Effects of Spinal Manipulation on Brain Activation in Individuals with Chronic Low Back Pain

Max K. Jordon

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EFFECTS OF SPINAL MANIPULATION ON BRAIN ACTIVATION IN INDIVIDUALS WITH CHRONIC LOW BACK PAIN

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DEDICATION

This dissertation is dedicated to my wife, Emily Jordon. Your support, encouragement, friendship, patience, and love throughout these years have meant more to me than I can adequately express in words. Your steadfast belief in me, even when I didn’t even believe in myself, is the only reason I made it. Thank you.
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ABSTRACT

Chronic low back pain (cLBP) continues to be one of the most common health conditions in the United States. Despite an enormous amount of research, there are no treatments for this condition that consistently improve outcomes. For decades health professionals have incorporated spinal manipulative therapy (SMT) into their practice, but the evidence to date has shown that SMT has only small to modest effect sizes when treating cLBP. One way to improve the effectiveness of SMT is by getting a better understanding of its underlying mechanisms so that the intervention be more specifically targeted to the appropriate individual.

While biomechanical theories exist to help explain how SMT works, they do not sufficiently explain all the phenomena associated with this treatment. To better understand the mechanisms behind SMT, researchers have begun to study the neurophysiological effects of SMT using functional magnetic resonance imaging (fMRI); however, to date there have been no published studies assessing the effects of SMT on the changes in brain activation during the performance of lumbopelvic motor tasks. Therefore, the overall purpose of this body of work was to describe the differences in brain activity between individuals with and without cLBP when performing lumbopelvic motor tasks, and to assess the effects of SMT on brain activity in these populations.
Results from this body of work will help health care professionals implement this technique in a more specific and focused manner.

Key findings from this study demonstrated how individuals with cLBP exhibit a broader network of brain activation compared to asymptomatic individuals when performing lumbopelvic motor tasks. Specifically, there appears to be two networks that are active during the performance of lumbopelvic tasks: a “motor network” that consists of the precentral gyrus and the supplemental motor area that is common in both groups, and a “motor-pain network” that is only active in individuals with cLBP consist of the Insula and Middle Cingulate Cortex. These two networks seem to share a common hub, the Putamen, that can assist in translating information between these two networks.

It is the Putamen that is impacted the most with spinal manipulation. Both the levels of activation and functional connectivity increases with spinal manipulation in individuals with cLBP, but not asymptomatic individuals. This suggests that spinal manipulation might affect the cortico-basal-ganglia motor loop in individuals with cLBP.
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CHAPTER 1

INTRODUCTION

Low back pain continues to be a debilitating condition that affects a large portion of the population [1]. It is estimated that approximately 40% of adults will suffer from low back pain at some point, with upwards of half of them meeting the criteria for chronic pain [2, 3]. Costs associated with chronic low back pain (cLBP) continue to rise at an alarming rate creating an imperative that more effective treatments be developed. One barrier to creating better treatments for cLBP is that its underlying mechanisms are poorly understood. For example, approximately 85% of people with cLBP [5] have no detectable anatomic, endocrine, vascular or peripheral nerve abnormalities that are likely to contribute to the development and persistence of pain. Therefore, with an absence of a clear pathoanatomical source of dysfunction, investigations have started to focus on additional etiologies.

One promising contribution to the chronicity of symptoms are alterations that occur in the central nervous system when individuals experience cLBP[6, 7]. Previous research using functional magnetic resonance imaging (fMRI) has reported alterations in certain regions of the brain that are responsible for the motor control of the low back muscles (i.e. cortical representation)[8-12]. For example, individuals with cLBP have differences in response to sensory stimuli [13-17] and, when at rest, the communication
between different regions of the brain is altered (i.e. the resting state functional connectivity) [15, 16, 18-22]. Taken together, there is ample evidence that individuals with cLBP experience changes in the central nervous system as measured by fMRI and specifically in the brain. However, most of the evidence to date has focused on the appreciation of sensory stimulus and individuals in a resting state. This has provided preliminary information; however, it has limited generalizability to clinical setting. There exists a need to investigate the changes in cortical function that occur in individuals with cLBP during the performance of salient motor tasks.

To study changes in cortical function during motor tasks, researchers have utilized functional magnetic resonance imaging (fMRI) [23-28]. Currently, the research into the role of motor systems and pain processing has primarily relied on the performance of upper extremity motor tasks [29, 30]. However, investigations into low back pain may necessitate utilization of lower extremity motor tasks. Previous research has demonstrated that cLBP results in specific cortical changes to the lumbopelvic region; during both muscle [10, 11, 31] and cutaneous [8, 9] stimulation. Furthermore, biomechanical research has suggested deficits in lumbopelvic motor control in individuals with cLBP [32-36]. Therefore, utilizing lumbopelvic systems in a fMRI task holds the great promise when studying motor system changes that occur in those with cLBP.

To address changes in motor systems and improve lumbopelvic motor control, physical therapists frequently incorporate spinal manipulation (SMT) into their treatment plan [37-41]. However, despite its widespread adoption into clinical practice,
several systematic reviews have reported small to modest effect sizes [42-44]. One potential reason for the small effect sizes is the lack of a clear understanding of its mechanisms [39, 40].

Therefore, the full scope for this body of work was to: 1.) examine the literature regarding the cortical changes that occur in individuals with cLBP, with a specific focus on changes in somatotopic organization, sensorimotor integration, functional connectivity, and cortical density; 2.) validate a series of previously established lumbopelvic motor tasks that can be performed in a fMRI scanner and to describe the cortical activation in an asymptomatic population (Aim 1); 3.) compare and contrast cortical activation during lumbopelvic tasks in individuals with and without cLBP (Aim 2); and 3.) assess the effects spinal manipulation on cortical activation in individuals with cLBP (Aim 3).

The first aim was to validate a previously described protocol to perform lumbopelvic tasks within the scanner and to more fully describe the cortical activation patterns of these tasks. While the previous study was able to describe the EMG activation and the concurrent whole brain activation, there was no evaluation of the functional connectivity during these exercises. Functional connectivity analysis examines the brain networks by correlating brain activity in spatially separated regions [45]. By getting a better understanding of the functional connectivity in asymptomatic individuals, we were better able to interpret changes that occurred in individuals with cLBP.
The second aim of this study was to compare and contrast differences in cortical activation between individuals with and without cLBP during the performance of lumbopelvic tasks. To our knowledge, there have been no reports on the performance of lumbopelvic tasks in individuals with cLBP. By addressing this key gap in the reported literature, this study will help clinicians better understand the role of pain on movement impairments and brain activation in individuals with cLBP.

Finally, the third aim of this study was to assess the effects of SMT on cortical activation during the performance of lumbopelvic tasks. Findings from this study contributed to the overall understanding of the mechanisms behind spinal manipulation and helped clarify the effects SMT has on cortical function. This in turn will help clinicians better incorporate SMT into their clinical decision making.
REFERENCES


CHAPTER 2

REVIEW OF THE LITERATURE

2.1. Changes in Cortical Processing of Sensorimotor Activity Associated with Low Back Pain

2.1.a Introduction

The inability to link structural abnormalities of the lumbar spine to low back pain [1, 2] has led researchers to search elsewhere for primary and secondary sources of low back pain. Supraspinal changes, i.e. changes of the structure and function of the central nervous system superior to the spinal cord, are receiving increased attention by researchers as they are commonly present in individuals with chronic low back pain (cLBP) [3-9]. While there are a multitude of central changes that occur in patients with cLBP [5, 6, 8, 10], alterations in somatotopic organization (SO), i.e. the brain’s topographical processing of sensory and motor information, and mal-adaptive changes in the integration of this information, more commonly referred to as sensorimotor integration, have received particular interest[11, 12]. The exact impact of these changes is unknown, but they may relate to the severity of low back pain [13] and are potentially able to be affected by spinal manipulation (SMT)[14-16]. Yet despite the increased interested in somatotopic organization and sensorimotor integration, there are some key knowledge gaps that need to be addressed.
2.1.b Somatotopic Organization in the Motor Cortex

Plow et. al. defined somatotopic organization (SO) as the way the brain represents movements and sensation of different body segments [17]. A generalized pattern is present at birth [18] with the pelvic floor[19] and lower limbs being closer to the midline and the hands being represented most laterally. This can change depending on the individual’s environment and experiences [4, 7, 9, 13, 20]. Initially described by Beevor et. al in 1890[21] in a series of excitation experiments, it was historically thought that the SO of the motor cortex (M1) maintained a discrete organization between-limbs [22], with within-limb organization occupying the same region of the cortex to allow for multi-joint coordination [23-25]. However, more recent research suggests that the within-limb somatotopy also contains discrete centers of control with overlap between regions to allow for coordinated movement [17, 26-28].

Evidence for this phenomenon comes from a 2010 study by Plow and colleagues [17]. Using fMRI data, they evaluated the activation patterns in 24 adults while performing finger, elbow, and ankle motor tasks. The authors reported that in each of the participants there were discrete, non-overlapping representations for each task with the finger representation occurring more laterally in the cortex than the elbow; also, the elbow was more lateral than the ankle. Furthermore, they found that while each task had a portion of their total active representation that was unique to the task, the finger and elbow did share some overlap. This demonstrated that while there are discrete centers of control for the elbow, overlap does exist. Ordered somatotopy has also been
described by Kapreli in the lower limb [28] and was subsequently supported by Cunningham et. al [27].

Somatotopic organization is thought to undergo changes in individuals with cLBP [4, 13, 29-31]. While exploration of this phenomenon has been ongoing [32], it wasn’t until 2011 that it was first quantified in the low back. Tsao and colleagues [29] evaluated the extent of cortical somatotopical reorganization on individuals with LBP. Twenty (20) individuals (recurrent LBP n=9) underwent transcranial magnetic stimulation (TMS) and electromyographic (EMG) recordings. First, they inserted EMG wires into the deep multifidus and the longissimus muscles. Then, they used single-pulse monophasic TMS to map the motor cortex. The authors found that individuals with recurrent LBP had overlapping areas of control for the deep multifidus and the longissimus, whereas the asymptomatic individuals maintained separate centers. This demonstrated for the first time that there was a loss of discrete organization in the motor cortex in individuals with LBP, which the authors termed “smudging”.

In 2015, Schabrun et. al. [13] built upon this work and demonstrated that the degree of smudging in the motor cortex is directly related to the severity of low back pain. The authors recruited 50 individuals (recurrent LBP n=27) to undergo both surface EMG and TMS. Surface EMG was used at the L3 and L5 paraspinal muscles to record signals generated from a single-pulse TMS. Additionally, they collected data on pain severity (11-point numerical rating scale (NRS)) and duration of pain. The authors found that in individuals with recurrent LBP, there were fewer discrete peaks at the L3 level when compared to healthy individuals. Fewer discrete peaks indicates that the degree
of over-lap and co-representation in the motor cortex is greater, indicating a loss of discrete cortical organization. Furthermore, in individuals with moderate-to-severe LBP (>5/10 on the NRS) had a single discrete peak whereas this was found in only 53% of participants with mild LBP (<5/10 on the NRS).

Changes in the cortical organization (i.e. cortical reorganization) of the primary motor cortex is not unique to individuals with cLBP. In 2015, Shanahan et. al. [33] used fMRI to assess the changes in the location of peak activation in the motor cortex in individuals with and without knee osteoarthritis (OA). A total of 18 participants (moderate/sever OA n=11) participated in the study and a significant anterior shift in the representation of the knee and ankle was discovered. There was also a significant difference in the somatotopic organization of knee and ankle movements in individuals with knee OA when comparted to asymptomatic controls. Furthermore, the authors were able to correlate these findings to poorer performance of the motor task, lending evidence to the theory that the poor motor control in individuals with knee OA could be cortically driven.

Further evidence of motor control being linked to changes in cortical organization comes from Tsao in 2008[30]. Tsao et. al. took 22 individuals (recurrent LBP n=11) through a similar EMG and TMS mapping sequence as described above; however, for this study they inserted the intramuscular fine-wire electrodes into the transverse abdominis muscle instead of the deep multifidus and longissimus muscles. The authors found that in symptomatic individuals the cortical mapping for the transverse abdominis was located posterior and lateral to that of the asymptomatic individuals. Additionally,
feed-forward activation of the transverse abdominis during a rapid arm flexion task was found to be latent in symptomatic individuals when compared to asymptomatic individuals. The authors concluded that the deep abdominal muscles reorganized in the motor cortex in individuals with recurrent LBP, and that this reorganization is related to the timing of onset of the transverse abdominis. However, it should be noted that they simply found both of these phenomena to be present in individuals with recurrent low back pain and made no effort to statistically correlate the two measures, making definitive conclusions difficult to draw.

As stated previously, multiple regions of the brain exhibit somatotopic organization. For the motor cortex, this organization manifests as discrete centers of control with considerable amount of overlap to allow for coordination of movement [17, 26-28]. The pelvic floor and lower limbs are organized more medially [19], with the upper extremities and specifically the hand being represented most laterally [18]. It has been demonstrated that the organization of the motor cortex is altered in individuals with low back pain [13, 29, 30, 33], and that the degree of alteration relates to the amount of pain and loss of motor control [29, 30]. However, any area associated with movement will, to some extent, exhibit somatotopic organization [34]. This includes, but is not limited to, the cerebellum [35-37], supplemental motor area [24, 27, 38, 39], parietal operculum [40], and importantly the primary and secondary sensory cortices [26, 27].
2.1.c Somatotopic Organization of the Sensory Cortices

The primary (S1) and secondary (S2) somatosensory cortex exhibit both organized somatotopic organization [26, 41-43] and functional reorganization in people with chronic pain [4, 7, 9, 20]. However, whereas the motor cortex exhibits distinct centers of control with areas of overlap to allow for coordinated movements [17, 26-28], the somatotopic organization in S1 and S2 is believed to be more discrete and segregated [26, 27]. Functionally this makes sense – while it would be beneficial for the overlap of cortical control for different joints in the coordination of movements, such overlap in the cortical control for sensory discrimination would limit the proprioceptive processing for different body parts [26].

Evidence of the discrete somatotopic organization in the sensory cortices comes from Cunningham and colleagues in 2013[27]. The investigators had 24 healthy individuals (male = 4) perform finger, ankle and elbow joint tracking tasks during fMRI scanning. The authors argued that based on previous research, the complex movements of joint tracking compared to simple motor tasks required greater planning and were more applicable to motor skills [26, 44-48]. Therefore, the joint tracking allowed the authors to more accurately assess a region’s role in motor skill and control. The authors confirmed that the motor cortex had distinct areas of representation with significant overlap for the elbow and finger task. However, in the sensory cortex there were distinct centers of representation for the separate ankle, elbow and finger tracking tasks with was minimal to no overlap in the representation.
Additionally, in 2001 Hlustik et. al. used high-resolution fMRIs obtained from healthy volunteers to map the somatotopic organization of both M1 and S1 [26]. Eleven healthy, right-handed volunteers performed motor tasks involving the first digit, the fifth digit and wrist, and the middle three digits. The authors found that orderly somatotopy existed in both M1 and S1; however, there were several significant differences between the two areas. First, there were significantly more clusters of activation in the S1 than the M1, suggesting that there was increased differentiation between tasks in S1. Second, there was significantly less overlap in the S1 than the M1, suggesting that the cortical representations in S1 is more discrete than M1.

The findings of Cunningham et. al., and Hlustik et. al., lend evidence to the theory that the somatotopic organization of M1 has discrete centers of control with significant overlap whereas the S1 remains more segregated in its organization. As previously stated, individuals who experience chronic pain are believed to undergo re-organization of these areas. For example, Hotz-Boendermaker et. al. in 2016 [4] used fMRI to assess the somatotopic organization of the low back in the S1 and S2 cortices of 26 individuals (cLBP n=13). The authors found that not only was there a reduction in activation in S2, but a blurring of the somatotopic representation. While this research demonstrated that in individuals with cLBP there is a reduction in the discrete organization in S2, it is not the only maladaptive change that occurs with chronic pain.
2.1.d Treatment of Impaired Somatotopic Organization

Individuals with cLBP are likely to exhibit a reduction in the discrete organization of several key sensorimotor areas. However, there is a paucity of literature describing treatments that are designed to restore the normal cortical organization of the sensorimotor areas of the cortex. Schabrun et. al. in 2014 [49] combined transcranial direct current stimulation (tDCS) and peripheral electrical stimulation (PES) in the treatment of chronic recurrent low back pain. Sixteen individuals were recruited to participate in a placebo-controlled crossover study where they received four treatments: 1) anodal tDCS/PES; 2) anodal tDCS/sham PES; 3) sham tDCS/PES; or 4) sham tDCS/sham PES. The authors sought to measure the post-intervention changes in pain, cortical organization of the motor cortex, sensitization and sensory function. To assess changes in pain, participants rated their pain on a 11-point numeric rating scale. To assess the cortical organization of the motor cortex, the authors utilized a single-pulse TMS stimulation using the same protocols as described above [13]. In order to assess the sensitization, pressure-pain thresholds were recorded over the greatest point of pain, and higher sensory function was determined by two-point discrimination testing of the lumbar area.

Treatment included a 30-minute session of concurrent tDCS and PES. tDCS was applied using saline-soaked sponge electrodes over the scalp at the approximate location of the motor cortex. Concurrently, PES was applied using electrodes placed over the lumbar paraspinals at the location of L3 and L5. The authors reported that when the participants received any combination of the four treatments that included an
active intervention there was a reduction in pain. However, when the participants received the combined active treatment of tDCS and PES they experienced improvements in all outcome measures. The authors suggested that the increased efficacy of the combined treatments reflected a priming mechanism of the two treatments that dually decreased pain sensitivity while normalizing cortical organization. This therefore allow the participants to receive greater pain reduction than either intervention alone.

2.2. Sensorimotor Integration

2.2.a Sensorimotor Integration – Introduction.

Baarbe et. al. defined sensorimotor integration (SMI) as the process by which the somatosensory information received by the brain during a motor task is integrated with the motor output in order to refine and improve the efficiency of the task performed [50]. Improper integration, due to abnormalities of the peripheral afferent input or following disruption in the processing of the neural networks involved in motor tasks, can lead to significant motor disturbances [11]. While disruptions naturally occur with aging[51], they have been observed in individuals with Parkinson’s disease[52, 53], Huntington’s disease[52], chronic regional pain syndrome[54], dystonia[55, 56], fibromyalgia[57, 58] and more consequential to the subject of this review, spinal pain[14, 59, 60].
2.2.b Sensorimotor Integration and Spinal Pain

As previously mentioned, deficits in sensorimotor integration are present in a variety of conditions. While sensorimotor integration deficits have not been directly observed in neck pain it has been inferred by several other sources. Individuals with chronic neck pain exhibit disturbances in cervical joint position sense [61-63], postural stability [61, 64-66], and even oculomotor control [62]. However, evidence for a lack of sensorimotor integration is more direct in individuals with cLBP.

In 2015, Pijnenburg et. al. [59] performed resting state fMRI on the sensorimotor network in individuals with nonspecific LBP (NSLBP). Seventeen individuals with NSLBP and 17 age-matched asymptomatic controls performed 5 sit-to-stand-to-sit (STSTS) tasks followed by fMRI resting state scanning. Not only did the NSLBP group have significantly slower STSTS times, there was a significant difference in the functional connectivity between the different sensorimotor areas. They found that decreased functional connectivity between the left motor cortex and lobules IV and V of the cerebellum were associated with decreased performance in individuals with non-specific LBP. Specifically, the researchers found that in individuals with NSLBP there was poor integration of the supplementary motor area and S1 cortex when compared to healthy controls. The connectivity of the M1 correlated significantly with the STSTS times, as well as the cerebellum. Simply stated, poor performance of the STSTS task was correlated to decreased functional connectivity of the motor cortex and cerebellum.
It is important to note that in the above study, the resting functional connectivity findings were not correlated to pain. Therefore, while deficits in SMI may be linked to poor motor control, one cannot use this finding to correlate it to pain [59]. However, in 2005 McCabe et. al. [58] performed the first of a series of studies to directly link sensory-motor incongruences to pain. Forty-one asymptomatic participants performed a series of bilateral upper and lower limb movements while viewing a mirror to simulate minor sensory-motor conflict. Each individual sat with the mirror placed between their limbs and performing alternating shoulder flexion and extension. The participants either performed this task in a congruent manner (i.e., both limbs moving into flexion and extension at the same time) or in an incongruent manner (i.e., one limb moving into flexion while the other moved into extension). However, as they were performing this task, the mirror was blocking their view of the contralateral limb. Therefore, when they were performing the task in a congruent manner, the visual feedback mirrored the motor output. However, when they were performing the task in an incongruent manner, they visual feedback contradicted the motor output.

