.727052	0.301031
29 L - 30 L	3.426683	2.299601	0.961958	-0.84014	-1.64782	-1.0793
29 L - 31 L	-0.30883	0.031017	-0.23437	-0.39723	-0.82132	-0.41089
29 L - 40 L	-0.8235	-0.03018	0.264588	0.753799	1.24268	1.181473
29 L - 46 L	-2.78742	-2.25207	-1.76641	-0.50419	0.40254	0.467173
30 L - 31 L	-0.76669	-0.49961	-0.15618	0.318963	1.375089	1.344334
30 L - 40 L	-4.3731	-1.50354	-0.94208	1.758548	2.158114	1.92887
30 L - 46 L	0.994412	1.339998	0.687893	-0.97075	-0.01352	-0.05159
30 L - 47 L	2.695196	2.484868	1.795453	0.265745	-1.17604	-0.62185
30 L - Amy L	0.480019	-0.59635	-0.77613	-0.27391	-0.98824	-0.58124
30 L - Hip L	0.952273	-0.40929	-0.7567	-0.69018	-0.96783	-0.58777
31 L - 40 L	-3.00743	-1.90402	-0.95792	1.682046	1.962445	1.61486
31 L - 46 L	-1.16228	-0.65747	-0.12032	-0.71776	0.821749	0.425122
31 L - 47 L	1.308576	0.937864	0.071898	-0.31719	-0.66386	-0.80183
40 L - 46 L	3.832831	2.713924	2.10066	0.883201	1.389612	1.882907

APPENDIX C

PARTIAL SAMPLE PHASE SLOPE INDEX DATA FILE DELTA THROUGH BETA TWO:

CHIROPRACTIC ADJUSTMENT PARTICIPANT

Subject ID:
Epoch Length
(sec): 120.39
LORETA Phase Slope Index
Left Hemisphere Phase Slope Index values from a single chiropractic adjustment participant one-week post baseline

Brodmann Areas	Delta	Thea	Alpha 1	Alpha 2	Beta 1	Beta 2
1 L - 2 L	1.790081	1.061758	0.902667	1.116452	1.315328	1.344548
1 L - 3 L	0.741874	0.576753	0.779515	0.828473	1.186431	1.146569
1 L - 6 L	0.800098	0.137319	0.504893	-0.50487	-0.25609	-0.41414
1 L - 7 L	0.775144	0.764049	0.867423	0.744773	0.036728	-0.14959
1 L - 9 L	-1.97507	-1.29381	-0.75858	-0.47315	-0.92106	-0.69154
1 L - 13 L	4.961232	3.548833	3.444222	0.93166	-0.79533	-0.18298
1 L - 18 L	1.20685	0.907401	0.329098	0.689356	-0.70322	-1.22745
1 L - 23 L	0.779824	-0.35875	-0.49042	0.436905	0.133467	-0.26709
1 L - 29 L	2.170047	0.535135	0.39492	0.997501	-0.16071	-0.18302
1 L - 30 L	1.134918	0.317589	0.588127	0.407145	-0.91647	-1.06782
1 L - 31 L	1.301071	0.628525	-0.11478	0.431935	-0.23469	-0.42806
1 L - 40 L	0.068101	0.097681	-0.10765	-0.23378	-0.62579	-0.90373
1 L - 46 L	-2.19119	-2.12206	-1.69208	-0.45955	-0.34852	-0.19272
2 L - 3 L	-1.23692	-0.93085	-0.75923	-0.32109	-0.20693	-0.09236
2 L - 6 L	-3.59009	-2.43129	-0.64887	0.541111	1.645666	1.493426
2 L - 7 L	2.654854	1.975494	1.448752	0.647164	-0.01424	-0.43892
2 L - 9 L	-3.68113	-2.65111	-1.6329	-0.7346	0.574341	0.57217
2 L - 13 L	-2.04184	-1.06415	-0.92633	-0.2058	-0.53076	-0.69906
2 L - 18 L	4.331652	2.323919	1.843365	0.395963	-0.83152	-1.10048
2 L - 23 L	1.892176	1.331986	1.275596	0.735906	-0.05725	-0.13175
2 L - 29 L	1.995008	1.451114	0.991445	1.480684	0.037406	-0.11846
2 L - 30 L	5.87543	3.525841	3.074811	0.784768	-0.24621	-0.57051
2 L - 31 L	3.784731	2.458358	1.908539	0.91747	-0.0515	-0.17866
2 L - 40 L	-2.90827	-1.16904	-1.11327	-0.18908	-1.60438	-2.64615