When the individuals performed the task in an incongruent manner, 66% of the participants reported feeling some sort of anomalous sensory symptom during the task. This could include pain, numbness/tingling, aching or changes in temperature, limb weight or altered body image. This was the first study to directly assess the effects of differences between motor and predicted somatosensory feedback. These findings help to formulate a basis for the cortical component of centrally mediated pain. However,
limitations to this study included the fact that only asymptomatic individuals were included.

In 2007 McCabe et. al. [57] expanded their protocol to include individuals with fibromyalgia syndrome (FMS). Twenty-nine adults with FMS and 26 healthy controls perform the aforementioned motor-sensory congruency task. The authors found that in almost 90% of the individuals with FMS there were reports of some degree of change in sensory perceptions, whereas in the asymptomatic control group that percentage was on 48%. These findings further support the hypothesis that motor-sensory incongruencies, or deficits in SMI, can lead to pain and sensory disturbances.

2.2.c Retraining of Sensorimotor Integration with Physical Therapy Interventions

With the growing body of literature finding sensorimotor integration deficits in individuals with chronic pain conditions, researchers have started to develop treatment techniques to directly target this condition. Some of the earlier attempts to address SMI deficits included graded motor imagery (GMI) and mirror therapy. Moseley in 2006 [12] established a protocol whereby individuals first performed limb laterality tasks, followed by imagined movements then mirror movements. In a sample of 50 participants with chronic regional pain syndrome (CRPS), 25 participants were randomized to receive GMI intervention and 25 to receive standard physical therapy care. Those who received the GMI intervention underwent a three-step protocol. First, they established right/left discrimination of their limbs as was found beneficial in previous studies [67]. Following the discrimination task, the second step was to have the participants imagine
performing movements in a pain free manner. Finally, the third step was to have participants perform mirror therapy. Moseley reported significantly greater improvements in pain and function in the GMI group when compared to the control group. He conjectured that these improvements could be contributed to the sequential activation of the pre-motor cortex, followed by the coordinated activation of the pre-motor and M1 cortex (thus improving the integration of information between these two areas) [12, 67].

While other researches have investigated the mechanisms and potential therapeutic effects of graded motor imagery and mirror therapy, there has not been any other studies that have investigated these mechanisms in specific context of sensorimotor integration. This remains a key knowledge gap and potential area for future research.

2.3 Alterations in Cortical Activity

2.3.a Mechanical Stimulation

Individuals with cLBP pain exhibit changes in cortical activation during mechanical stimulation. In 2009, Kobayashi et. al. recruited 14 individuals (cLBP = 6) to undergo fMRI while applying manual pressure to the L4-L5 lumbar spinal interspace [68]. They found that in both groups there was activation in the prefrontal, insular, posterior cingulate cortex (PCC), supplementary motor area (SMA), and premotor areas. However, in individuals with cLBP, there was increased activation in the right insula, SMA, and PCC when compared to asymptomatic individuals. Interestingly, there was no
activation in the primary or secondary somatosensory regions (S1/S2). They hypothesized that since S1/S2 is primarily activated during superficial pain stimulation, that the mechanical compression present in their study induced deep tissue pain and thus did not result in activation in these regions. Taken together, they concluded that individuals with cLBP exhibit a unique network of activation in response to mechanical pain.

In 2004 Giesecke et. al. compared activation across individuals with cLBP (n=11), fibromyalgia (n=16), and no symptoms (n=11) [69]. They found that when equal pressure was applied to tender locations, individuals with cLBP had activation in the contralateral S1, S2, ipsilateral S2, inferior parietal lobule, and the cerebellum. When this same stimulus was applied in asymptomatic individuals, only the contralateral S2 was activated. This demonstrated that in individuals with cLBP, there was a broader network of activation in regions associated with pain processing.

Taken together, these two studies demonstrate that individuals with cLBP exhibit a broader network of activation in response to mechanical stimulus. While the role of S1 and S2 is not clear, there seems to be increased activation in regions specifically associated with the appraisal of pain.

2.3.b Thermal Stimulation

Individuals with cLBP also exhibit changes in cortical activation in response to thermal stimulation. In 2006, Baliki et. al. recruited 22 individuals (cLBP = 11) to undergo fMRI while simultaneously receiving thermal stimulation. While both groups
demonstrated increased activity in bilateral insula, thermal stimulation in individuals with cLBP revealed increases in the dorsolateral (DLPFC) and medial pre-frontal cortex (mPFC). During high pain epochs, the activation in these two regions (mPFC and DLPFC) were negatively correlated with one another.

In a follow up study in 2010[70], Baliki et. al. demonstrated that during thermal stimulus, individuals with cLBP and asymptomatic individuals demonstrated similar activation patterns. However, the nucleus accumbens activity significantly differed between the groups, and was able to differentiate between the groups at a very high accuracy. Therefore, these two studies suggest that during thermal stimulus, there is abnormal activation in the mPFC and the DLPFC, while the nucleus accumbens is able to differentiate activity between the two groups.

2.3.c Lumbopelvic Tasks

As stated before, fMRI is a safe and non-invasive measurement tool that can be used to indirectly assess cortical activation. However, one of the limitations of fMRI is that you must remain very still in a small, confined space as head movement can easily lead to artifact[71]. This has limited the mapping of the motor cortex in the fMRI to primarily upper extremity and distal lower extremity tasks. To date, there has only been two published studies that have utilized fMRI to assess cortical activation related to activation of the lumbopelvic musculature.

Moseley in 2005 [72] and Louw et. al. in 2015 [73] reported similar case studies where they assessed the effect of therapeutic neuroscience education on activation of
the cortex following contraction of the transverse abdominis. The each evaluated a young female who experienced multiple years of low back pain. Prior to the intervention, both studies found significant activations in the areas related to the aforementioned pain matrix; however, in the Moseley case study [72] he found post-education that the participant has significant reductions in all areas except the S1. Comparably, Louw[73] found dramatic reductions in the cerebellum and PAG, with a noticeable increase in the motor cortex.

There are, however, several limitations to these studies. First, neither group assessed a control participant or condition. Therefore, it is difficult to determine if the changes in activation are due to the condition or simply natural variations in activity to a task. Second, both studies were case studies, limiting their external validity. Third, neither had the subject more the multiple segments of the lumbopelvic region. A more complex task would theoretically require increased coordination between joints and greater demands for motor control. Regardless, these two studies suggest a proof of concept that lumbopelvic tasks can be performed within the MRI environment without causing excess head motion, and also that the BOLD response to an abdominal motor task is something that can be quickly and purposely manipulation within an experimental design.
2.4 Functional Connectivity

2.4.a Overview

Functional connectivity is defined as “statistical dependencies among remote neurophysiological events [74].” In resting state functional connectivity studies, brain networks are defined by correlating brain activity in spatially separated regions at rest [75]. Of particular interest is the default mode network, which has been shown to have functional connectivity in a resting state [76-78]. As this is commonly thought of the brain’s intrinsic activity, several researchers have sought to elucidate changes in this network, as well as attempt to demonstrate different networks that might be affected.

2.4.b Changes in Resting State Functional Connectivity

Multiple studies have investigated changes associated with resting state functional connectivity [79-88]. In general, the results from these studies demonstrate that there are reorganizations in the functional connectivity in individuals with cLBP. Overall, changes in functional connectivity were found in the insula [85-88], middle frontal gyrus [87], mPFC [79-82, 88], S1[84, 88], ACC [86], inferior parietal lobule [86], nucleus accumbens [81], and the dorsolateral PFC[85].

Of specific interest is the changes in the nucleus accumbens and the mPFC [81]. In 2012, Baliki et. al. recruited 39 individuals with acute low back pain, and followed them for a duration of one year. They separated the groups into those who had persistent LBP (n=19) and those who recovered (n=20). They discovered that at baseline, those who
had a higher positive functional connectivity between the nucleus accumbens and the mPFC were more likely to develop persisting pain. These results suggest that corticostriatal functional connectivity is important in predicting those who will develop persistent low back pain.

2.5 Cortical Changes Resulting from Spinal Manipulative Therapy

2.5. An Overview

Spinal manipulation is a key intervention commonly utilized by physical therapists to treat painful disorders of the spine [89-93]. While a full review of the mechanisms behind spinal manipulative therapy is beyond the scope of this literature review (for a detailed report of the mechanisms of SMT see Bialosky et. al. [94]), it is important to review its potential impact in changing the cortical processing of somatosensory information.

2.5.b Effects of Spinal Manipulation on Sensorimotor Integration

In addition to graded motor imagery, spinal manipulative therapy (SMT) has been investigated as a potential treatment technique to help restore SMI [14-16, 95, 96]. In 2007, Haavik-Taylor and Murphy [16] used somatosensory-evoked potentials (SEPs) to assess the somatosensory integration in 12 individuals with recurrent neck stiffness or pain. The authors found that following a cervical spine manipulation, there was a significant decrease in the amplitude of the parietal N20 and frontal N30 SEP components. The N20 SEP peak represents the arrival of the afferent information coming into the sensory cortex [14]. A decrease in this indicates that there was a
general decrease in S1 processing post manipulation [16]. The N30 SEP component is more complicated, and is generated by the motor, premotor and prefrontal cortex network activity, indicating that it is a marker of neural processing in these regions [14]. Significant decrease in this region suggest that there is a decrease of activity in these cortical loops, indicating a more normalized integration process, e.g. co-evaluation of sensory and motor information, and a reduction in physiological noise in the system [16].

In 2008, a similar study was reported by Haavik-Taylor and Murphy [97] that assessed changes using transcranial magnetic stimulation (TMS). The authors assessed the changes in sensorimotor integration following spinal manipulation in individuals with sub-clinical neck pain (i.e., individuals who have recurrent neck pain but none at the time of testing). Their outcome measures included short interval intracortical inhibition (SICI), short interval intracortical facilitation (SICF), and cortical silent periods (CSPs). Short interval intracortical inhibition and facilitation is a technique that involves subthreshold conditioning of a targeted cortical area followed by a suprathreshold test stimulus [98]. At higher frequencies of stimulation (1 to 6 milliseconds between stimuli), the test has an inhibitory response on the motor cortex [99], yet at lower frequencies (8 to 30 milliseconds between stimuli) the test has a facilitatory effect [99]. It is thought that the SICI is likely to relate to cortical inhibition of movement [100], whereas SICF is directly related to cortical facilitation of movement [101]. Motor evoked potentials (MEPs) are the recorded electrical activity in a muscle following activation of central motor pathways [102] as a direct result of TMS. CSPs relate to the changes in
proprioceptive input and partly by activation of descending inhibitory controls [103]. It has been reported CSPs decrease in SMI disorders like dystonia [104, 105].

To determine the SICI and the SICFs, Haavik-Taylor et al. measured MEPs in the abductor pollicis brevis muscle following the suprathreshold test stimulus of the testing paradigm. The authors found that immediately after the cervical spine manipulation, there was an increase in the SICF, a decrease in the SICI and a shortening of the CSP in the abductor pollicis brevis. However, when the measures were repeated in the extensor indices, they found the opposite effect: decreased SICF and lengthening of the CSP. Therefore, they concluded that SMT may alter SMI, however it was difficult to determine where the beneficial effects were occurring [97].

Several other studies have investigated the mechanisms into which SMT might help restore disordered SMI [15, 96]. However, it is important to mention the significant limitations of these papers [14-16, 95-97]. Each of the aforementioned papers include in their design sub-clinical neck pain participants. The authors define sub-clinical neck pain as intermittent pain that is absent on the day of testing. While there may be legitimate reasons to bar painful participants in EEG studies [106], there is no reason to exclude them from TMS studies. Additionally, these studies claimed to have manipulated a sub-clinical dysfunctional joint that was painful upon palpation. However, reliability of passive assessment of intervertebral motion is poor at best [107]. Furthermore, their control condition was a sham manipulation in lieu of an asymptomatic population. Thus, while it is fair to claim that spinal manipulation may improve SMI, claims that subluxed vertebral joints cause SMI deficits are hard to support.
2.5.c Effects of SMT as Assessed by Functional Magnetic Resonance Imaging

As illustrated above, the supraspinal effects of SMT have been measured by a variety of measurement tools. TMS, EEG, and SEP have all been used to assess changes associated with SMT. While fMRI has been used extensively to measure cortical organization [19, 28, 33, 37, 40, 42, 44, 46, 108], there has been relatively few studies that have utilized it to study the effects of SMT. Functional MRI is a safe and non-invasive imaging modality that can assess changes in oxidation states. Hemoglobin has different magnetic properties depending on the concentration of oxygen [109]. Therefore, as different parts of the brain activate, there is an increase in the oxyhemoglobin to that area. By measuring this change in the oxyhemoglobin, one can have an indirect or proxy measurement of the amount of activation in the area [109].

A seminal study that utilized fMRI to assess the central changes associated with spinal manipulation was reported in 2013 by Sparks et. al. Ten healthy volunteers (female n=5) received noxious stimuli to the cuticle of the index finger while undergoing fMRI. Following the baseline fMRI, the individuals then received a thoracic manipulation targeting the mid-thoracic spine. After the manipulation, the participants underwent a follow-up fMRI after which they rated their perceived pain to the noxious stimulant. The authors found that following spinal manipulation there was a decrease in activation as measured by BOLD response in the bilateral cerebellum, amygdala, thalami, periaqueductal gray (PAG), insular cortex, anterior cingulate cortex (ACC), somatosensory cortices, supplementary motor area (SMA) and the premotor area.
Overall, there was a 31% reduction in the BOLD response with a significant relationship between the insular cortex and pain reduction.

While there was no control group to compare the manipulation to and there was a limited sample size, this was the first study that assessed the cortical changes following SMT utilizing fMRI. Each of the aforementioned locations where a reduction of signal was observed is frequently associated with what is known as the “pain matrix.” While the pain matrix is thought to be a genetically pre-determined network of neurons that activate in response to pain[110, 111], its capacity to discriminate pain from salient information has been questioned[112, 113]. Regardless, this study demonstrated that by performing spinal manipulation to the mid thoracic spine, significant reductions in BOLD activation occur. However, a significant limitation to this study was the absence of individuals with pain. Sparks et. al. only imaged asymptomatic individuals, making the extrapolation of these findings difficult.

In 2014, Gay et. al. [114] assessed changes in resting state functional connectivity in 24 asymptomatic participants. Put simply, functional connectivity it is the level of concurrent activation between two remote regions of the brain [115]. The 24 participants were divided into three groups: SMT, spinal mobilization, or therapeutic touch. The functional connectivity was measured via fMRI between the S1, S2, thalamus, ACC, posterior cingulate cortices (PCC), anterior and posterior insula, and PAG. The authors found that following spinal manipulation there were system wide changes in connectivity, both increased and decreased depending on the regions
selected. However, while it was shown that SMT can alter functional connectivity, the amount change did not differ between any of the treatment groups.

One of the biggest limitations of this study was the lack of a symptomatic population. With no marker for improvement, it would be erroneous to conclude that the alteration of the resting functional connectivity between different regions or the brain indicates any sort of improvement. Also, they made no attempt to determine the stability of the functional connectivity measure by a lack of a control group.

There are several limitations in these studies that need to be addressed. First, neither study used a symptomatic population. Sparks et al. used a completely asymptomatic population while Gay et al. used an asymptomatic population with induced low back pain. The effects of spinal manipulation may be different in individuals with chronic pain and so future studies should address this gap. Second, neither study used a true control group; therefore, the effects of their treatment may simply be due to test-retest variability inherent in fMRI. Future studies should incorporate a no-intervention control to assess for the effects unique to the manipulation.

Taken together, these Sparks et. al., and Gay et. al., provide preliminary proof of concept that spinal manipulation has a central effect. These two studies demonstrate that spinal manipulation has a potential effect on brain activation in the pain matrix, while also altering resting state functional connectivity. However, a key knowledge gap is how spinal manipulation might affect cortical activation in during lumbopelvic tasks, as it is during these motions that individuals with cLBP commonly report having pain.
REFERENCES


CHAPTER 3

TASK-BASED FUNCTIONAL CONNECTIVITY AND BOLD ACTIVATION DURING WITHIN-SCANNER PERFORMANCE OF LUMBOPELVIC MOTOR TASKS: AN fMRI STUDY

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1 Jordon MK, Beattie PF, Silfies SP, Bialosky JE and Stewart J. To be submitted to *Neuroimage*. 
ABSTRACT

Introduction: Chronic low back pain (cLBP) continues to be one of the most common health conditions in the United States. Despite an enormous amount of published research, there are no treatments for this condition that consistently improve outcomes. To identify more effective interventions, researchers having increasingly shifted their focus toward the role of cortical function on the development and persistence of cLBP.

Purpose: The purpose of the current study is to determine the cortical activation response and functional connectivity that occurs during performance of lumbopelvic tasks in healthy individuals.

Methods: Seventeen pain-free, right-handed adults participated in this study (10 female, age 27.8 ± 5.8 years). Participants were trained to perform a modified bridging task in which they pushed the back of the left knee, right knee, or both knees into a 22 cm bolster while undergoing scanning. Whole brain activation and functional connectivity of a constrained motor network (bilateral precentral gyrus (PreCG), bilateral postcentral gyrus (PostCG), and bilateral supplementary motor area (SMA)) were analyzed.

Results: Whole brain activation during the bilateral bridging task included multiple areas in the sensorimotor network (bilateral PreCG, right PostCG, and left SMA). Group-level ROI-to-ROI analysis revealed significant correlations between all ROIs within the constrained motor network except for the left SMA to left PostCG during the unilateral
bridging tasks. The seed-to-voxel analysis demonstrated significant correlations between the sensorimotor network of the bilateral SMA, PreCG, and PostCG.

**Conclusion:** This is the first study to report in depth assessment of whole brain activity and measurement of functional connectivity of a restricted motor network during lumbopelvic task performance. Although our results are preliminary, there appears to be lower connectivity during lumbopelvic task performance when compared to literature of the upper extremity.

**Key words** [Back pain, motor control, brain imaging]

1.0 Introduction

Chronic low back pain (cLBP) continues to be one of the most common health conditions in the United States resulting in increasingly higher economic and social burdens on society [1-6]. Interestingly, despite an enormous amount of published research, there are no treatments for this condition that consistently improve outcomes. To identify more effective interventions, researchers having increasingly shifted their focus toward the role of cortical function on the development and persistence of cLBP. For example, alterations in cortical representation [7-11], response to sensory stimuli[12-16], and resting state functional connectivity[14, 15, 17-21] have been observed. There is, however, a paucity of research reporting the changes in cortical function that occur in individuals with cLBP during the performance of motor tasks.
Currently, the research into the role of central motor systems and pain processing has relied on the performance of upper extremity motor tasks [22, 23]. However, investigations into low back pain may necessitate utilization of lumbopelvic motor tasks. Previous research has demonstrated that cLBP results in specific cortical changes to the lumbopelvic region; during both muscle [9, 10, 24] and cutaneous [7, 8] stimulation. Furthermore, biomechanical research has suggested deficits in the lumbopelvic motor control in individuals with cLBP [25-29]. Therefore, utilizing lumbopelvic systems in a fMRI task holds great promise when studying motor system changes directly associated with lumbopelvic movement that occur in those with cLBP.

In a previous study, we utilized a combination of EMG and fMRI to describe a series of motor tasks that recruited lumbopelvic musculature while being performed in the MRI scanner [66]. During this previous study, we were able to establish the feasibility of measuring BOLD patterns while performing these lumbopelvic tasks in the scanner. In the current study we build on these findings by describing in detail the whole brain activation and functional connectivity patterns during task performance in a larger sample. Additionally, this research will help address a gap in the literature. Previous research has investigated the effective connectivity during an ankle flexion task [30], but we are not aware of any studies that have described the relative strengths of functional connectivity during lumbopelvic motor tasks. Addressing this deficit in the literature is important, as understanding the normative data is imperative before examination of changes that may occur in individuals with cLBP.
The purpose of the current study is to determine the cortical activation response and functional activity that occurs during performance of lumbopelvic tasks in healthy individuals. This study tested 3 hypotheses: 1). Pain-free individuals would have strong activation in the sensorimotor network that was medially-oriented in the precentral gyrus (PreCG) and postcentral gyrus (PostCG); 2). During the bilateral bridging task there would be bilateral activation, with the unilateral bridging tasks resulting in unilateral, contralateral activation; and 3). The functional connectivity of the sensorimotor network would be robust. Confirmation of these hypotheses would allow for future studies to better interpret the differences observed in individuals with cLBP.

2.0 Material and methods

2.1 Subjects

Seventeen pain-free participants were recruited to participate in this study (10 female, age 27.8 ± 5.8 years). Inclusion criteria included: 1) being right-hand dominant; 2) being between the ages of 18-60; 3) no history of activity limiting low back pain; 4) no history inflammatory joint disease or cancer; and 5) no contraindications for undergoing MRI. Informed consent was obtained from all participants, and approval for this study was given by the University of South Carolina Institutional Review Board.

2.2 Motor Task

Participants were trained in the different motor tasks prior to undergoing fMRI. The tasks included a modified bridging task where participants pushed the back of the left knee (unilateral left), right knee (unilateral right), or both knees (bilateral) into a
firm 22 cm bolster to slightly unweight their hips. Instructions to breathe normally were given to minimize the potential for physiological noise in the BOLD response. Training for the task was also done inside the MRI to familiarize the participant with the scanning environment. The bridging tasks were chosen to activate the muscles recruited during the performance of functional movements such as ambulation or sit-to-stand transitions. Additionally, these tasks resemble exercises that are routinely utilized by Physical Therapists to treat individuals with low back pain. In our previous work, we demonstrated that participants were able to follow the instructions accurately and that the bridging tasks elicited activation in the lumbar multifidus, erector spinae, the internal oblique/transverse abdominis, external oblique, rectus abdominis, gluteus maximus, and the hamstring muscles[31]. Participants were also trained in a bilateral ankle plantarflexion and abdominal tightening task; however, these data were not included in the current analysis.

Participants were trained to minimize head movement during motor task performance prior to scanning. Additionally, all participants were scanned with the head secured with foam pads within the MRI head coil in order to further reduce head movement.

2.3 fMRI Data Acquisition

Data were collected using a 3T Siemens MRI. Eight participants completed fMRI on a 3T Trio scanner using a 12-channel head coil (447 volumes; 42 axial slices; 2.5 mm thick; TR = 1550ms; TE = 34ms; matrix = 64x64 voxels; flip angle = 71°, 215x215mm FOV)
while 9 completed their fMRI on a 3T Prisma scanner using a 20-channel head coil (765 volumes; 58 axial slices; 2.5 mm thick; TR = 1000ms; TE = 37ms; matrix 64 x 64 voxels; flip angle =61˚; 220x220mm FOV). For both scanners, a sagittal T1-weight MPRAGE protocol was used to acquire high-resolution structural images (192 slices; 1mm thick; TR = 2250ms; TE = 4.11ms; matrix=1 x 1 x 1mm3; 256x256 FOV).

A block design was utilized where each task was performed in random order for 12 seconds with a 9.5 second verbal instruction period preceding each task. There were at total of six task blocks with a 12 second rest period interleaved between each one (Figure 3.1). Participants were visually monitored to ensure they were performing the correct task throughout. The task order was recorded and the instructions were delivered to the participants using EPrime (Psychology Software Tools, Inc., Sharpsburg, PA).

2.4 Data Preprocessing

All data were processed using Statistical Parametric Mapping (SPM 12, Wellcome Department of Cognitive Neurology, London, UK), implemented in MATLAB R2017a (Mathworks, Natick, MA, USA). Initially, for each run, every volume was realigned to the first and unwarped. The mean image for each participant was then normalized to standard Montreal Neurological Institute (MNI) space. Once the normalization was completed, the parameters were then applied to each volume in the functional run and data were resampled to 2 mm x 2 mm x 2 mm voxels. Smoothing was then applied using an isotropic Gaussian kernel 8 x 8 x 8 mm3 full width at half maximum. Head motion
was then assessed for all analyzed data using the Artifact Detection Tool toolbox (http://www.nitric.org/projects/artifact_detect). The first derivative of the head motion was used to screen for excessive head motion, and all outliers (defined as a greater than 2mm difference from the previous volume) were de-weighted during the statistical analysis (mean number of outliers per run = 2, ranged from 0 to 8).

2.5 Statistical Analysis

2.5.1 Functional Imaging Analysis

First-level analysis was performed using a general linear model for each participant [32, 33]. Contrast maps were calculated for each task period versus rest using the first derivative of head motion for all six directions as a regressor of no interest. The contrast maps for each of the bridging tasks were then moved to a second-level random effects analysis. A group analysis using a factorial design was performed with a factor for condition (bilateral, unilateral left, and unilateral right). We analyzed the main effect for each condition, as well as the combined effect for all bridging tasks. Additionally, a t-contrast between the unilateral left and right tasks was created in order to determine differences in activation during unilateral bridging. Group-level results were thresholded at a p-value less than 0.05 that was corrected for multiple comparisons using familywise error (FWE).

2.5.2 Task-Based Functional Connectivity Analysis

Functional connectivity during movement was analyzed using the CONN toolbox[34]. Each participant’s data was imported into the toolbox along with the task
onsets and durations. This allowed for the accounting of each task in the BOLD time-series. Confounds were then removed via CONN’s CompCor algorithm for physiological noise [35] to reduce their effect on the functional connectivity values. We selected six seed ROIs we believed represented the motor network likely to be utilized during the motor tasks based on previous work[31]. These included the bilateral precentral gyrus (PreCG), bilateral postcentral gyrus (PostCG), and bilateral Supplementary Motor Cortex (SMA). To create the ROIs, we first created an overall activation map of the mean activation of the three bridging tasks against rest. We then used previously defined masks of PreCG, PostCG and SMA [36] to extract the peak of activation from within these different regions. This resulted in the MNI coordinates: Right PreCG = 8, -34, 60, Left PreCG = -14, -30, 64, Right SMA = 6, -18, 62, Left SMA = -6, -20, 62, Right PostCG = 14, -38, 66, Left PostCG = -20, -36, 60. A 5 mm radius sphere centered on the peak of activation was created using MarsBaR, and then used as our seed ROIs.

We then performed an ROI-to-ROI analysis to determine the functional connectivity strength among a priori seed ROIs and target regions in the brain. This allowed us to investigate the connectivity within our predefined network. However, as this approach limits the scope of inquiry to only the a prior ROIs, we also performed a seed-to-voxel analysis between each ROI and every other voxel in the brain in order to see if different regions of the brain were functionally connected to our proposed motor network during the performance of the lumbopelvic motor tasks.

We used a weighted GLM approach for the ROI-to-ROI connectivity analysis. A bivariate correlation was computed separately on the individual’s BOLD time series for
each pair of source and targeted ROIs. Standardized procedures programmed within the CONN toolbox performed a Fisher’s Z-transformation to the bivariate correlations to improve the assumptions of normality [34]. ROI-to-ROI correlation matrices were produced and the Z-transformed correlation values from our ROIs were extracted for each participant. The correlation values were then imported into a second-level group analysis to determine mean functional connectivity values between our ROIs. A one-way ANOVA was performed to assess differences between the tasks. While in our analysis of overall activation we chose to correct for multiple comparisons using FWE, we chose to use the False Discovery Rate (FDR) method in our ROI-to-ROI analysis. We chose to do this because within the CONN toolbox the FWE correction is applied over the entire connectivity matrix while FDR correction is applied over just the chosen seed ROIs.

We also performed a seed-to-voxel analysis to measure the strength between each of the a priori ROIs and all the other voxels in the brain. First-level seed-to-voxel analysis consisted of performing bivariate temporal correlations among the individuals’ time-series data from our generated a priori ROIs and all the other voxels in the brain for each of the fMRI runs. We then used the standardized approach within the CONN tool box to perform a Fisher’s Z-transformation [34]. These correlations were then imported into a second-level group analysis to determine mean levels of connectivity within our group and to determine if there were any differences in connectivity patterns between tasks. A one-way ANOVA with the within-subject variable of task was used to determine if any differences were found between the ROIs in both the ROI-to-ROI and the Seed-to-Voxel analysis. Group-level results were thresholded at a p-value less than
0.05 that was corrected for multiple comparisons using FDR in order to stay consistent with the ROI-to-ROI analysis.

3.0 Results

3.1 Brain Activation Patterns

3.1.1 General Activation Pattern

A summary of the whole brain activation can be found in (Table 3.1). Activation during the bilateral bridging task included multiple areas in the sensorimotor network (bilateral PreCGs, right PostCG, and left SMA). Additionally, the peaks of activation (PoA) present in the PreCG and PostCG were located medially in the respective gyri.

Sensorimotor activation was found during the unilateral bridging tasks, with the strongest activation found in the contralateral PostCG, PreCG and the SMA. Similar to the bilateral bridge task, the location of the POA in the PostCG and PreCG clusters was along the medial border. Interestingly, while there was strong activation in the contralateral hemisphere during the unilateral bridging tasks (Figure 3.2), when comparing the right and left unilateral bridging tasks against each other there were no significant differences in activation found using a FWE corrected p-value= 0.05.

Additional cortical activation during the bridging tasks was found in the left Putamen, left Rolandic Operculum, left Inferior Frontal Gyrus, left Midcingulate Cortex, and right Supramarginal Gyrus as outlined in Table 3.1.
3.2 Functional Connectivity Analysis

3.2.1 ROI-to-ROI Analysis

Figure 3.2 summarizes the connectivity values within the motor network that was analyzed. Group-level ROI-to-ROI analysis revealed significant correlations between all ROIs except for Left SMA to Left PostCG during the unilateral bridging tasks. There were consistently stronger correlations in the right hemisphere during performance of the left bridging task compared to the right bridge. However, in the left hemisphere there was no consistent trend towards a particular pattern. Interestingly, the Left SMA to Left PostCG connection was not significant during the unilateral bridging tasks and had a very low correlations when compared to the other conditions. The ANOVA revealed that the functional connectivity between the ROIs did not significantly differ between the tasks.

3.2.2 Seed-to-Voxel Analysis

The seed-to-voxel analysis demonstrated similar findings to that of the whole brain analysis (Figure 3.3). As outlined in Tables 3.2-3.19, there were strong connections within the sensorimotor network of the bilateral SMA, PreCG, and PostCG. Bilateral PostCG had strong connections with the left precuneus during all bridging tasks, while the left PostCG had strong connections to the right precuneus during the bilateral and left bridging tasks only. Also, the left PreCG had a strong functional connection to the left superior frontal gyrus during all three bridging tasks.
A one-way ANOVA by task found there to be a significant difference in functional connectivity between the right SMA and a cluster of voxels centered in the posterior portion of the midcingulate cortex (MNI coordinates -2, -32, 38) when corrected at the p-FWE 0.05 level. To further explore this, we created a functional ROI from the connectivity results using MarsBar and performed an ROI-to-ROI analysis between the functional ROI and the right SMA. We found that during the bilateral bridge there was no statistically significant connection between these two regions, while during the unilateral bridging tasks they were strongly anti-correlated (Table 3.20).

Other regions that were found to be functionally connected to the restricted sensorimotor network were the bilateral anterior cingulate cortex, bilateral superior parietal lobule, bilateral superior frontal gyrus, right central opercular cortex, right inferior frontal gyrus, right insular cortex, and left thalamus (Tables 3.2-3.19).

4.0 Discussion

4.1 Sensorimotor activation during lumbopelvic motor tasks.

As hypothesized, during the bridging tasks we found strong activation in the sensorimotor areas of the brain. While this study is unique in using lumbopelvic motor tasks, previous literature investigating the cortical activation during similar lower limb tasks supports the general activation patterns we found. During investigations into unilateral ankle[37-40], knee[39-42], and toe[39, 40] movements, previous research report consistent activation in the SMA, Precentral Gyrus, and Postcentral Gyrus. These
findings support our inclusion of these three regions into our motor network during the functional connectivity analysis.

Previous studies have found that the pre- and postcentral gyrus are somatotopically organized [37, 39, 43-45]. Specifically, the feet are represented medially and the hands are represented laterally. For example, Kapreli et. al. [39] assessed lower limb sensorimotor networks during opposition of the fingers and extension-flexion of the knee, ankle, and toes. These authors reported that during highly controlled extension and flexion movements of the knees, ankles, and toes, the activation was located medially in the sensorimotor cortex when compared to the activity observed during finger opposition. In our study, during the bridging tasks, the activation also occurred medially in both the PreCG and the PostCG.

Activation during the bilateral bridge occurred nearly equally between the hemispheres in the sensorimotor regions, while during the unilateral bridging tasks the stronger activation was in the contralateral hemisphere. Our findings are consistent with previous investigations reporting the laterality of lower limb movement tasks [40, 42, 46]. However, activation was present in bilateral hemispheres during the unilateral bridging tasks. These results can in part be explained by the findings of Volz et. al. in 2015[30] who reported that during lower extremity task performance the ipsilateral M1 was not inhibited by the premotor areas and actually exerted a significant excitatory influence on the contralateral M1. Therefore, while task performance is predominately represented in the contralateral PreCG, a lack of inhibition and contralateral excitation might result in increased activation in the ipsilateral PreCG relevant to task.
Furthermore, in our previous work we demonstrated via EMG that these tasks require stiffening of the bilateral trunk musculature[31]. During the isometric hold of the bridging tasks, the participants are required to stabilize their trunk as they unweight their hips from the table. As this stabilization requires bilateral trunk activation, this may further explain the bilateral activation in the sensorimotor cortices.

4.2 Connectivity of sensorimotor regions of the brain during lumbopelvic motor tasks

To the authors’ knowledge, this is the first time that functional connectivity during lumbopelvic task performance has been described. With the exception of the left SMA to left PostCG connectivity during unilateral bridging tasks, the sensorimotor network we described was significantly connected during the performance of lumbopelvic tasks. However, while the ROIs were significantly connected, the relative strength of these connections were relatively weak.

Aside from the weaker connectivity, the results from the ROI-to-ROI analysis were largely as hypothesized. The function of the SMA is largely devoted to movement planning and early motor preparation[47] facilitated by structural connections with the PreCG[48]. These strong structural connections have also been found between the PostCG and PreCG[48, 49] which is imperative for translating sensory information into action. Considering the strong structural connections and similarities in function, our results fit well within the established literature.

Several areas were functionally connected to ROIs within our constrained motor network that are important for execution and performance of motor tasks. For
example, the precuneus was functionally connected with the PostCG during performance of all three bridging tasks. In previous studies, the precuneus has been found to play an important role in the execution of spatially complex tasks and coordinating of movements [50]. Our previous study using EMG revealed that participants have to utilize thigh, hip, lumbar, and abdominal musculature in order to perform the different motor tasks[31]. The coordination between these four different muscle groups along with the ongoing sensory feedback during the isometric contractions could help to explain the connectivity between the PostCG and the Precuneus. The right inferior frontal gyrus has been has also been implicated in the initiation of motor movements[51], while the right superior frontal gyrus helps to generate complex movements that involve several muscle groups[52, 53]. Our task was deliberately created to involve complex motor patterns that incorporated multiple muscles groups, so activation in these areas was expected.

The superior parietal lobule has strong and reciprocal connections with the PreCG which allows for the processing of different types of “sensorimotor transformations”. This connection contributes to the superior parietal lobule's role in sensorimotor integration as well as motor control and planning[54], which hypothetically would be required during the performance of a sustained bridge. Additionally, the anterior cingulate cortex, which plays a key role in spatially complex bimanual coordination[50], was only found to be active during the bilateral bridging tasks but not the unilateral bridging tasks.
Lastly, when we performed a one-way ANOVA to determine if there were any differences in functional connectivity between the bridging tasks, we found that during the bilateral bridging task the right SMA and midcingulate cortex were not significantly correlated, while during the unilateral bridging tasks they were significantly anti-correlated. While speculative, this may be the result of default coupling that is inherent in bilateral limb tasks[50]. Wenderoth et. al. in 2005 [50] performed a study comparing bimanual to unimanual hand task performance. These authors reported that areas of the cingulate cortex that were associated with the bilateral task were not correlated during the unilateral task. They hypothesized that the cingulate cortex exerted a modulatory effect on the supplementary motor area to suppress the default coupling, or “intrinsically favored coordination tendencies”, of the bilateral task. This may indicate that during performance of the unilateral bridging task, the midcingulate cortex was decoupled with the SMA to allow for a unilateral motor task. However, it should be noted that neither the ACC nor the MCC were active during the whole brain analysis.

4.3 Limitations

Unlike previous research using lower extremity tasks, we did not incorporate external stabilization devices to reduce motion artifact and control movement. [38-40, 55]. While stabilizing the joint decreases task-related head movement, this isolation may influence the findings. There is an inherent motor variability during movement performance[56] and the ability to compensate for this variation is vital for optimal feedback control[57]. Supplementing joint support during a task may reduce the ability to detect changes in individuals with chronic pain. Stabilizing joint motion appears to
improve sensorimotor function[58-60] and may inadvertently diminishes differences that may be found between asymptomatic individuals and individuals with cLBP [9, 10, 24]. As such, lower extremity motor tasks that are unencumbered by external support may be the best method of elucidating the cortical changes associated with cLBP. Furthermore, with an average of 2 out of 765 volumes being removed for excessive motion, our task did not seem to create excessive artifact. Finally, two separate MRIs were used for data collection: a 3T Siemens Trio scanner and a 3T Siemens Prisma scanner. While the scanning parameters were slightly different between the two different scanners, there did not appear to be large differences in the first level analysis between the subjects.

5.0 Conclusions

We examined activation and functional connectivity during the performance of unsupported bilateral and unilateral lumbopelvic motor tasks. Robust activation patterns were observed in the sensorimotor network that demonstrated laterality specific to the task. Within our constrained motor network of the PreCG, PostCG, and SMA we found extensive connectivity between these regions and among a wider motor network. Although our results are preliminary, there appears to be lower connectivity during lumbopelvic task performance when compared to literature of the upper extremity. This study lays a foundation for future investigations that examine how this motor network might be altered in individuals who exhibit low back pain.
Figure 3.1 - Outline of fMRI protocol.
Table 3.1 – Results from the whole brain analysis during the three different tasks

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<th>Cluster p(FWE-corr)</th>
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<th>T-Score</th>
<th>x,y,z (mm)</th>
<th>Location</th>
</tr>
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BB > Rest - Bilateral bridge task compared to rest
LB > Rest - Left Unilateral Bridge compared to rest
RB > Rest - Right Unilateral Bridge compared to rest.
All p-Values are FWE corrected at 0.05.

Figure 3.2 – Cortical activation patterns in the Bilateral Bridge, Left Unilateral Bridge, and Right Unilateral Bridge tasks. Scale is Z-Scores.
Figure 3.3 – Seed-to-Voxel results for the right Precentral Gyrus during the left bridging task. Scale is Z-Scores

Figure 3.4 - Graphical representation of bivariate correlations between ROIs for the three different motor tasks. All correlations are significant at FWE 0.05 unless indicated with a * (* - non-significant correlation)

Table 3.2 – Results from Seed-to-Voxel analysis for the right Supplemental Motor Area during the bilateral bridging task.

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p-FDR indicates that the p-value is False Discovery Rate corrected.

Table 3.3 – Results from Seed-to-Voxel analysis for the left Supplemental Motor Area during the bilateral bridging task.

p-FDR indicates that the p-value is False Discovery Rate corrected.
Table 3.4 – Results from Seed-to-Voxel analysis for the right Precentral Gyrus during the bilateral bridging task.

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p-FDR indicates that the p-value is False Discovery Rate corrected.
Table 3.5 – Results from Seed-to-Voxel analysis for the left Precentral Gyrus during the bilateral bridging task.

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p-FDR indicates that the p-value is False Discovery Rate corrected
## Table 3.6 – Results from Seed-to-Voxel analysis for the left Postcentral Gyrus during the bilateral bridging task.

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<th>peak p-FDR</th>
<th>peak T</th>
<th>x,y,z (mm)</th>
<th>Location</th>
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p-FDR indicates that the p-value is False Discovery Rate corrected
Table 3.7 – Results from Seed-to-Voxel analysis for the right Postcentral Gyrus during the bilateral bridging task.