2 L - 46 L	-1.59434	-1.67262	-1.09544	-0.59692	-0.34268	0.279935
3 L - 6 L	-2.42972	-1.81218	-0.59703	0.35763	1.220861	0.933105
3 L - 7 L	2.384675	1.705438	1.753294	0.98756	-0.1274	-0.32167
3 L - 9 L	-3.24169	-2.69901	-1.18717	-0.73731	0.67855	0.502872
3 L - 13 L	0.612124	0.468653	0.515928	0.047962	-0.81642	-0.62108
3 L - 18 L	2.819133	1.22831	1.346481	0.390558	-0.66965	-1.05739
3 L - 23 L	1.994155	1.149672	0.813119	0.817422	0.02549	-0.17533
3 L - 29 L	1.641741	0.934736	0.518108	1.614705	-0.03774	-0.28284
3 L - 30 L	5.063754	3.39005	2.561253	0.870432	-0.53932	-0.93363
3 L - 31 L	3.003836	2.071942	1.776163	0.76592	-0.03844	-0.41729
3 L - 40 L	-1.56704	-0.4579	-0.62791	-0.46978	-1.7369	-2.22825
3 L - 46 L	-2.71735	-2.18696	-1.54683	-0.70312	-0.16014	0.259831
6 L - 7 L	2.550853	1.615252	1.898505	1.515477	1.592763	0.790688
6 L - 9 L	4.457052	2.983045	2.423214	0.622562	-0.47202	-0.3318
6 L - 13 L	-0.25008	-0.20555	-0.38244	0.16705	-0.67805	-0.47278
6 L - 18 L	-1.22264	-0.55655	-0.38209	-0.18335	-0.32088	-0.32011
6 L - 23 L	2.17623	1.154287	1.148446	0.669001	-0.07656	-0.29248
6 L - 29 L	-0.05599	-0.05508	0.710535	1.115275	0.650839	0.277162
6 L - 30 L	1.704221	1.358352	1.489046	0.411655	-0.23457	-0.49924
6 L - 31 L	2.086685	1.206803	1.146128	0.932842	-0.07429	-0.37116
6 L - 40 L	-2.73989	-1.36024	-0.5508	1.805958	0.907328	0.558516
6 L - 46 L	4.89374	3.460483	1.907921	0.331205	-0.50523	-0.21566
7 L - 9 L	-2.91354	-2.12929	-1.75617	-0.64126	-0.08602	0.116485
7 L - 13 L	0.809321	0.441572	0.263952	-0.73462	-0.47921	-0.57298
7 L - 18 L	0.980735	0.459666	0.194828	-0.2094	0.209473	0.535268
7 L - 23 L	-1.72202	-0.53643	0.296272	0.710439	0.326432	0.182597
7 L - 29 L	0.126709	0.799495	1.330544	0.821905	0.629446	0.379024
7 L - 30 L	-0.5281	0.240625	0.50577	0.149645	0.220871	-0.22805
7 L - 31 L	-3.45923	-0.75007	0.244008	0.788653	0.475436	-0.17041
7 L - 40 L	0.738483	0.034798	-0.25146	-0.07309	0.210257	-0.15515
7 L - 46 L	-2.94739	-2.88887	-1.96728	-0.59881	-0.05385	0.249299
9 L - 13 L	2.870746	2.292854	1.416937	-0.10299	-0.68505	-0.73218
9 L - 18 L	2.936882	2.025185	1.238859	0.580413	0.022597	0.138474
9 L - 23 L	-0.0297	0.996189	0.939552	0.919944	0.580362	0.152818
9 L - 29 L	0.83982	1.280755	1.141653	1.439492	0.647357	0.032828
9 L - 30 L	1.788314	1.56109	1.38998	0.52182	0.419581	0.050853
9 L - 31 L	0.898384	1.013648	1.168923	0.772081	0.201352	0.041661
9 L - 40 L	-1.81938	-0.70043	-0.45949	0.741433	0.223393	0.653033
9 L - 46 L	8.583028	5.976308	4.517998	1.26162	0.697696	0.659401
13 L - 18 L	5.068924	4.147164	3.106985	0.640315	0.219262	0.005338

13 L - 23 L	0.453261	0.826456	0.76894	0.289036	0.444237	0.249102
13 L - 29 L	1.250161	0.732604	0.452588	-0.16197	0.829974	0.60388
13 L - 30 L	2.343211	1.233945	1.027082	0.189224	0.573925	1.056576
13 L - 31 L	1.478439	1.710486	1.05742	0.20287	0.821527	0.755242
13 L - 40 L	-4.14126	-2.68796	-2.2156	-1.29246	-0.08591	0.143526
13 L - 46 L	-2.69595	-1.60716	-1.17404	0.726957	1.195696	0.788075
18 L - 23 L	-0.03883	0.271737	0.699561	0.665115	0.971876	0.698248
18 L - 29 L	0.892388	-0.19188	0.265972	0.145254	0.25143	0.284724
18 L - 30 L	-1.91864	-1.56705	-0.5542	0.619579	1.178415	1.041377
18 L - 31 L	0.216495	0.248412	0.362955	0.56442	0.524313	0.356247
18 L - 40 L	0.298863	-0.06023	0.401024	-0.6396	1.002358	1.278843
18 L - 46 L	-2.85264	-2.00277	-1.636	-0.22569	-0.16988	0.021493
23 L - 29 L	3.014183	1.513147	0.8598	-0.28257	-0.67055	-1.09503
23 L - 30 L	-0.05649	-0.18702	-0.29476	-0.15033	-1.19494	-1.62516
23 L - 31 L	0.783289	0.409479	0.176493	-0.12257	-0.45076	-0.35429
23 L - 40 L	1.020451	1.137296	0.698445	-0.12705	0.346959	0.311629
23 L - 46 L	-2.19179	-1.67404	-1.78818	-1.15834	-0.32219	-0.20484
29 L - 30 L	-1.17271	-0.50303	-0.3648	0.246573	-0.88821	-0.44073
29 L - 31 L	-1.63841	-1.07222	-0.45845	0.095479	-0.12119	0.564217
29 L - 40 L	-1.3224	0.039526	-0.39231	-0.62061	0.371634	0.225901
29 L - 46 L	-1.71277	-1.45406	-2.00252	-1.13391	-0.40182	-0.35341
30 L - 31 L	-0.05546	-0.17088	-0.05889	0.052718	1.117037	1.336106
30 L - 40 L	2.21795	1.737946	1.112069	-0.17113	0.433426	0.613481
30 L - 46 L	-3.62652	-2.73274	-2.22073	-0.96292	-0.61912	-0.53596
31 L - 40 L	0.205962	0.578992	0.656716	0.075755	0.621012	0.394765
31 L - 46 L	-2.07611	-2.09199	-1.67942	-1.07181	-0.35238	-0.46871
40 L - 46 L	1.322377	1.230242	0.600311	0.14605	-0.21187	-0.44893