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<th>x,y,z (mm)</th>
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p-FDR indicates that the p-value is False Discovery Rate corrected
Table 3.8 – Results from Seed-to-Voxel analysis for the right Supplemental Motor Area during the left bridging task.

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<th>peak T</th>
<th>x,y,z (mm)</th>
<th>Location</th>
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p-FDR indicates that the p-value is False Discovery Rate corrected
Table 3.9 – Results from Seed-to-Voxel analysis for the left Supplemental Motor Area during the left bridging task.

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<th>x,y,z (mm)</th>
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p-FDR indicates that the p-value is False Discovery Rate corrected
Table 3.1 – Results from Seed-to-Voxel analysis for the right Precentral Gyrus during the left bridging task.

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p-FDR indicates that the p-value is False Discovery Rate corrected.
Table 3.1 – Results from Seed-to-Voxel analysis for the left Precentral Gyrus during the left bridging task.

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<th>peak T</th>
<th>x,y,z (mm)</th>
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p-FDR indicates that the p-value is False Discovery Rate corrected
Table 3.1 – Results from Seed-to-Voxel analysis for the left Postcentral Gyrus during the left bridging task.

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<th>cluster p-FDR</th>
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2 0.0000 63 0.1717 10.91 14,-6,72 Right Supplemental Motor Area

3 0.0000 35 0.1737 9.99 2,-16,56 Right Supplemental Motor Area

p-FDR indicates that the p-value is False Discovery Rate corrected
Table 3.13 – Results from Seed-to-Voxel analysis for the right Postcentral Gyrus during the left bridging task.

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p-FDR indicates that the p-value is False Discovery Rate corrected
Table 3.1 – Results from Seed-to-Voxel analysis for the left Supplemental Motor Area during the right bridging task.

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p-FDR indicates that the p-value is False Discovery Rate corrected
Table 3.15 – Results from Seed-to-Voxel analysis for the right Supplemental Motor Area during the right bridging task.

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p-FDR indicates that the p-value is False Discovery Rate corrected
Table 3.1 – Results from Seed-to-Voxel analysis for the left Precentral Gyrus during the right bridging task.

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p-FDR indicates that the p-value is False Discovery Rate corrected
Table 3.1 – Results from Seed-to-Voxel analysis for the right Precentral Gyrus during the right bridging task.

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p-FDR indicates that the p-value is False Discovery Rate corrected
Table 3.1 – Results from Seed-to-Voxel analysis for the left Postcentral Gyrus during the right bridging task.

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<th>x, y, z (mm)</th>
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p-FDR indicates that the p-value is False Discovery Rate corrected
Table 3.19 – Results from Seed-to-Voxel analysis for the right Postcentral Gyrus during the right bridging task.

<table>
<thead>
<tr>
<th>Cluster Number</th>
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p-FDR indicates that the p-value is False Discovery Rate corrected
Table 3.20 – Results from Seed-to-Voxel One-Way ANOVA with subsequent ROI-to-ROI posthoc analysis

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<th>size p-FDR</th>
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### R SMA to MCC

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<th>T</th>
<th>p-FDR</th>
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</thead>
<tbody>
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<td>-1.26</td>
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</tr>
<tr>
<td>Left Bridge</td>
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<tr>
<td>Right Bridge</td>
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</tbody>
</table>

R SMA - right supplementary motor area; MCC - Midcingulate Cortex
REFERENCES


CHAPTER 4

INDIVIDUALS WITH CHRONIC LOW BACK PAIN EXHIBIT ALTERATIONS IN CORTICAL ACTIVITY DURING LUMBOPELVIC MOTOR TASKS

ABSTRACT

Introduction: Chronic low back pain (cLBP) continues to be a major burden on the US economy. Despite enormous amount of research, changes that occur in the central nervous system associated with cLBP remain unclear. A better understanding of these changes will have a meaningful impact for the targeting of specific systems during the rehabilitation of people with cLBP.

Purpose: The purpose of the current study is to determine the differences in cortical activation between individuals with and without cLBP while performing lumbopelvic motor tasks during functional magnetic resonance imaging.

Methods: A total of 19 asymptomatic (12 female, age 29 ± 4.5 years) and 23 symptomatic individuals (19 female, age 30 ± 11 years) completed the study. Participants were trained to perform a bridging task in which they pushed the back of their legs unilaterally and bilaterally into a 22 cm firm bolster while undergoing scanning. Whole brain activation and functional connectivity of a constrained “motor network” (bilateral precentral gyrus (PreCG), supplementary motor area (SMA), and putamen) and a “motor-pain network” (bilateral insula, bilateral midcigulate cortex (MCC), and putamen) were analyzed.

Results: The whole brain analysis revealed that individuals with cLBP exhibited a broader network of activation (additional activation in the insula, MCC, putamen, Rolandic operculum, amygdala, and supramarginal gyrus) when performing lumbopelvic tasks when compared to asymptomatic individuals. Those with cLBP had greater
activation in the ipsilateral hemisphere when performing unilateral bridging tasks than did the asymptomatic individuals.

**Conclusion:** Individuals with cLBP exhibited a broader network of activation with decreased laterality during unilateral tasks. Our findings suggest a network consisting of the Putamen, the MCC, and the Insula that contribute to the appraisal of pain perception and its integration with motor performance. Within this network, and a truncated motor network, there is a tendency for stronger connectivity in the symptomatic group with the exception of the Putamen.

**Key words** [fMRI, motor control, brain imaging]

**INTRODUCTION**

Chronic low back pain (cLBP) continues to be a major burden on the US economy, affecting up to 14% of the US population [1] and resulting in the largest health care costs and lost productivity time of any musculoskeletal disease [2-6]. Surprisingly, despite an enormous amount of research, the physiologic reasons for the development and persistence of cLBP remain unclear [7, 8]. Historically, researchers and clinicians have focused upon events occurring in body wall structures, spinal joints and peripheral nociceptive structures as being the key triggers for cLBP. Recent advances in neural imaging however, have revealed that central neural events may also be strongly linked to the symptoms and recovery potential for individuals with cLBP [9-12]. For example, functional magnetic resonance imaging (fMRI) findings of alterations in cortical representation [13-17], sensory perception[18, 19], and resting state functional
connectivity[9, 10, 20, 21] have all been shown to be different in people with cLBP when compared to asymptomatic individuals.

One emerging, yet under-reported phenomena is the way in which variations in cortical activity during the performance of lumbopelvic motor tasks may be linked to cLBP. Functional MRI has been used to describe changes in cortical activation during motor performance in individuals with chronic knee pain [22] and jaw pain[23], but to the authors’ knowledge not in individuals with cLBP. Furthermore, utilization of condition specific motor tasks is important in understanding the role of cLBP in movement systems. In previous research assessing experimental painful stimulation, different neural networks are activated when the painful stimulus is applied to a clinically relevant site compared to a neutral one [12]. Therefore, assessing brain activity in individuals with cLBP while performing tasks that involve the affected body region may provide key insights into the effects of pain on motor systems.

In previous studies we evaluated the feasibility of performing lumbopelvic tasks that engage the abdominal, gluteal, and low back musculature during fMRI[24]. These muscles were chosen because improving their strength and control are key components of intervention during rehabilitation [25], and understanding the cortical impact of pain during activation of these regions is of particular importance. We were able to verify using EMG that these lumbopelvic motor tasks activated the lumbopelvic musculature[24], and with a follow-up fMRI study we observed that asymptomatic individuals were able to perform these tasks within a scanner with acceptably low levels
of head movement and that performance of these lumbopelvic tasks produced anticipated activation within the sensorimotor network[26].

It has been shown that individuals with cLBP typically present with abnormal, and potentially injurious, spinal movement patterns [27-29]; however, it is unclear if these maladapted behaviors are driven by the peripheral or central nervous system. A better understanding of the mechanisms will have a meaningful impact for the targeting specific systems during the rehabilitation of people with cLBP.

Therefore, the purpose of the current study is to determine if differences in cortical activation exist between individuals who have cLBP and those who do not while performing condition specific motor tasks. This study tested two primary hypotheses: 1). individuals with cLBP would exhibit increased activation in pain-related cortical regions during motor performance; and 2). individuals with cLBP would demonstrate altered functional connectivity between cortical regions associated with pain and movement. Addressing these hypotheses will help clinicians better understand the role of pain on movement impairments in individuals with cLBP.

METHODS

Subjects

Participant demographics are outlined in Table 4.1. A total of twenty-five individuals with chronic low back pain (cLBP) and twenty-one asymptomatic individuals were recruited to participate in this study. In the symptomatic cohort, one participant became claustrophobic and was unable to complete the scan while technical difficulties
with the scanner prevented a second participant from completing the study. In the asymptomatic cohort, one participant was removed due to low signal while another participant exhibited abnormal brain morphology and was unable to participate in the study. This left a total of 19 asymptomatic (12 female, age 29 ± 4.5 years) and 23 symptomatic individuals (19 female, age 30 ± 11 years) who completed the study.

Study-wide inclusion criteria included that participants: 1) were right-hand dominant as determined by the Edinburgh Handedness Inventory [30]; 2) be between the ages of 18-60; 3) reported no inflammatory joint disease or cancer within the last 5 years; and 4) reported no medical or psychological conditions that would contraindicate an MRI. To be included in the asymptomatic group individuals had to have no history of activity-limiting low back pain. To be included in the symptomatic group individuals must have reported experiencing at least 3/10 pain during the majority of the days of the week for each week in the past six months. Study-wide exclusion criteria included: 1) a confirmed diagnosis of osteopenia/osteoporosis; 2) being pregnant or have been pregnant in the last year; 3) weighing more than 280 lbs; 4) currently taking narcotic medication regularly for back pain and unable to abstain for 48 hours; 5) having a loose metal object in the body; 6) receiving disability payments for a spinal problem or currently have a Worker’s Compensation claim; and/or 7) being involved in personal litigation for back pain. Informed consent was obtained from all participants, and approval for this study was given by the University of South Carolina Institutional Review Board. This data was collected from a larger randomized control trial which was
registered with ClinicalTrials.gov (ClinicalTrials.gov ID NCT02828501) prior to the recruitment of the first participant.

Motor Task

Participants were trained in a series of lumbopelvic motor tasks that are based on previously established studies. The tasks included a modified bridge where participants were instructed to push the back of their right knee (unilateral right), left knee (unilateral left), or both knees (bilateral) into a 22 cm firm bolster in order to slightly unweight their hips (Figure 4.1). The bridging tasks were chosen to activate the muscles recruited during the performance of functional movements such as ambulation or sit-to-stand transitions. Additionally, these tasks resemble exercises that are routinely utilized by Physical Therapists to treat individuals with low back pain. Prior to each scan the participants were instructed to breath normally to minimize the potential for physiological noise in the BOLD response and to keep their eyes closed. Additionally, the participants were trained in the task both outside of and within the scanner to ensure task fidelity and to reduce potential anxiety by familiarizing the participant with the scanning environment. A bilateral ankle plantarflexion and abdominal contraction task was included in the study but was not included in the current analysis.

To reduce head motion, participants were extensively trained in the tasks prior to the first scan with verbal feedback about performance. Additionally, the participants’ head was securely supported within the head coil with foam pads. In between the scans
the participants were reminded to keep their head as still as possible and to only move as much as the task required.

**fMRI Data Acquisition**

Data were collected on a 3T Siemens Prisma scanner using a 20-channel head coil (502 volumes; 58 axial slices; 2.5 mm thick; TR = 1000ms; TE = 37ms; matrix 64 x 64 voxels; flip angle =61˚; 220x220mm FOV). A sagittal T1-weight MPRAGE protocol was used to acquire high-resolution structural images (192 slices; 1mm thick; TR = 2250ms; TE = 4.11ms; matrix=1 x 1 x 1mm³; 256x256 FOV).

A block design was utilized that consisted of alternating blocks of task and rest (Figure 4.2). The task block consisted of each task being performed in random order for 11 seconds with a 4 second relaxation period following each task. After each task block there was an 8 second rest block where the participants were instructed to relax. This sequence was repeated six time per run, with each participant completing two runs. This led to a total of 132 seconds of each task being performed during the study.

Throughout each run, an investigator monitored the participants to ensure that they were performing the correct task. The task order was recorded, and the verbal instructions were delivered in a randomized order to the participants using the e-Prime system (Psychology Software Tools, Inc., Sharpsburg, PA).
Data Preprocessing

All data were processed using the Statistical Parametric Mapping (SPM 12, Wellcome Department of Cognitive Neurology, London, UK), implemented in MATLAB R2017a (Mathworks, Natick, MA, USA). For each run every volume was realigned to the first and unwarped. The mean image was then normalized to the standard Montreal Neurological Institute (MNI) space. The normalization parameters were then applied to each volume and the data were resampled to 2mm x 2mm x 2mm voxels. The data was then smoothed using an isotropic Gaussian kernel 8x8x8mm3 full width at half maximum. The Artifact Detection Tool (http://www.nitric.org/projects/artifact_detect) was then used to assess head motion during the scans. The first derivative of the head motion was used to screen for excessive motion with outliers being used as covariates of no interest during the statistical analysis (mean number of outliers = 0.5, ranging from 0 to 20 of 502 volumes).

Statistical Analysis

Functional Imaging Analysis

A general linear model (GLM) was used for the first level analysis for each individual[31, 32]. First-level contrast maps were calculated for each task period versus rest. To reduce noise, the first derivative of head motion for all six directions were used as a regressor of no interest. Following the head motion correction, the contrast maps for each of the bridging tasks were then moved to a second-level random effects analysis. A group analysis using a factorial design was performed with within-subject
factors of each condition and a between-subject factor of group. The main effect for each condition was analyzed as well as an overall activation map of the combined groups and tasks. This overall activation map served as a guide when choosing our ROIs for the connectivity analysis. The group-level results were thresholded at a p-value less than 0.05 corrected for multiple comparisons using familywise error (FWE).

Task-Based Functional Connectivity Analysis

We used the CONN toolbox implemented in MATLAB in order to assess the functional connectivity during movement. Each participant’s data was imported into the toolbox along the task onsets and durations to allow for the BOLD time series to be correctly accounted for. Confounds were then removed via CONN’s CompCor algorithm [33] in order to reduce the effect of physiological noise on the functional connectivity values. We then performed an ROI-to-ROI analysis using seed regions derived from our whole brain analysis.

Based on the results from the whole brain analysis we created nine ROIs: bilateral precentral gyrus (PreCG), bilateral insula, bilateral midcingulate cortex (MCC), bilateral putamen, and the supplementary motor area (SMA). Using MarsBAR, we created a 5 mm radius sphere centered on the maximum peak of activation found within these regions (MNI coordinates: SMA = 0, -16, 62; Right PreCG = 10, -30, 72; Left PreCG = -8, -30, 70; Right Insula = 46, 4, 8; Left Insula = -44, 2, 8; Right MCC = 10, -4, 44; Left MCC = -6, -6, 46; Right Putamen = 30, -10, 6; Left Putamen = -28, -14, 8). These ROIs were then imported into the CONN toolbox for our ROI-to-ROI analysis.
We used a weighted GLM approach for the ROI-to-ROI connectivity analysis. First level bivariate correlations were computed separately based on the individual’s BOLD time series between each ROI. In order to improve the assumptions of normality, we applied a Fisher’s Z-transformation to the bivariate correlations using a standardized procedure programmed within the CONN toolbox [34]. Correlation matrices were then produced for each of the ROI-to-ROI values and were then imported into a second-level group analysis in order to determine mean functional connectivity values between our ROIs.

RESULTS

Whole Brain Analysis

A summary of the whole brain activation can be found in Tables 2 and 3. In general, the asymptomatic group demonstrated activation in the PreCG, PostCG, SMA, and cerebellum. While this activation was found in both hemispheres during the bilateral bridging task, the unilateral bridging task demonstrated laterality (Figure 4.3). Activation was found solely in the contralateral PreCG and SMA and the ipsilateral cerebellum during the unilateral bridging tasks.

The symptomatic group demonstrated a broader network of activation during the bridging tasks (Table 4.3). In addition to the locations active in the asymptomatic group, the symptomatic group had activation in the insula, MCC, putamen, Rolandic operculum, amygdala, and supramarginal gyrus. Of these regions, the putamen, MCC, and Insula demonstrated consistency in the location of activation across the three tasks.
The symptomatic group showed bilateral activation during the unilateral bridge tasks in addition to the bilateral bridge task (Figure 4.3). During each of the bridging tasks, the symptomatic group had bilateral activation of the PreCG and the cerebellum. As demonstrated in Figure 4.4, when we extracted parameter estimates for the right and left PreCG ROIs, the symptomatic group had larger magnitudes of activation during the ipsilateral bridging task. The trend for higher activation was exaggerated across the bridging tasks when we did the same for the right insula (Asymptomatic vs Symptomatic: Bilateral Bridge beta = -0.096 vs 0.124, Left Bridge beta = -0.042 vs 0.285, Right Bridge beta = -0.269 vs -0.004) and left insula (Asymptomatic vs Symptomatic: Bilateral Bridge beta = -0.067 vs 0.141, Left Bridge beta = -0.217 vs 0.051, Right Bridge beta = 0.049 vs 0.173) ROIs.

Functional Connectivity Analysis

Based on the results from the whole brain analysis, the nine ROIs were subdivided into two networks: 1) a Motor Network which consisted of the PreCG, SMA, and Putamen, and 2) a Motor-Pain Network which consisted of the Insula, Putamen, and MCC[35-39]. We chose the motor regions a priori based on the results of our previous work[26]. In that study, we found the PreCG, SMA, Postcentral Gyrus (PostCG) and the Putamen to be active across all three bridging tasks. Since our whole brain analysis did not show consistent activation in the PostCG, we only used the PreCG, SMA, and Putamen in this analysis as our motor network. These regions have previously been found to assist with motor production [22, 40-44].
Both groups had positive connections between the regions in both networks. For the motor network, relative strengths of the correlations between the ROIs were higher in the symptomatic group but not statistically different at p-FDR 0.05 (Figures 5-7). However, the connection between the Putamen and ipsilateral PreCG was different. While the connectivity between the ROIs was generally higher in the symptomatic group, the connectivity between the putamen and the ipsilateral PreCG fluctuated between being higher for the symptomatic or the asymptomatic group. This inconsistency was unique to the Putamen to ipsilateral PreCG connection.

For the Motor-Pain Network the symptomatic group again had stronger connectivity values but were not statistically different at p-FDR 0.05 across all three tasks (Figures 8-10). However, only in the symptomatic group was the putamen to insula connection significant during the bilateral bridging task (Figure 4.8). With the exception of the bilateral Putamen to ipsilateral Insula, all connectivity results were statistically different from zero within-group, but not statistically different between the groups.

DISCUSSION

This study assessed the differences in brain activation during the performance of lumbopelvic tasks between individuals with and without cLBP. We found that asymptomatic individuals have largely unilateral activation in the sensorimotor regions of the cortex when performing a unilateral bridging task compared to that of individuals with cLBP while the overall activation patterns and connectivity levels were generally consistent with what we reported in a previous investigation. Furthermore, we found
that individuals with cLBP exhibited a larger network of activation during the
performance of all motor tasks and demonstrated less laterality of activation during
unilateral bridging tasks.

The three tasks—bilateral bridge, right bridge, and left bridge—were chosen
because of the varied amount of difficulty they presented. We propose that the bilateral
bridge is the easiest of the three tasks as it requires the least amount of coordination
between the trunk and the lower extremities and it offers the greatest amount of
stability. The unilateral bridging tasks were considered to be more difficult due to the
required inhibition of the contralateral lower extremity and the increased demand for
trunk stability. In addition, the left bridge was considered more challenging than the
right due to the anticipated right leg dominance. We anticipated right leg dominance
because inclusion criteria for the study required individuals to be right handed, and
hand and foot dominance are strongly correlated[45].

The asymptomatic group demonstrated activation in the SMA, cerebellum,
PreCG, and the putamen during the performance of lower extremity motor tasks. This
finding was largely consistent with our previous report in a separate sample using a
similar task. Upon visual inspection, both studies demonstrated distinctions between
the activation patterns of the bilateral, right, and left bridging task. Specifically, during
the unilateral bridging tasks there was more evident activation in the contralateral
hemisphere while during the bilateral bridging task the activation was seen bilaterally
across the sensorimotor region. Additionally, we reported in a previous paper that the
levels of connectivity between the regions were smaller than what we expected when
taking into consideration the literature on upper extremity tasks. In this current study, we found that the levels of connectivity between the bilateral PreCG and between the PreCG and the SMA was similar, supporting our findings of lower levels of connectivity in lower extremity tasks.

In contrast to the asymptomatic group, the symptomatic group lacked the laterality of activation during the unilateral bridging tasks. As is seen in Figure 3, the ipsilateral hemisphere had activation during the unilateral task. This can in part be explained by the biomechanical literature, which has suggested that individuals with cLBP exhibit trunk stiffening that is achieved through co-activation of the trunk musculature[46-50]. As Hodges et. al. proposed in 2011[27], individuals in chronic pain exhibit altered movement patterns in order to protect a painful part of the body from further pain or injury. For individuals with cLBP this alteration of movement patterns results in changes in the kinematics of the spine, leading to increased stiffness of the trunk musculature[27]. This stiffness leads to loss of movement specificity and results in en bloc movements of the trunk. While beneficial in the short term, prolonged maladaptive motor patterns may result in abnormal biomechanical stresses that result in continued pain[27]. Therefore, we hypothesize that the bilateral activation observed during the unilateral bridging tasks may result from the maladaptive trunk stiffening motor pattern exhibited by individuals with cLBP.

Our study contributes to this theory of altered motor control by providing evidence of cortical activation changes in individuals with cLBP. We believe the lack of laterality reflects the trunk stiffening strategy employed by individuals with cLBP in
order to protect the spine. Our findings together with previous work[15-17, 27, 50, 51] contribute to the notion that the altered motor control exhibited by individuals with cLBP is reflected both in the brain and the trunk musculature. However, as we did not collect concurrent EMG data on the trunk musculature, we cannot conclude from our study if the changes in cortical activation we observed resulted directly from the trunk stiffening or if from another source.

Individuals with chronic pain also exhibited a wider network of activation compared to asymptomatic individuals. In addition to the PreCG, SMA and Putamen, those in the cLBP group had activation in the insula, MCC, Rolandic operculum, amygdala, and supramarginal gyrus. Of this wider network, the activation in the MCC, insula and putamen were of particular interest because not only were they active across the three tasks, but the coordinates of peak activity were within a few voxels. Therefore, we divided our areas of activation across two networks based on our data: a motor-pain network that consisted of the insula, MCC, and Putamen; and a motor network that consisted of the PreCG, SMA, and Putamen.

In a review and meta-analysis of insular function, Kurth et.al. [39] described the role of the insula in pain appraisal. While they found that painful stimuli resulted in extended activation on virtually the entire insula, the central and posterior insula demonstrated extended activation. In this region, the peak coordinates that they report (-44,2,7) are almost identical to the ones we found in our study (-44,2,8). This region of the insula also has strong structural connections to the MCC and the PreCG [52], further supporting our theory of a pain-motor network.
The left middle cingulate gyrus had the same region activated across all three bridging tasks (-6, -6, 46) and the right middle cingulate gyrus was active during the left bridging task (10, -4, 44). There is previous evidence that activity in this region relates to the integration of motor function and pain processing[35, 36]. While previous reports[35] indicate that the region of the MCC that is related to integration of motor function and pain processing is further rostral (0,9,48) compared to our location, this may be due to the MCC being organized somatotopically [53]. Misra et. al. utilized grip force while we utilized lower extremity movement. This could help to explain the discrepancy in the y-axis.

The putamen was another region that was consistently active in the symptomatic group at approximately the same location. There is evidence to support that the putamen, along with the insula, assists in the processing of both motor and pain signals[37]. Furthermore, it has a role in coordinating multiple inputs of information, ranging from nociceptive, sensory, and cognitive-emotional pain processing[38]. This region is not typically associate with the pain neuromatrix[54, 55] and may be unique during the performance of a motor task.

Additionally, for the motor-pain network, there was a tendency for stronger connectivity between the ROIs in the symptomatic group. This was especially true during the bilateral bridging task where the connection between the Putamen to Insula was only statistically significant in the symptomatic group. As previously stated, we are proposing that the insula is assisting in the evaluation of painful stimulus while the putamen is processing information required for both motor control and pain processing.
The integration of these two regions during a motor performance would be important for those in pain as this would allow for the concurrent evaluation of painful stimulus and motor adaptation to avoid harm.

**Limitations**

There were several limitations to this study. First, the symptomatic group had a disproportionate number of females compared to the asymptomatic group. This study used a sample of convenience and did not actively balance the two groups. While there are no statistical differences between the baseline characteristics for any of the other demographics, there was for the number of females. However, we believe that this represents the chronic pain population as a whole. Several studies have shown that cLBP has a higher prevalence in women compared to men[1, 56-59], indicating that our sample may be indicative of the chronic pain population as a whole.

Our symptomatic population also exhibited relatively low levels of pain and disability. The average NPRS was a 4/10, with the majority of the symptomatic individuals still participating in either school or work activities. However, most had sought medical attention for their cLBP and had undergone some form of treatment. Therefore, we believe that our sample represents a clinical population albeit one that is still relatively able bodied.

Another limitation was that we did not collect EMG data concurrently with our fMRI data. This would have allowed us to make firmer conclusions regarding the true nature of the biomechanical differences during the lumbopelvic tasks.
CONCLUSION

This paper contrasted whole brain activation and functional connectivity during lumbopelvic motor tasks between individuals with and without cLBP. We demonstrated that individuals with cLBP exhibit a broader network of activation with decreased laterality during unilateral tasks. Within our sample there appears to be a network consisting of the Putamen, the MCC, and the Insula that contribute to the appraisal of pain perception and it’s integration with motor performance. Within this network, and a truncated motor network, there is a tendency for stronger connectivity in the symptomatic group. Consistent with prior literature, this tendency is especially noticeable in the right insula. This study offers critical insights into the cortical differences during a lumbopelvic task between individuals with and without cLBP.
Figure 4.1 - Participant in the scanner performing the lumbopelvic exercises.

Table 4.1 – Participant Demographics

<table>
<thead>
<tr>
<th></th>
<th>N (Female)</th>
<th>Age</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Pain</th>
<th>RMDQ</th>
<th>FABQ</th>
<th>CES-D</th>
<th>PCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatics</td>
<td>20 (12)</td>
<td>29 (4.5)</td>
<td>71.7 (18)</td>
<td>172 (13)</td>
<td>0</td>
<td>0</td>
<td>1.9</td>
<td>4.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Symptomatics</td>
<td>23 (19)</td>
<td>30 (11)</td>
<td>78.9 (22)</td>
<td>167 (9)</td>
<td>4</td>
<td>5.96</td>
<td>29.2</td>
<td>14.8</td>
<td>13.3</td>
</tr>
</tbody>
</table>

N = number of individuals in group with the number of females in parentheses. Age displayed in years. Weight displayed in kilograms. Height displayed in centimeters. Pain scores as reflected on 0-10 numeric pain rating scale. RMDQ – Roland Morris Disability Questionnaire. FABQ – Fear Avoidance Belief Questionnaire. CES-D – Center for Epidemiologic Studies Depression Scale. PCS – Pain Catastrophizing Scale. All standard deviations in parentheses.
Figure 4.2 - Task Paradigm. Eight second “rest blocks” were interwoven between 75 second “task blocks”. The bilateral bridge, unilateral bridge, abdominal tightening, and ankle plantarflexion were randomized throughout the task blocks.
Table 4.2 – Summary of Whole Brain Analysis for the asymptomatic group across the three tasks.

<table>
<thead>
<tr>
<th>Asymptomatic Bilateral Bridge</th>
<th>Cluster p-FWE</th>
<th>Cluster Size</th>
<th>Peak p-FWE</th>
<th>Peak Z-Score</th>
<th>X,Y,Z Coordinates</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0006</td>
<td>142</td>
<td>0.0000</td>
<td>5.88</td>
<td>0,-16,66</td>
<td>Right Supplemental Motor Area (BA 6)</td>
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</tr>
<tr>
<td>0.0003</td>
<td>171</td>
<td>0.0001</td>
<td>5.78</td>
<td>-10,-40,-16</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.0010</td>
<td>5.30</td>
<td>8,-42,-16</td>
<td>Right Cerebelum (BA 30)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.0084</td>
<td>4.84</td>
<td>16,-38,-20</td>
<td>Right Cerebelum (BA 5)</td>
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<tr>
<td>0.0052</td>
<td>52</td>
<td>0.0014</td>
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<table>
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<tr>
<th>Asymptomatic Left Bridge</th>
<th>Cluster p-FWE</th>
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<tr>
<td></td>
<td></td>
<td>0.0001</td>
<td>5.81</td>
<td>12,-30,68</td>
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<table>
<thead>
<tr>
<th>Asymptomatic Right Bridge</th>
<th>Cluster p-FWE</th>
<th>Cluster Size</th>
<th>Peak p-FWE</th>
<th>Peak Z-Score</th>
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<td>0.0003</td>
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<tr>
<td></td>
<td></td>
<td>0.0002</td>
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<td>-2,-18,62</td>
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Cluster p-FWE – Cluster p-value after FWE correction. Peak p-FWE – Peak p-value after FWE correction.
Table 4.3 – Summary of the Whole Brain Analysis for the symptomatic group across the three tasks.

<table>
<thead>
<tr>
<th>Symptomatic Bilateral</th>
<th>Cluster p-FWE</th>
<th>Cluster Size</th>
<th>Peak p-FWE</th>
<th>Peak Z-Score</th>
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<td>Left Cerebellum (BA 30)</td>
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<tr>
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<tr>
<td></td>
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<td>Cluster Size</td>
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<tr>
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<td>Peak Z-Score</td>
<td>X,Y,Z Coordinates</td>
<td>Location</td>
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<td>8,-40,-18</td>
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<tr>
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<td>20,-34,-26</td>
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</tr>
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<td>6.22</td>
<td>-28,-14,8</td>
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<td>0.0112</td>
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<td>0.0019</td>
<td>5.17</td>
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<td></td>
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Cluster p-FWE - Cluster p-value after FWE correction. Peak p-FWE - Peak p-value after FWE correction
Figure 4.3 – Statistical parameter maps of mean areas of cerebral blood oxygenation level-dependent activation during the bilateral, left unilateral, and right unilateral bridging tasks in the asymptomatic (left) and symptomatic (right) groups.

Figure 4.4 - Beta values for the bilateral, left, and right bridging tasks in the Right PreCG, Left PreCG, Right Insula, Left Insula in the asymptomatic and symptomatic groups.
Figure 4.5 - Functional connectivity during the bilateral bridge in the proposed motor network. Asymp - Asymptomatic group. Symp - Symptomatic group. All correlations are significant at p-FDR < 0.05 when compared to rest.

Figure 4.6 - Functional connectivity during the left bridge in the proposed motor network. Asymp - Asymptomatic group. Symp - Symptomatic group. All correlations are significant at p-FDR < 0.05 when compared to rest.
Figure 4.7 - Functional connectivity during the right bridge in the proposed motor network. Asymp - Asymptomatic group. Symp - Symptomatic group. All correlations are significant at p-FDR < 0.05 when compared to rest.

Figure 4.8 - Functional connectivity during the bilateral bridge in the proposed motor-pain network. Asymp - Asymptomatic group. Symp - Symptomatic group. All correlations are significant at p-FDR < 0.05 when compared to rest.
Figure 4.9 - Functional connectivity during the left bridge in the proposed motor-pain network. Asymp - Asymptomatic group. Symp - Symptomatic group. All correlations are significant at p-FDR < 0.05 when compared to rest.

Figure 4.10 - Functional connectivity during the right bridge in the proposed motor-pain network. Asymp - Asymptomatic group. Symp - Symptomatic group. All correlations are significant at p-FDR < 0.05 when compared to rest.
REFERENCES


CHAPTER 5

SPINAL MANIPULATION ALTERS ACTIVATION AND CONNECTIVITY OF THE PUTAMEN DURING PERFORMANCE OF LUMBOPELVIC TASKS IN INDIVIDUALS WITH CHRONIC LOW BACK PAIN – AN fMRI STUDY.³

³ Jordon MK, Beattie PF, Silfies SP, Bialosky JE, and Stewart J. To be submitted to Journal of Orthopedic and Sports Physical Therapy
ABSTRACT

STUDY DESIGN: Prospective randomized controlled trial.

OBJECTIVES: The purpose of this study was to investigate the effects of spinal manipulation on brain activation during lumbopelvic exercises in individuals with and without chronic low back pain (cLBP).

BACKGROUND: Despite frequent uses, the effect sizes of spinal manipulation remains disappointingly low. This may be in part due to a lack of understanding of the mechanisms behind this intervention.

METHODS: 19 individuals without cLBP and 22 individuals with cLBP performed lumbopelvic motor tasks while undergoing functional magnetic resonance imaging of the brain before and after spinal manipulation or control condition sidelying rest.

RESULTS: Following spinal manipulation individuals with cLBP experienced a within-group increase in activation in the Putamen, Insula, and Midcingulate Cortex (MCC) during the performance of a modified right bridging task. This corresponded with an increase in the connectivity between the Putamen and the MCC, Precentral Gyrus (PreCG), and the Supplemental Motor Area (SMA). The asymptomatic individuals experienced an increase in activation in the PreCG and the MCC during the left bridging task.

CONCLUSION: The increases in activation and functional connectivity in individuals with cLBP is consistent with a “motor-pain” network of which the Putamen may play a
central role. The clinical implications of these findings are uncertain; however, they may suggest at least one of the effects of the stimuli generated by spinal manipulation is an improvement in the cortico-basal-ganglia motor loop.

**KEY WORDS:** [Motor Control – Brain Imaging – Manual Therapy]

**INTRODUCTION**

Spinal manipulation therapy (SMT) is routinely used by physical therapist to treat low back pain[1, 2]. However, despite its widespread adoption into clinical practice, several systematic reviews have reported small to modest effect sizes[3-5]. One potential reason for the small effect sizes is the lack of a clear understanding of the mechanisms by which SMT influences the nervous system [6, 7]. Previous research has suggested that SMT is associated with reductions in global pain sensitivity[8-12] and improvements in pain modulation[13], supporting the hypothesis that SMT has a modulatory effect on the central nervous system[1, 6, 7, 14]. However, direct evidence of SMT’s effects on brain activity is limited, resulting in a need for more conclusive evidence.

Functional magnetic resonance imaging (fMRI) is an established technique to measure changes in brain activity[15]. As brain activity increases there is a concurrent increase in the demand for oxygenated blood. fMRI can measure the perfusion to a given area which gives an indication of changes in blood oxygenation levels, resulting in what is known as a blood oxygenation level dependent (BOLD) measure. The BOLD response is then used as a proxy measurement for neural activity[16]. By correlating
brain activity in spatially separated regions one can start to understand “brain networks” or regions that work together during specific circumstances. These networks can be described by determining functional connectivity[16].

In previous work we described a protocol in which asymptomatic individuals performed lumbopelvic exercises while undergoing fMRI[17]. We then refined this protocol and compared the differences in brain activity between individuals with and without cLBP [18]. We found that in those study participants who had cLBP there was a tendency to exhibit bilateral activation in the sensorimotor regions of the cortex. Additionally, there appeared to be a unique motor-pain network that consisted of the Insula, Putamen, and the Middle Cingulate Cortex (MCC). However, the effects of SMT on brain activity during exercise has yet to been reported. In fact, to the authors’ knowledge, there have only been two published reports on the effects of SMT on supraspinal function using fMRI. Sparks et. al. used fMRI to study the effects of thoracic SMT on thermal pain sensitivity in asymptomatic individuals[19]. The investigators had pain-free participants undergo thermal stimulation before and after thoracic SMT and noted a reduction in peak BOLD response in multiple sensorimotor and pain regions of the brain. Gay et. al. assessed changes in functional connectivity following spinal manipulation[20] in healthy individuals with induced low back pain. The authors reported a shift in connectivity values within several of the same regions that were explored by Sparks et al. In the present study, we build on their work by incorporating a symptomatic population, and transitioning from a resting[20] or sensory[19] task, to one
that involves activation of both the sensory and motor pathway during voluntary lumbopelvic movements.

The purpose of the present study was to investigate the effects of spinal manipulation on brain activation during lumbopelvic motor tasks in individuals with and without chronic low back pain (cLBP). Findings from this study will contribute to the overall understanding of the mechanisms behind spinal manipulation and help clarify the effects SMT has on brain function. We tested three primary hypotheses: during performance of motor tasks 1) individuals with cLBP would experience a reduction in activation in key pain and sensorimotor regions following thrust manipulation compared to baseline; 2) functional connectivity between the insular cortex and somatosensory cortices would decrease after manipulation compared to baseline; and 3) individuals without cLBP would exhibit changes in brain activity following SMT different than that observed in individuals with cLBP.

METHODS

Participants

Participant demographics are outlined in (Table 5.1). A total of twenty-five individuals with cLBP and twenty-one asymptomatic individuals enrolled in this study. In the asymptomatic group one participant was removed due to low signal while another demonstrated benign abnormal brain morphology that prevented participation in this study. In the symptomatic cohort, one participant became claustrophobic and two more were unable to complete the scan due to technical difficulties with the scanner. This
resulted in a total of 19 asymptomatic (12 female, age 29 ± 4.5 years) and 22 symptomatic (18 female, age 30 ± 11.5 years) individuals completing the study. Both the asymptomatic and symptomatic groups were then further subdivided into those who would receive spinal manipulation (asymptomatic manipulation – AM, symptomatic manipulation – SM) and those who would receive the control condition of side-lying rest (asymptomatic side-lying rest – AC, symptomatic side-lying rest – SC).

To be included in the asymptomatic group participants had to have had no history of activity limiting low back pain. Inclusion criteria for the symptomatic group were perceiving 3/10 back pain the majority days of the week for the past six months. Informed consent was obtained from all participants, and approval for this study was given by the University of South Carolina Institutional Review Board. This randomized control trial was registered with ClinicalTrials.gov (ClinicalTrials.gov ID NCT02828501) prior to the recruitment of the first participant.

Motor Task

Participants were trained in an established protocol [17, 18, 21] to activate the lumbopelvic musculature. The task involved the participants slightly unweighted their hips by pushing the back of their right knee (right bridge) and left knee (left bridge) into a 22cm bolster (Figure 1). Participants were instructed to keep their eyes closed and to breath normally in order to reduce the potential of physiological noise[22]. In order to ensure task fidelity, the participants were trained in the tasks both inside and outside of the scanner and were visually monitored during the duration of the scan. A bilateral
ankle plantarflexion and abdominal contraction task was included in the study but was not included in the current analysis. The participants also performed a bilateral bridging task that was not included. Based on our previous work, we found that the unilateral bridging tasks were better able to differentiate between individuals with and without cLBP than the bilateral bridging task[18]. While individuals with cLBP exhibited a broader network of activation during all three bridging tasks, only during the unilateral bridging tasks did activation in the sensorimotor regions differ. Specifically, individuals with cLBP demonstrated bilateral activation in the sensorimotor regions where individuals without pain only demonstrated contralateral hemisphere activation.

The participants underwent thorough training prior to the first scan served not only to ensure task fidelity but also to reduce the potential of head motion. Additionally, the participants’ head were securely supported within the head coil with foam pads. In between the scans the participants were reminded to keep their head as still as possible and to only move as much as the task required.

After thoroughly training the participants in the motor tasks, we collected pressure-pain threshold (PPT) measurements from the left and right upper trapezius, lumbar paraspinals at L4, and tibialis anterior. Methods used to acquire the PPT measurements are described in previous studies[23].

*fMRI Data Acquisition*

Data were collected on a 3T Siemens Prisma scanner using a 20-channel head coil (502 volumes; 58 axial slices; 2.5 mm thick; TR = 1000ms; TE = 37ms; matrix 64 x 64
voxels; flip angle =61°; 220x220mm FOV). A sagittal T1-weight MPRAGE protocol was used to acquire high-resolution structural images (192 slices; 1mm thick; TR = 2250ms; TE = 4.11ms; matrix=1 x 1 x 1mm3; 256x256 FOV).

A block-design with alternating blocks of task and rest (Figure 5.2) was utilized for this study. The task block consisted of each task being performed in random order for 11 seconds with a 4 second relaxation period following each task. After each task block there was an 8 second rest block where the participants were instructed to relax. This sequence was repeated six times per run, with each participant completing two runs prior to the intervention. After completion of the two runs (Baseline), participants were removed from the bore and either received manipulation or a control intervention.

For those participants in the manipulation group, a side-lying lumbar manipulation targeting the L4-5 motion segment was applied first in right side-lying and then left, as described in previous studies[23, 24]. The manipulation was provided by a licensed physical therapist with over 7 years of experience in manipulation. For those in the side-lying rest group, the participants first laid on their right side in a comfortable position. After 60 seconds the participants rotated to their left side for an additional 60 seconds. This was to simulate the length of time it would take to perform a lumbar manipulation. Following the intervention, the participants repeated the two fMRI runs (Figure 3). Visual monitoring of the participants ensured that they were performing the correct task at the correct time. The instructions were delivered in a randomized order
to the participants using the e-Prime system (Psychology Software Tools, Inc.,
Sharpsburg, PA).

The fMRI data were the preprocessed using Statistical Parametric Mapping (SPM
12, Wellcome Department of Cognitive Neurology, London, UK), implemented in
MATLAB R2017a (Mathworks, Natick, MA, SUA). Every volume was realigned to the first
and unwarped. The mean image was normalized to Montreal Neurological Institute
(MNI) space and the normalization parameters were then applied to each volume. The
data were resampled to 2mm x 2mm x 2mm voxels smoothed using an isotropic
Gaussian kernel 8x8x8mm3 full width at half maximum. The Artifact Detection Tool was
then used to assess head motion during the scans. The first derivative of the head
motion was used to screen for excessive motion with outliers being used as covariates
of no interest during the statistical analysis (mean number of outliers = 0.4, ranging
from 0 to 20 of 502 volumes).

Data Analysis

Baseline Characteristics, NPRS, and PPT

Baseline characteristics were compared across groups. A one-way ANOVA was
used to assess if there were differences in the age, weight, height, the Roland Morris
Disability Questionnaire (RMDQ), the Fear Avoidance Belief Questionnaire (FABQ), the
Center for Epidemiologic Studies Depression Scale (CES-D), and the Pain Catastrophizing
Scale (PCS). Since the requirements for the asymptomatic groups were such that they
had to have had no pain, an independent-sample t-test was used to assess for
differences in baseline pain. A Chi-Squared tested was used to determine if there was a difference in gender by group. To assess if there was a change in pain following intervention, a repeated measures ANOVA (rm-ANOVA) with a between-subject factor of time and within-subject factor of group was performed on the NPRS. We only included the symptomatic manipulation and symptomatic control groups in the rm-ANOVA.

Pressure-pain threshold (PPT) ratings were collected as a behavioral measure of perceived pain sensitivity. As previous research has demonstrated that individuals with cLBP exhibit PPT measures that are lower than in individuals without cLBP [25-29], we were interested to see if our pain population followed this trend. Therefore, we performed a multifactorial ANOVA to assess differences in PPT between individuals with and with pain across the six regions.

Region of Interest (ROI) Analysis

For the first level analysis, a general linear model (GLM) was used for each individual[30, 31]. Contrast maps were calculated for each task period versus rest using the first derivative of head motion for all six directions as a regressor of no interest. Then, we performed a ROI analysis based on previous work that described a motor-pain network[18]. The motor-pain network included the bilateral precentral gyrus (PreCG), bilateral insula, bilateral midcingulate cortex (MCC), bilateral putamen, and the supplementary motor area (SMA). In order to create the ROIs, we used MarsBAR to generated a 5mm radius sphere centered on these regions (MNI coordinates: SMA = 0, -
16, 62; Right PreCG = 10, -30, 72; Left PreCG = -8, -30, 70; Right Insula = 46, 4, 8; Left
Insula = -44, 2, 8; Right MCC = 10, -4, 44; Left MCC = -6, -6, 46; Right Putamen = 30, -10,
6; Left Putamen = -28, -14, 8) (Figures 5.4).

We then extracted the mean parameter estimates from the ROIs for each
individual’s first-level analysis using MarsBar. Parameter estimates are an estimation of
the magnitude of the BOLD signal, often conceptualized as the strength of brain
activation[16]. Next, we imported the parameter estimates into SPSS in order to
determine differences in activation between the groups. After dividing the groups based
on pain, we performed a repeated measures ANOVA with a between-subject factor of
intervention (manipulation vs sidelying rest), and a within-subject factor of time for
each task and region. For ROI that was significantly different between the groups, we
calculated the effect size to better interpret the data[32].

Functional Connectivity Analysis

To assess functional connectivity during our tasks we used the CONN toolbox[33]
implemented in MATLAB. Each participant’s data was imported into CONN to correctly
account for the BOLD time series. CONN’s CompCor algorithm[34] was used to remove
confounds in order to reduce the effect of physiological noise on the functional
connectivity values. Next, we imported the ROIs into CONN in order to perform an ROI-
to-ROI analysis of the motor-pain network.

For the ROI-to-ROI analysis we used a weighted GLM approach. First level
bivariate correlations were computed separately based on the individual’s BOLD time
series between each ROI. In order to improve the assumptions of normality, we applied a Fisher’s Z-transformation to the bivariate correlations using a standardized procedure programmed within the CONN toolbox[33]. Correlation matrices were then produced for each of the ROI-to-ROI values and were then imported into a second-level group analysis in order to determine mean functional connectivity values between our ROIs.

A baseline comparison between the tasks was completed by performing a group x task MANOVA. We then performed a repeated measures ANOVA (rmANOVA) with within-subject factors of time and task to assess changes in connectivity between the ROIs. This was completed separately for each of the four groups. The results were then thresholded at p-FWE of 0.05. To calculate effect sizes, we first transformed all r-values to z-scores using a Fisher Z transformation. Next, we used Cohen’s d to calculate the effect sizes using the transformed Z-scores [32].

To better interpret our data, we calculated the MDC$_{90}$ in the control groups using the change from the pre to post intervention scanning runs. We used this as a measure of the amount of variation that normally occurs between scans. Then, we looked at the pre to post intervention change scores for each individual in the manipulation groups and calculated how many exceeded the MDC$_{90}$.

**Responder Analysis**

For any significant changes found in the ROI or the functional connectivity analysis, we followed up with a responder analysis based on changes in pain rating. We used a reduction in 2/10 pain as the definition of positive responder and plotted each
individual’s change from pre- to post-intervention on a graph. As the number of individuals who received a manipulation was small, we decided to visually inspect the graphs as opposed to running statistical tests.

RESULTS

Baseline Characteristics and NPRS

There was no significant difference in the baseline characteristics of age, weight and height between the groups (Table 5.2). Furthermore, there was no significant difference in pain between the SM and SC groups. The Chi-Squared test demonstrated an imbalance in the distribution of females between the groups, with the SM having the largest number of females. For the change in the NPRS score, the SM group reported a significant decrease in the NPRS of 1.08 where the SC group remained the same. The PPT measures indicated that the chronic low back pain group exhibited lower pain thresholds in the right low back, left upper trapezius, and right upper trap, with a trend towards lower pain thresholds in the left low back (Table 5.3).

Region of Interest Analysis

The ROI analysis demonstrated significant changes in the magnitude of activation for both sets of groups. Between the asymptomatic groups (AC and AM) during the left bridge, there was an increase in activation for the right PreCG with four of the individuals in the AM group exceeding the MDC$_{90}$ (Figure 5.5). The rmANOVA revealed a decrease in activation in the SMA; however, no one in the AM group exceeded the MDC$_{90}$ for the SMA (Figure 5.6). While the group activation increased in
the right PreCG during the left bridging task, following the SMT three individuals experienced a reduction in magnitude of activation.

For the symptomatic groups (SC and SM) the rmANOVA revealed an increase in activation of the left insula with 7 of 12 individuals in the SM group exceeding the MDC$^{90}$ (Figure 5.7). There was an increase in activation of the left MCC with 2 individuals exceeding the MDC$^{90}$ (Figure 5.8). There was an increase in activation of the left putamen with 4 individuals exceeding the MDC$^{90}$ (Figure 5.9). For the right insula there was an increase in activation with 4 individuals exceeding the MDC$^{90}$ (Figure 5.10), and finally for the right putamen there was an increase in activation with 7 individuals exceeding the MDC$^{90}$ (Figure 5.11) (Table 5.2). The responder analysis did not demonstrate a consistent relationship between changes in brain activation and reduction of pain in the SM and SC groups (Figure 5.12 – 5.16).

While the mean activation in these ROIs increased following SMT, several individuals did experience a decrease greater than the MDC$^{90}$. In the left Insula, left MCC, and right Putamen four individuals, one individual, and one individual respectively experienced a reduction in activation.

**Functional Connectivity**

At baseline there were no differences between the groups in the connectivity between the ROIs. Following the manipulation, neither of the control groups experienced a significant change in connectivity. However, during the left bridging task the AM group had an increase in the Left MCC to SMA connection. Furthermore, the SM
had significant increases in the connectivity between the Right Putamen and the Right MCC, the Right PreCG, the SMA, and between the SMA and the Left PreCG during the right bridging task (Table 5.4). The responder analysis did not reveal a pattern regarding who improved and who did not (Figure 5.17 – 5.20).

**DISCUSSION**

This study assessed the effects of a single spinal manipulation on the brain response to the performance of lumbopelvic motor tasks. Individuals with cLBP experienced increases in both the BOLD response and functional connectivity in a select motor-pain network following spinal manipulation. Interestingly, these changes were largely unique to individuals with cLBP while asymptomatic individuals demonstrated little change following manipulation.

Individuals with cLBP had increased activation following SMT in the putamen, insula, and MCC. Together, these three regions represent a network that has the potential to assess the presence and intensity of pain and integrate that information with motor performance[35-38]. Of specific interest is the role that the putamen might play; the left and right putamen demonstrated the greatest consistency in increased activation, as well as greater functional connectivity between regions, following SMT. The putamen is one of five major nuclei within the basal ganglia (BG) which can both excite and inhibit regions of the brain to regulate motor processes[39]. As outlined by Da Cunha and colleagues in 2015[40], the literature suggests a model whereby different pathways between the portions of the basal ganglia, such as the internal segment of the
globus pallidus (GPi), can directly disinhibit thalamic neurons projecting to the motor
areas of the cortex; while other areas of the BG inhibit different thalamocortical
neurons. This balance between disinhibition and inhibition facilitates desired
movements while preventing unwanted motor patterns[41, 42]. Additionally, the
putamen receives projections from sensory, motor, and limbic regions of the cortex[43],
including premotor areas like the SMA[44]. It has been implicated in both pain
processing and motor production[36], making it key region of interest for individuals
with pain performing a salient motor task. Within the context of motor processing,
bilateral activation of the putamen has been specifically implicated in the modulation of
force[45] which is required by our task.

In our study we found that individuals with cLBP who received a spinal
manipulation exhibited an increased in the functional connectivity between the
putamen and the ipsilateral PreCG, MCC, and the SMA during a right bridging task.
Therefore, one mechanism by which spinal manipulation might affect motor
performance is through the alterations in the cortico-basal-ganglia (e.g. putamen to
cortex) motor loop. While speculative, the alterations in the cortico-basal-ganglia motor
loop may be due to changes in proprioceptive input.

Spinal manipulation results in the rapid stretch of the paraspinal muscles[46].
Muscle spindles are densely found within these muscles[47] and are the primary
proprioceptive sensory organ in the musculoskeletal system[48]. They continuously
inform the CNS about muscle length and joint positioning[48]. Following SMT, there is
an increased rate of discharge in the muscle spindles[49-51]. This proprioceptive
information is then carried from the muscle spindles to the thalamus vial the dorsal column-medial laminiscal tract in the spinal cord[52, 53]. Multiple neuroimaging studies have shown that once proprioceptive information reaches the brain it is processed in the motor cortex (located within the PreCG), premotor cortex, SMA, and cingulate motor areas (MCC) [54-57]. An additional region of the brain that has been found to process proprioceptive information is the putamen[58]. This is of key interest because in 2012 Goble et. al. found that structural changes within the right putamen were related to reduced activation following proprioceptive stimulus in older adults compared to younger adults[59]. In our study, we found that it was the right putamen that was most affected by spinal manipulation. Therefore, one hypothesis as to why there was increased activation in the right putamen and improved connectivity following spinal manipulation may be the increased rate of discharge from the muscle spindles located within the paraspinal muscles. This then leads to increased proprioceptive information being evaluated at the right Putamen.

For both the functional connectivity analysis and the whole brain analysis, the symptomatic group experienced within-group changes in brain activity following spinal manipulation during the right bridging task whereas those without cLBP experienced changes while performing the left bridging task. While speculative, this may be due to the differences in the difficulty of the tasks. During the training of the limb tasks, most participants had a more difficult time learning to isolate the use of the proximal leg musculature during the left bridging task compared to the right primarily manifesting as difficulty relaxing the side not involved in the task. While this is anecdotal, it concurs
with the reported limb dominance. With the exception of two individuals, all the participants reported being right limb dominate. We hypothesize that the reason why individuals had this difficulty with left unilateral task isolation was due, in part, to difficulty inhibiting contralateral muscle activation or coordinating inter-hemisphere activity during a less familiar task. Coactivation of lumbopelvic musculature has been reported in individuals with cLBP[60], presumably secondary to protection of injured structures. Those participants without LBP were potentially able to adapt performance more quickly and with less variability during task switching than those with cLBP. However, in those with cLBP the result of changes in brain control of movement may take away some movement flexibility. Thus, the challenge associated with unilateral task performance was not equal between sides or groups. The small sample size in conjunction with the within and between subject variance during the unilateral bridging tasks made it difficult to find statically significant differences pre to post manipulation within these tasks and between groups.

However, in those tasks where change was found the effect sizes were medium to large. This indicates that the observed change was not only statistically significant but also meaningful. One potential mechanism to explain the change in observed signal in the Putamen has been described above; however, following SMT the asymptomatic group experienced changes in the PreCG and the SMA. As discussed above, both the PreCG and the SMA evaluate proprioceptive information [54-57]. As both of these regions are important in the production and monitoring of movement[61] the ongoing proprioceptive information would be necessary for their functions. Additionally, SMT
has been linked with changes in maximal volitional contractions[62], electromyographical activity[63-65], and alterations in motor neuron firing[66] which potentially could reflect the changes in PreCG and SMA function.

The effects of spinal manipulation on brain function seemed to be independent of pain reduction. When we reviewed the responder analysis to look for a relationship between pain reduction and changes in activation, there was no clear pattern of change between those who had a 2/10 or greater reduction in pain compared to those who did not. Overall, both the magnitude of activation in the ROI analysis and the correlations in the functional connectivity analysis increased following the spinal manipulation regardless of the reduction in pain.

Limitations

While our total study size was large (n=41), after randomizing the sample we ended up with rather small group sizes (between 9 and 12 per group). This limited our ability to detect changes and increases the risk of a Type 2 error. Gender was not evenly distributed between the groups. In the symptomatic groups we had a disproportionate number of females compared to the asymptomatic group. However, we believe that this may better represent a symptomatic population as several studies have demonstrated that females exhibit greater prevalence of chronic pain[67-70]. Our groups were relatively young, with mean ages varying between 28 and 34 and with relatively low amounts of pain (NPRS = 4 of 10). However, as assessed by PPT, there was a reported increase in subjective sensitivity in our symptomatic group. This suggests that while our
population was relatively young and on the lower end of the NPRS scale, our population
demonstrated increases in subjective sensitivity to mechanical stimuli that has been
previously reported in other cLBP populations [25, 27, 71-75].

Another potential limitation to our study was the decision to utilize a single
session of SMT as an intervention for individuals with cLBP. Current guidelines
recommend SMT for acute LBP and had the duration of symptoms for our population
been less than three months we might have found more significant findings. However,
as stated above we did observe changes in the brain activation independent of pain
reduction which is the basis for the current guidelines. This might suggest that there
could be some benefit by including SMT in chronic populations.

Clinical Applications

The effects of spinal manipulation are likely to go beyond pain reduction. Many
clinicians do not incorporate spinal manipulation into their treatment of individuals with
cLBP due to current guidelines recommending against it. However, these guidelines are
based solely on pain response. This study suggests that SMT might have a transient
effect on an individual’s motor control and might be used as an adjunct to motor
control-based interventions in addition to its current use of pain control.

CONCLUSION

In individuals with cLBP, there were increases in both the functional connectivity
and activation within a motor-pain network that consisted of the insula, putamen, and
the MCC. Of particular note was the putamen, as it demonstrated the largest increase in
activation as well as increases in functional connectivity. This suggests that some of the effects of spinal manipulation may result from the increases in activation and connectivity of the Putamen as it is a key component of the cortico-basal-ganglia motor loop.
### Table 5.1 - Participant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Asymp Control</th>
<th>Asymp Manip</th>
<th>Symp Control</th>
<th>Symp Manip</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (female)</td>
<td>8 (4)</td>
<td>10 (8)</td>
<td>10 (8)</td>
<td>12 (10)*</td>
</tr>
<tr>
<td>Age (sd)</td>
<td>29 (4.98)</td>
<td>28 (4.29)</td>
<td>34 (13.17)</td>
<td>28 (9.56)</td>
</tr>
<tr>
<td>Weight (sd)</td>
<td>79 (23.7)</td>
<td>63.9 (6.4)</td>
<td>90.3 (16.07)</td>
<td>69.3 (16.41)</td>
</tr>
<tr>
<td>Height (sd)</td>
<td>174.24 (11.18)</td>
<td>168.91 (16)</td>
<td>173.23 (9.63)</td>
<td>166.12 (8.2)</td>
</tr>
<tr>
<td>Baseline Pain</td>
<td>0</td>
<td>0</td>
<td>4.2</td>
<td>4.1</td>
</tr>
<tr>
<td>Follow-up Pain</td>
<td>0</td>
<td>0</td>
<td>3.83</td>
<td>2.75**</td>
</tr>
<tr>
<td>RMDQ</td>
<td>4.75</td>
<td>0</td>
<td>5.3</td>
<td>6.8</td>
</tr>
<tr>
<td>FABQ</td>
<td>7.4</td>
<td>2.7</td>
<td>10.8</td>
<td>17.25</td>
</tr>
<tr>
<td>CES-D</td>
<td>2.2</td>
<td>0.8</td>
<td>9.9</td>
<td>16.6</td>
</tr>
</tbody>
</table>

*Age displayed in years. Weight displayed in kilograms. Height displayed in centimeters. Pain scores as reflected on 0-10 numeric pain rating scale. RMDQ – Roland Morris Disability Questionnaire. FABQ – Fear Avoidance Belief Questionnaire. CES-D – Center for Epidemiologic Studies Depression Scale. PCS – Pain Catastrophizing Scale. * - Indicates more females based on Chi Squared test. ** - Indicates significant decrease in pain at p < 0.05. All standard deviations in parentheses.*
Figure 5.11 - A individual in the testing position within the scanner.

Figure 5.2 - Graphical representation of the block design. Each “Task Block” on the first row was subdivided as described in the second row.
Figure 5.3 - Flow of study.

Figure 5.4 - Location of ROIs. L - Left; R - Right; PreCG - Precentral Gyrus; SMA - Supplementary Motor Area; MCC - Midcingulate Cortex; Put - Putamen; In - Insula
Table 5.2 - Parameter estimates for each of the regions that changed from pre to post intervention based on the results from the rmANOVAs.

<table>
<thead>
<tr>
<th>Region</th>
<th>Asymptomatic Group</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control Pre</td>
<td>Control Post</td>
</tr>
<tr>
<td>LB R PreCG</td>
<td>1.421</td>
<td>1.985</td>
</tr>
<tr>
<td>LB SMA</td>
<td>0.779</td>
<td>1.34</td>
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<table>
<thead>
<tr>
<th>Symptomatic Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>RB L In</td>
</tr>
<tr>
<td>RB L MCC</td>
</tr>
<tr>
<td>RB L Put</td>
</tr>
<tr>
<td>RB R In</td>
</tr>
<tr>
<td>RB R Put</td>
</tr>
</tbody>
</table>

LB – Left Bridge; RB – Right Bridge; L – Left; R – Right; PreCG – Precentral Gyrus; In – Insula; MCC – Midcingulate Cortex; Put – Putamen; SMA – Supplementary Motor Area; Pre – Pre-intervention; Post – Post-intervention.
Table 5.3 – Baseline Pressure-Pain Threshold testing results from ANOVA.

<table>
<thead>
<tr>
<th>Pressure-Pain Threshold</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left Low Back Pre Average</strong></td>
<td>Asymptomatic</td>
<td>62.2050</td>
<td>23.25</td>
<td>2.861</td>
</tr>
<tr>
<td></td>
<td>Symptomatic</td>
<td>51.3818</td>
<td>18.11</td>
<td></td>
</tr>
<tr>
<td><strong>Right Low Back Pre Average</strong></td>
<td>Asymptomatic</td>
<td>66.1700</td>
<td>29.75</td>
<td>4.456</td>
</tr>
<tr>
<td></td>
<td>Symptomatic</td>
<td>49.5614</td>
<td>20.84</td>
<td></td>
</tr>
<tr>
<td><strong>Left Upper Trap Pre Average</strong></td>
<td>Asymptomatic</td>
<td>52.4215</td>
<td>25.24</td>
<td>4.234</td>
</tr>
<tr>
<td></td>
<td>Symptomatic</td>
<td>39.8886</td>
<td>12.81</td>
<td></td>
</tr>
<tr>
<td><strong>Right Upper Trap Pre Average</strong></td>
<td>Asymptomatic</td>
<td>49.5400</td>
<td>20.68</td>
<td>4.575</td>
</tr>
<tr>
<td></td>
<td>Symptomatic</td>
<td>37.7182</td>
<td>14.92</td>
<td></td>
</tr>
</tbody>
</table>

Figure 5.12 - Change in parameter estimates for asymptomatic individuals performing left bridging task in the right precentral gyrus ROI. PreCG - Precentral Gyrus
Figure 5.13 - Change in parameter estimates for asymptomatic individuals performing left bridging task in the supplemental motor area ROI.

Figure 5.14 - Change in parameter estimates for symptomatic individuals performing right bridging task in the left insula ROI.
Figure 5.15 - Change in parameter estimates for symptomatic individuals performing right bridging task in the left midcingulate cortex ROI.

Figure 5.16 - Change in parameter estimates for symptomatic individuals performing right bridging task in the left putamen ROI.
Figure 5.17 - Change in parameter estimates for symptomatic individuals performing right bridging task in the right insula ROI.

Figure 5.18 - Change in parameter estimates for symptomatic individuals performing right bridging task in the right Putamen ROI.
Table 5.4 – ROI-to-ROI connectivity levels for those connections that changed following SMT.

<table>
<thead>
<tr>
<th>Asymptomatic Manipulation Group</th>
<th>Task</th>
<th>Connection</th>
<th>Pre</th>
<th>Post</th>
<th>Change</th>
<th>p-FWE</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Bridge</td>
<td>Left MCC to SMA</td>
<td>0.31</td>
<td>0.43</td>
<td>0.12</td>
<td>0.033</td>
<td>0.98</td>
<td></td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Symptomatic Manipulation Group</th>
<th>Task</th>
<th>Connection</th>
<th>Pre</th>
<th>Post</th>
<th>Change</th>
<th>p-FWE</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Bridge</td>
<td>Right Put to Right MCC</td>
<td>0.09</td>
<td>0.17</td>
<td>0.08</td>
<td>0.041</td>
<td>1.09</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right Put to Right PreCG</td>
<td>0.04</td>
<td>0.16</td>
<td>0.12</td>
<td>0.041</td>
<td>1.04</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right Put to SMA</td>
<td>0.03</td>
<td>0.17</td>
<td>0.14</td>
<td>0.005</td>
<td>1.86</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SMA to Left PreCG</td>
<td>0.28</td>
<td>0.38</td>
<td>0.10</td>
<td>0.027</td>
<td>0.91</td>
<td></td>
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</tbody>
</table>

Figure 5.19 - Change in the parameter estimates during the right bridging task in the left insula ROI in symptomatic individuals who improved in the NPRS (responders) compared to those who did not (non-responders).
Figure 5.20 - Change in the parameter estimates during the right bridging task in the left Midcingulate Cortex ROI in symptomatic individuals who improved in the NPRS (responders) compared to those who did not (non-responders).
Figure 5.21 - Change in the parameter estimates during the right bridging task in the left Putamen ROI in symptomatic individuals who improved in the NPRS (responders) compared to those who did not (non-responders).
Figure 5.22 - Change in the parameter estimates during the right bridging task in the right Insula ROI in symptomatic individuals who improved in the NPRS (responders) compared to those who did not (non-responders).
Figure 5.23 - Change in the parameter estimates during the right bridging task in the right putamen ROI in symptomatic individuals who improved in the NPRS (responders) compared to those who did not (non-responders).
Figure 5.24 - Change in correlation in activity between the right putamen and the right midcingulate cortex from pre- to post-intervention in individuals with chronic low back pain during the right bridging task.
Figure 5.25 - Change in correlation in activity between the right putamen and the right Supplemental Motor Area from pre- to post-intervention in individuals with chronic low back pain during the right bridging task.
Figure 5.26 - Change in correlation in activity between the right putamen and the right Precentral Gyrus from pre- to post-intervention in individuals with chronic low back pain during the right bridging task.
Figure 5.27 - Change in correlation in activity between the Supplemental Motor Area to the Left Precentral Gyrus from pre- to post-intervention in individuals with chronic low back pain during the right bridging task.


12. Martinez-Segura, R., et al., Immediate Changes in Widespread Pressure Pain Sensitivity, Neck Pain, and Cervical Range of Motion After Cervical or THoracic


6.1 Asymptomatic Individuals Demonstrate Robust Functional Connectivity Within Sensorimotor Networks During Lumbopelvic Motor Tasks

Asymptomatic individuals exhibited a broad, robust network of functionally connected regions during the performance of lumbopelvic motor tasks. Within our ROI-to-ROI analysis of the restricted sensorimotor network, we found significant correlations between the supplemental motor area (SMA), the precentral gyrus (PreCG), and the postcentral gyrus (PostCG). However, while these connections were significant, there appeared to be lower connectivity values when compared to literature of the upper extremity, suggesting that other structures (i.e., the spinal cord) may mediate some of the control of the lower extremity[1, 2].

The results of the seed-to-voxel analysis yielded results similar to the whole brain activation in that there were significant correlations between our sensorimotor network and the precuneus, superior frontal gyrus, anterior cingulate cortex, superior parietal lobule, central opercular cortex, inferior frontal gyrus, right insular cortex, and the thalamus. Interestingly, during the performance of the bilateral bridge there was no significant correlation between the SMA and the midcingulate cortex (MCC), while during the unilateral bridging tasks they were significantly anti-correlated. We
hypothesize that this may be the result of default coupling that is inherent in bilateral limb tasks[3].

6.2 Individuals with Chronic Low Back Pain Demonstrate a Broader Network of Activation During Lumbopelvic Exercises

Both individuals with and without chronic low back pain (cLBP) demonstrate activation in the PreCG, putamen, cerebellum, and the SMA. However, only the individuals with cLBP had activation in the MCC, insula, and supramarginal gyrus. Furthermore, the location of activation in the MCC, insula, and putamen was consistent across the tasks in individuals with cLBP. Due to the consistency and the function of these regions, we decided to define two networks. First, we designated the SMA, PreCG, and the Putamen as the motor pathway, which was present in both populations. These regions are involved in the planning, execution, and modulation of motor tasks which make them very salient to our task [4, 5].

Next, we designated the insula, MCC, and putamen as part of the motor-pain network. Both the insula and the MCC have strong structural connections to the sensorimotor regions of the cortex. The insula has been found to be active in response to pain and integrate the emotional aspect with the sensory component [6]. The MCC, on the other hand, has been demonstrated to integrate both motor function and pain processing [7, 8].
6.3 Individuals with Chronic Low Back Pain Lack Distinct Hemispheric Laterality When Performing Unilateral Bridging Tasks.

Asymptomatic individuals demonstrated unilateral activation in the sensorimotor regions of the cortex when performing a unilateral bridging task compared to individuals with cLBP. When individuals with cLBP perform unilateral bridging tasks, upon visual inspection of the data bilateral hemispheres are activated. This can in part be explained by the biomechanical literature, which has suggested that individuals with cLBP exhibit trunk stiffening that is achieved through co-activation of the trunk musculature [9-13]. As Hodges et. al. proposed in 2011 [14], individuals in chronic pain exhibit altered movement patterns in order to protect a painful part of the body from further pain or injury. For individuals with cLBP this alteration of movement patterns results in changes in the kinematics of the spine, leading to increased stiffness of the trunk musculature. This stiffness leads to loss of movement specificity and results in en bloc movements of the trunk. While beneficial in the short term, prolonged maladaptive motor patterns may result in abnormal biomechanical stresses that result in continued pain [14].

6.4 Individuals with Chronic Low Back Pain Generally Demonstrate Higher Levels of Functional Connectivity During Lumbopelvic Exercises.

In our designated motor-pain network of the insula, MCC, and putamen, those with cLBP exhibited higher levels of connectivity. While the levels of connectivity were not statistically different between the groups, across the tasks those with cLBP had
higher levels. This was especially true during the bilateral bridging task where the connection between the Putamen and Insula was only statistically significant in the symptomatic group.

This trend for greater connectivity in those with cLBP remained consistent in the motor network (PreCG, SMA, and Putamen) with one exception: The Putamen to PreCG connection. The two groups exhibited closer relative strengths in the connectivity between these regions with neither group consistently demonstrating greater connectivity. This is of interest because in those who received spinal manipulation it was the connectivity between the Putamen and other key regions of the cortex that statistically increased.

6.5 Spinal Manipulation Alters Cortical Activation Differently Between Those With and Without Chronic Low Back Pain.

In individuals with cLBP, we found a significant increase in the activation of the putamen and the insula whereas in asymptomatic individuals there was a significant decrease in the activation of the PreCG. The increase in activation in those with cLBP may reflect changes in the cortico-basal-ganglia motor loop. The putamen is one of five major nuclei within the basal ganglia (BG) which can both excite and inhibit regions of the brain to regulate motor processes[15]. As outlined by Da Cunha and colleagues in 2015 [16], the literature suggests a model whereby different pathways between the portions of the basal ganglia, such as the internal segment of the globus pallidus (GPI), can directly disinhibit thalamic neurons projecting to the motor areas of the cortex;
while other areas of the BG inhibit different thalamocortical neurons. This balance between disinhibition and inhibition facilitates desired movements while preventing unwanted motor patterns [17, 18].

Additionally, the putamen receives projections from sensory, motor, and limbic regions of the cortex [19], including premotor areas like the SMA [20]. It has been implicated in the both pain processing and motor production [7], making it key region of interest for individuals with pain performing a salient motor task. Furthermore, within the context of motor processing, bilateral activation of the putamen has been specifically implicated in the modulation of force [21] which is required by our task.

In asymptomatic individuals the right PreCG demonstrated a general decrease in activation following spinal manipulation in the left bridging task. In a separate, unpublished data set we found similar findings where following spinal manipulation those without cLBP exhibited a general decrease in activity in bilateral PreCG, with the right PreCG having a greater amount of decrease compared to the left. It is unclear why the right PreCG would exhibit greater decreases following spinal manipulation, but one possibility is that it is related to an effect of the non-dominate LE. In our current dataset only one individual without cLBP was left lower-limb dominate, and that individual was in the control group. Therefore, there may be a greater effect on cortical activation levels in the non-dominate hemisphere. Additionally, this decrease was not found in individuals with cLBP, suggesting that spinal manipulation might alter cortical activation differentially based on the presence of pain.
6.6 Spinal Manipulation Increases Functional Connectivity Between the Putamen and the Precentral Gyrus, Midcingulate Cortex, and the Supplemental Motor Area in Individuals with Chronic Low Back Pain.

In our study we found that individuals with cLBP who received a spinal manipulation exhibited an increased in the functional connectivity between the putamen and the ipsilateral PreCG, MCC, and the SMA during a right bridging task. Therefore, one mechanism by which spinal manipulation might affect motor performance is through the alterations in the cortico-basal-ganglia (e.g. putamen to cortex) motor loop. However, as we did not have a direct measure of motor performance this conclusion is speculative.

6.7 Limitations for the Overall Study.

One of the largest limitations to this study was the small sample size. While there were an original 41 individuals recruited for this study each of the subgroups only had anywhere from 9 to 12 people per group. Unfortunately, this limited the overall power of the study and the inferences we could make on the potential changes following spinal manipulation. A larger sample size would have allowed us to gain a better understanding of the effects of spinal manipulation both in the symptomatic and asymptomatic populations.

Another limitation to the overall study was that gender was not evenly distributed between the groups. In the symptomatic groups we had a disproportionate number of females compared to the asymptomatic group. However, we believe that this
may better represent a symptomatic population as several studies have demonstrated that females exhibit greater prevalence of chronic pain [22-25].

Our groups were relatively young, with mean ages varying between 28 and 34 and with relatively low amounts of pain (NPRS = 4). However, as assessed by PPT, there did seem to be centralized sensitivity in our symptomatic group. This suggests that while our population was relatively young and on the lower end of the NPRS scale, there was evidence of central nervous system alterations within our group [26-32].

An additional limitation to our study was that we did not measure the movement while in the scanner. First, we did not collect EMG data concurrently with our fMRI data. This would have allowed us to make firmer conclusions regarding the linkage between the changes in cortical activation and muscular activation. Also, unlike previous research using lower extremity tasks, we did not incorporate external stabilization devices to reduce motion artifact and control movement. [33-36]. While stabilizing the joint decreases task-related head movement, this isolation may influence the findings. There is an inherent motor variability during movement performance [37] and the ability to compensate for this variation is vital for optimal feedback control[38]. Supplementing joint support during a task may reduce the ability to detect changes in individuals with chronic pain.

6.8 Future Directions

Future studies should focus on increasing sample sizes and including EMG recordings of the lumbopelvic musculature. In a previous study we found that when
individuals performed the modified bridging tasks they activated relative trunk musculature. Being able to measure changes in the EMG activity and correlate that with the changes in the BOLD response would give a much better understanding of the relationship between the two and how changes in cortical activity reflect changes in motor control.

Additionally, future studies should consider removing the bilateral and left bridging tasks. For symptomatic individuals, the right bridging task was the one most responsive to the changes elicited by spinal manipulation. By removing the other tasks, one could add an ankle plantarflexion and hand grasping task. The inclusion of these different tasks would contribute to our understanding in several ways.

First, by adding the ankle plantarflexion task we would be able to see if low back pain modulates the laterality of all lower extremity tasks or just the ones that are relevant to the lumbopelvic musculature. Also, by adding a hand grasping task we would be able to see if changes in cortical activation were present during the performance of all motor tasks or just those relevant to the pain. This would inform us if the changes in the central nervous system were specific to the task or the pain.

Additionally, by adding these two tasks we could start to get a better understanding of the changes in somatotopic organization that occur in individuals with cLBP. Previous research has reported that individuals with cLBP exhibit changes in the organization of the motor cortex[39-42]. However, these previous studies have been limited by the fact that they only assessed the changes in a single muscle[41-43]. By
including both ankle and hand tasks, we could see if the overall somatotopic organization changes (i.e., the distance between the representations of the feet and hands) or if it is just a change in the representation of the low back (i.e., the distance between the representation of the low back and the feet or hands).

Diffusion tensor images (DTI) would also be a useful addition to this study. DTI data would allow us to determine if the differences between individuals with and without cLBP result not only in changes in brain function but structure as well. Lastly, in lieu of a physical intervention (i.e. spinal manipulation) a psychosocial intervention could be used in its place. Previous research has examined the effects of therapeutic neuroscience education, but additional interventions like mindfulness-based stress reduction or cognitive behavior therapy could easily be used in lieu of spinal manipulation. As both approaches have been shown to be beneficial for those with cLBP, it would be interesting to see if their mechanism of improvement is similar to that of SMT.


APPENDIX A

PARTICIPANT OUTCOME MEASURES

Name _____________________________________________   Date _______________

Daytime Phone_______________________ email ____________________________

Occupation ____________________________________________________

1. Which statement best describes your lifetime history of back pain? (Check only one):
   - Prior to my current problem, I never had back pain that had caused me to change or avoid any of my daily activities or recreational pursuits.
   - Prior to my current problem, there were times when back pain caused me to change or avoid my daily activities or recreational pursuits

2. On the pain drawing below please fill the area that corresponds to your current pain:

2. 3. Do you have any of the following symptoms?
   - Numbness or tingling   If yes, circle side(s): R leg,   Left leg
   - Weakness in the legs   If yes, circle side(s): R leg,   Left leg
   - Pain in the legs        If yes, circle side(s): R leg,   Left leg
   - Change in bowel or bladder function
3. To your knowledge, do you now or have you ever had any of the following conditions?

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>☐</td>
<td>☐</td>
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<td></td>
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<tr>
<td></td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

- Osteoporosis?
- Spondylolisthesis (a permanently slipped bone in the back)?
- Inflammatory joint disease such as Rheumatoid arthritis?
- Cancer?
- Infection or inflammation of the lumbar disc?
- Too many or too few vertebrae (lumbarization or sacralization)?
- Broken bone in the back?
- Lumbar stenosis (narrowing of nerve canals in the back)?
- Leg numbness caused by diabetes or blood vessel disease?
- Stomach or bowel problems such as inflammatory bowel disease?
- Aortic aneurysms (a bulging of an artery in the chest or stomach)

5. Please list any other health conditions that you have.

___________________________________________________________________________
___________________________________________________________________________
___________________________________________________________________________
___________________________________________________________________________

6. Please list any medications that you are taking.

___________________________________________________________________________
___________________________________________________________________________
___________________________________________________________________________
___________________________________________________________________________

7. If you are taking pain medication, how long ago was your last dose? _______(hours)
RMDQ

When your back hurts, you may find it difficult to do some of the things you normally do. This list contains some sentences that people have used to describe themselves when they have back pain. When read them, you may find that some stand out because they describe you today. As you read the list, think of yourself over the last 24-hours. When you read a sentence that describes you within the last 24-hours, fill the box to the left of the sentence. If the sentence does not describe you, then leave the box blank and go on to the next one. Remember; only mark the sentence if you are sure it describes you in the last 24-hours.

☐ 1. I stay at home most of the time because of my back.
☐ 2. I change positions frequently to try and get my back comfortable.
☐ 3. I walk more slowly than usual because of my back.
☐ 4. Because of my back, I am not doing any of the jobs that I usually do around the house.
☐ 5. Because of my back, I use a handrail to get upstairs.
☐ 6. Because of my back, I lie down to rest more often.
☐ 7. Because of my back, I have to hold on to something to get out of an easy chair.
☐ 8. Because of my back, I try to get other people to do things for me.
☐ 9. I get dressed more slowly than usual because of my back.
☐ 10. I only stand up for short periods of time because of my back.
☐ 11. Because of my back, I try not to bend or kneel down.
☐ 12. I find it difficult to get out of a chair because of my back.
☐ 13. My back is painful almost all the time.
☐ 14. I find it difficult to turn over in bed because of my back.
☐ 15. My appetite is not very good because of my back pain.
☐ 16. I have trouble putting on my socks (or stockings) because of pain in my back.
☐ 17. I only walk short distances because of my back pain.
☐ 18. I sleep less well because of my back.
☐ 20. I sit down for most of the day because of my back pain.
☐ 21. I avoid heavy jobs around the house because of my back.
☐ 22. Because of my back pain, I am more irritable and bad tempered with people than usual.
☐ 23. Because of my back, I go upstairs more slowly than usual.
☐ 24. I stay in bed most of the time because of my back.
Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

Instructions:
*We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.*

<table>
<thead>
<tr>
<th>RATING</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEANING</td>
<td>Not at all</td>
<td>To a slight degree</td>
<td>To a moderate degree</td>
<td>To a great degree</td>
<td>All the time</td>
</tr>
</tbody>
</table>

*When I’m in pain …*

<table>
<thead>
<tr>
<th>Number</th>
<th>Statement</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I worry all the time about whether the pain will end.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>I feel I can’t go on.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>It’s terrible and I think it’s never going to get any better</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>It’s awful and I feel that it overwhelms me.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>I feel I can’t stand it anymore</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>I become afraid that the pain will get worse.</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>I keep thinking of other painful events</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>I anxiously want the pain to go away</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>I can’t seem to keep it out of my mind</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>I keep thinking about how much it hurts.</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>I keep thinking about how badly I want the pain to stop</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>There’s nothing I can do to reduce the intensity of the pain</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>I wonder whether something serious may happen.</td>
<td></td>
</tr>
</tbody>
</table>

FABQ

Here are some of the things other patients have told us about their pain. For each statement please mark the number from 0-6 to indicate how much physical activities such as bending, lifting, walking or driving affect or would affect your back pain.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Completely Disagree</th>
<th>Completely Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) My pain was caused by physical activity</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
</tr>
<tr>
<td>2) Physical activity makes my pain worse</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
</tr>
<tr>
<td>3) Physical activity might harm my back</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
</tr>
<tr>
<td>4) I should not do physical activities which (might) make my pain worse</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
</tr>
<tr>
<td>5) I cannot do physical activities which (might) make my pain worse</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
</tr>
</tbody>
</table>

The following statements are about how your normal work affects or would affect your back.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Completely Disagree</th>
<th>Completely Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>6) My pain was caused by my work or by an accident at work</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
</tr>
<tr>
<td>7) My work aggravated my pain</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
</tr>
<tr>
<td>8) I have a claim for compensation for my pain</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
</tr>
<tr>
<td>9) My work is too heavy for me</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
</tr>
<tr>
<td>10) My work makes or would make my pain worse</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
</tr>
<tr>
<td>11) My work might harm my back</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
</tr>
<tr>
<td>12) I should not do my regular work with my present pain</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
</tr>
<tr>
<td>13) I cannot do my normal work with my present pain</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
</tr>
<tr>
<td>14) I cannot do my normal work until my pain is treated</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
</tr>
<tr>
<td>15) I do not think that I will be back to my normal work within 3 months</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
</tr>
<tr>
<td>16) I do not think that I will ever be able to go back to work</td>
<td>0 1 2 3 4 5 6</td>
<td></td>
</tr>
</tbody>
</table>
TKS

1 = strongly disagree
2 = disagree
3 = agree
4 = strongly agree

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>I’m afraid that I might injury myself if I exercise</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2.</td>
<td>If I were to try to overcome it, my pain would increase</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3.</td>
<td>My body is telling me I have something dangerously wrong</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4.</td>
<td>My pain would probably be relieved if I were to exercise</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5.</td>
<td>People aren’t taking my medical condition seriously enough</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6.</td>
<td>My accident has put my body at risk for the rest of my life</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7.</td>
<td>Pain always means I have injured my body</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8.</td>
<td>Just because something aggravates my pain does not mean it is dangerous</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9.</td>
<td>I am afraid that I might injure myself accidentally</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>10.</td>
<td>Simply being careful that I do not make any unnecessary movements is the safest thing I can do to prevent my pain from worsening</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>11.</td>
<td>I wouldn’t have this much pain if there weren’t something potentially dangerous going on in my body</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>12.</td>
<td>Although my condition is painful, I would be better off if I were physically active</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>13.</td>
<td>Pain lets me know when to stop exercising so that I don’t injure myself</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>14.</td>
<td>It’s really not safe for a person with a condition like mine to be physically active</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>15.</td>
<td>I can’t do all the things normal people do because it’s too easy for me to get injured</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>16.</td>
<td>Even though something is causing me a lot of pain, I don’t think it’s actually dangerous</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>17.</td>
<td>No one should have to exercise when he/she is in pain</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>


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A total score is calculated after inversion of the individual scores of items 4, 8, 12 and 16
**CES-D, NIMH**

Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way during the past week.

<table>
<thead>
<tr>
<th>Week</th>
<th>During the Past</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rarely or none of the time (less than 1 day)</td>
<td></td>
</tr>
<tr>
<td>Some or a little of the time (1-2 days)</td>
<td></td>
</tr>
<tr>
<td>Occasionally or a moderate amount of time (3-4 days)</td>
<td></td>
</tr>
<tr>
<td>Most or all of the time (5-7 days)</td>
<td></td>
</tr>
</tbody>
</table>

1. I was bothered by things that usually don’t bother me. □ □ □ □
2. I did not feel like eating; my appetite was poor. □ □ □ □
3. I felt that I could not shake off the blues even with help from my family or friends. □ □ □ □
4. I felt I was just as good as other people. □ □ □ □
5. I had trouble keeping my mind on what I was doing. □ □ □ □
6. I felt depressed. □ □ □ □
7. I felt that everything I did was an effort. □ □ □ □
8. I felt hopeful about the future. □ □ □ □
9. I thought my life had been a failure. □ □ □ □
10. I felt fearful. □ □ □ □
11. My sleep was restless. □ □ □ □
12. I was happy. □ □ □ □
13. I talked less than usual. □ □ □ □
15. People were unfriendly. □ □ □ □
16. I enjoyed life. □ □ □ □
17. I had crying spells. □ □ □ □
18. I felt sad. □ □ □ □
19. I felt that people dislike me. □ □ □ □
20. I could not get “going.” □ □ □ □

**SCORING:** zero for answers in the first column, 1 for answers in the second column, 2 for answers in the third column, 3 for answers in the fourth column. The scoring of positive items is reversed. Possible range of scores is zero to 60, with the higher scores indicating the presence of more symptomatology.
HANDEDNESS INVENTORY

**Edinburgh Handedness Inventory (revised)**

Please mark the box that best describes which hand you use for the following activities.

<table>
<thead>
<tr>
<th>Activity</th>
<th>ALWAYS LEFT</th>
<th>USUALLY LEFT</th>
<th>NO PREFERENCE</th>
<th>USUALLY RIGHT</th>
<th>ALWAYS RIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>WRITING</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>THROWING</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCISSORS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOOTHBRUSH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KNIFE (WITHOUT FORK)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPOON</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MATCH (WHEN STRIKING)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COMPUTER MOUSE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Which foot do you prefer to kick with?

Which eye do you use when using only one?
Patient Specific Functional Score (0= no limitation / pain; 10= unable to perform)

<table>
<thead>
<tr>
<th>Task</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td></td>
</tr>
</tbody>
</table>
Minimal Dataset

(PROMIS items marked with ¹; STarT Back or nearly identical items marked with ²; RTF Impact Classification items marked with *)

1. How long has low-back pain been an ongoing problem for you?
   - □ Less than 1 month
   - □ 1–3 months
   - □ 3–6 months
   - □ 6 months–1 year
   - □ 1–5 years
   - □ More than 5 years

2. How often has low-back pain been an ongoing problem for you over the past 6 months?
   - □ Every day or nearly every day in the past 6 months
   - □ At least half the days in the past 6 months
   - □ Less than half the days in the past 6 months

3. In the past 7 days, how would you rate your low-back pain on average?*¹,²

   1 2 3 4 5 6 7 8 9 10
   No pain

Worst Imaginable pain

4. Has back pain spread down your leg(s) during the past 2 weeks?²
   - □ Yes
   - □ No
   - □ Not sure

5. During the past 4 weeks, how much have you been bothered by ... Not bothered at all Bothered a little Bothered a lot
   - Stomach pain
   - Pain in your arms, legs, or joints other than your spine or back
   - Headaches
   - Widespread pain or pain in most of your body

6. Have you ever had a low-back operation?
   - □ Yes, one operation
   - □ Yes, more than one operation
   - □ No
7. If yes, when was your last back operation?
   ☐ Less than 6 months ago
   ☐ More than 6 months but less than 1 year ago
   ☐ Between 1 and 2 years ago
   ☐ More than 2 years ago

8. Did any of your back operations involve a spinal fusion? (also called an arthrodesis)
   ☐ Yes
   ☐ No
   ☐ Not sure

In the past 7 days…

9. How much did pain interfere with your day-to-day activities?*\(^1\)
   ☐ Not at all
   ☐ A little bit
   ☐ Somewhat
   ☐ Quite a bit
   ☐ Very much

10. How much did pain interfere with work around the home?*\(^1\)
   ☐ Not at all
   ☐ A little bit
   ☐ Somewhat
   ☐ Quite a bit
   ☐ Very much

11. How much did pain interfere with your ability to participate in social activities?*\(^1\)
   ☐ Not at all
   ☐ A little bit
   ☐ Somewhat
   ☐ Quite a bit
   ☐ Very much

12. How much did pain interfere with your household chores?*\(^1\)
   ☐ Not at all
   ☐ A little bit
   ☐ Somewhat
   ☐ Quite a bit
   ☐ Very much

13. Have you used any of the following treatments for your back pain? (Check all that apply)
   ☐ Yes
   ☐ No
   ☐ Not sure
   - **Opioid painkillers** (prescription medications such as Vicodin, Lortab, Norco, hydrocodone, codeine, Tylenol #3 or #4, Fentanyl, Duragesic, MS Contin, Percocet, Tylox, OxyContin, oxycodone, methadone, tramadol, Ultram, Dilaudid)
     If you checked yes, are you currently using this medication?..............
   - Injections (such as epidural steroid injections, facet injections) ............
   - Exercise therapy.............................................................................................
   - Psychological counseling, such as cognitive-behavioral therapy..............

The next two questions are for people who normally work outside the home.

14. I have been off work or unemployed for 1 month or more due to low-back pain.
   ☐ Agree
   ☐ Disagree
   ☐ Does not apply

15. I receive or have applied for disability or workers’ compensation benefits because I am unable to work due to low-back pain.
   ☐ Agree
   ☐ Disagree
   ☐ Does not apply
<table>
<thead>
<tr>
<th>Physical Function</th>
<th>Without any difficulty</th>
<th>With a little difficulty</th>
<th>With some difficulty</th>
<th>With much difficulty</th>
<th>Unable to do</th>
</tr>
</thead>
<tbody>
<tr>
<td>16. Are you able to do chores such as vacuuming or yard work?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>17. Are you able to go up and down stairs at a normal pace?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>18. Are you able to go for a walk of at least 15 minutes?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>19. Are you able to run errands and shop?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

**In the past 7 days...**

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>20. I felt worthless</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>21. I felt helpless</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>22. I felt depressed</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>23. I felt hopeless</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

**In the past 7 days...**

<table>
<thead>
<tr>
<th></th>
<th>Very poor</th>
<th>Poor</th>
<th>Fair</th>
<th>Good</th>
<th>Very good</th>
</tr>
</thead>
<tbody>
<tr>
<td>24. My sleep quality was</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

**In the past 7 days...**

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>25. My sleep was refreshing</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>26. I had a problem with my sleep</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>27. I had difficulty falling asleep</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

28. It's not really safe for a person with my back problem to be physically active. | ☐ Agree | ☐ Disagree |
29. I feel that my back pain is terrible and it's never going to get any better. | ☐ Agree | ☐ Disagree |
30. Are you involved in a lawsuit or legal claim related to your back problem? | ☐ Yes | ☐ No | ☐ Not sure |
In the past year:

31. Have you drunk or used drugs more than you meant to? □ □ □ □
32. Have you felt you wanted or need to cut down on your drinking or drug use? □ □ □ □

33. Age: ______ years

34. Gender:
☐ Female
☐ Male
☐ Unknown
☐ Unspecified

35. Ethnicity: (“X” ONLY one with which you MOST CLOSELY identify)
☐ Hispanic or Latino
☐ Not Hispanic or Latino
☐ Unknown
☐ Not Reported

36. Race: (“X” those with which you identify)
☐ American Indian or Alaska Native
☐ Asian
☐ Black or African-American
☐ Native Hawaiian or Other Pacific Islander
☐ White
☐ Unknown
☐ Not Reported

37. Employment Status:
☐ Working now
☐ Looking for work, unemployed
☐ Sick leave or maternity leave
☐ Disabled due to back pain, permanently or temporarily
☐ Disabled for reasons other than back pain
☐ Student
☐ Temporarily laid off
☐ Retired
☐ Keeping house
☐ Other, Specify: ________________
☐ Unknown
38. Education Level: (select the highest level attained)
   □ No high school diploma
   □ High school graduate or GED
   □ Some college, no degree
   □ Occupational/technical/vocational program
   □ Associate degree: academic program
   □ Bachelor's degree
   □ Master's degree (e.g., M.A., M.S., M.Eng., M.Ed., M.B.A.)
   □ Professional school degree (e.g., M.D., D.D.S., D.V.M., J.D.)
   □ Doctoral degree (e.g., Ph.D., Ed.D.)
   □ Unknown

39. How would you describe your cigarette smoking?
   □ Never smoked
   □ Current smoker
   □ Used to smoke, but have now quit

40. Height: _____  Weight: _____
   □ Inches  □ pounds
   □ centimeters  □ kilograms
   □ measured  □ measured
   □ self-reported  □ self-reported
APPENDIX B

DATA COLLECTION FORM

fMRI DATA COLLECTION FORM = MASTER

<table>
<thead>
<tr>
<th>Consent &amp; Confirm Eligibility</th>
<th>Administer MRI Screen</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOB <strong>/</strong>/____ Weight _______</td>
<td>Review Completed Self Reports</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>(if not completed do intake now, rest after MRI protocol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Task Instructions (outside MRI)</td>
<td>Tasks (BB, LB, RB, AC, PF)</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Clinical Examination</td>
<td>Physical Examination</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Safe to Manipulate</td>
<td>Safe to Manipulate</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Initial Pain Assessment</td>
<td>Pain Intensity, Stiffness, Pain Pressure Threshold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Review the Exercises</td>
<td>Practice Task on MRI Scanner Table</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Complete Task Accuracy &amp; Symptom Sheet (pre)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Review Instructions and Flow of Scans</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fMRI e Prime</td>
<td>Ready to run e-prime: program files</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lumbar_muscle_move_R4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Intervention Imaging</td>
<td>Localizer</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>fMRI of the Brain with Pneumatic Tactor</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>fMRI Performance of Back Exercises (accuracy check)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start time _______</td>
<td>Complete Task Accuracy Sheet (during 2/10 blocks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T1-Weighted Imaging of the Brain (if L-tactor only)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>Lumbar Joint Manipulation</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>Cavitation Left side lying</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>Cavitation Right side lying</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Post-Intervention Imaging</td>
<td>Localizer</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>fMRI of the Brain with Pneumatic Tactor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start time _______</td>
<td>fMRI Performance of Back Exercises</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T1-Weighted Imaging of the Brain (if all tactors used)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-Intervention Pain Assessment</td>
<td>Pain Intensity; Stiffness, Pain Pressure Threshold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Move Images from System to Disc/Server</td>
<td>File name: ____________________________</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Current pain intensity: /10  Range of last week: /10 - /10

<table>
<thead>
<tr>
<th>Observation</th>
<th>Y</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral shift</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar Movement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single flexion</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Repeated flexion</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Single extension</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Waiters bow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic tilt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One leg stance</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Seated Tests</th>
<th>Pain</th>
<th>ROM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting Knee Extension</td>
<td>R Positive Negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L Positive Negative</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quadruped Tests</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocking backwards</td>
<td>Positive Negative</td>
<td></td>
</tr>
<tr>
<td>Rocking forward</td>
<td>Positive Negative</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prone Tests</th>
<th>Pain</th>
<th>ROM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip extension</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>L Internal rotation</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>R Internal rotation</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>L External rotation</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>R External rotation</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Test</td>
<td>Pain</td>
<td>ROM</td>
</tr>
<tr>
<td>----------------------</td>
<td>------</td>
<td>-----</td>
</tr>
<tr>
<td>Hip flexion</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>L Straight leg raise</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>R Straight leg raise</td>
<td>Y</td>
<td>N</td>
</tr>
</tbody>
</table>

**NOTES:**

---

**Subject cleared for Participation in Study:**

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Subject cleared for Manipulation:**

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Score on Motor Control Tests:** /6 points
## Pain Reports and Pain Pressure Threshold Pre and Post Intervention

### Pre-scan Pain Intensity / 10

**Range of last week:** \( \frac{10}{10} \)

### Pre-scan Spinal Stiffness / 10

**Range of last week:** \( \frac{10}{10} \)

#### Pre-scan

<table>
<thead>
<tr>
<th>Pain Pressure Threshold</th>
<th>LEFT</th>
<th>RIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Back</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Trapezius</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior Tibia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

### Post-scan Pain Intensity / 10

### Post-scan Spinal Stiffness / 10

#### Post-scan

<table>
<thead>
<tr>
<th>Pain Pressure Threshold</th>
<th>LEFT</th>
<th>RIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Back</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Trapezius</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior Tibia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**NOTES:**
TASK TRAINING AND ACCURACY SHEET

Training Protocol: Follow the full instructions on the protocol instruction sheet. When reviewing once positioned on the MRI table use these brief commands.

You will first hear the task command, then a START command, complete the task and hold the position until you hear the RELAX command.

Push the back of both knees into the roll. START, wait 10 seconds, then tell subject to RELAX.

Push the right knee into the roll. START, wait 10 seconds, then tell subject to RELAX.

Push the left knee into the roll. START, wait 10 seconds, then tell subject to RELAX.

Tighten your stomach muscles. START, wait 10 seconds, then tell subject to RELAX.

Point feet and toes down. START, wait 10 seconds, then tell subject to RELAX.

Accuracy PRE

Verbal Instruction Match

Task (circle all that match): BB RB LB AC PF

Q: Which task is most challenge or the one you have to think about the most to be able to complete?

Most challenging task for subject (circle): BB RB LB AC PF

Do you have increased pain with any of the tasks? (circle all that apply):

BB RB LB AC PF

What intensity of pain does it cause? (circle):

1 2 3 4 5 6 7 8 9 10

How long does it stay increased? (circle): goes away after relax remains increased

Accuracy DURING Scan

Task match e-Prime random instruction

Bout # ______ Task 1 2 3 4 5

Bout # ______ Task 1 2 3 4 5

Comments:
INTRODUCTION

You are invited to participate in a research study performed by the members of the Doctorial Program in Physical Therapy and Department of Psychology at the University of South Carolina. We request that you read this form completely and ask the researchers or the person obtaining the consent any questions you may have regarding this study and your participation.

In this study, we will be using magnetic resonance imaging (MRI) to investigate the relationship between your reported intensity of back pain and the areas to which blood travels within your brain during exercises. MRI is a procedure using a magnetic field and radio frequency pulses (instead of X-rays) by which a picture of the inside of the human body can be obtained. This procedure does not use harmful radiation, and if you are screened properly, the procedure is completely safe. In addition, we are interested in determining how changes in blood flow to the brain correlates to reported intensity of back pain following a single session of spinal manipulation. This procedure will be performed gently and will not be strong enough to cause pain.

Forty adults (20 with and 20 without low back pain) will be recruited for this study to determine the relationship between changes in pain intensity and regions to which blood travels in your brain. This information will be of great value to us as we do more studies to help understand the causes of back pain.
ELIGIBILITY FOR PARTICIPATION IN THIS STUDY

People between the ages of 18 and 60 years may be eligible for this study. You will be excluded from this study if you have had a more serious problem with your back such as:

- A recent broken bone
- A back bone that has slipped forward (known as spondylolisthesis)
- An infection involving the spine
- A history of surgery to your spine
- Severe Arthritis.

In addition, you will not be eligible for this study if:

- You have a substantial loss of bone mass in your spine (known as osteopenia)
- You are pregnant or have been pregnant in the last year
- You weigh more than 280 lbs.
- You are taking narcotic medication regularly for your back pain and are unable to abstain for 48 hours
- You have loose metal objects in your body
- You are receiving disability payments for a spinal problem or currently have a Worker’s Compensation claim
- You are involved in personal litigation for your back problem.

To determine if you are eligible for this study, we will ask you a series of questions, and then ask you to complete a questionnaire that addresses other questions about your current back problem and general health.

DESCRIPTION OF STUDY PROCEDURES

If you are eligible and willing to enroll in this study, you will be assigned to one of two groups.

Group One:

- We will start by performing a physical examination to ensure the safety of your inclusion into the study.
- We will perform pressure-pain threshold (PPT) testing. This will be done by applying gentle, but increasing pressure to different areas of your body. You will be asked to tell the examiner when the pressure first becomes mildly unpleasant, at which point the examiner will stop the pressure and record the reading. The muscles tested will include those at your right and left shoulder blade, low back, and leg, a total of 6 sites.
- Following the PPT, you will undergo the first series of scans. During one of the scans, you will be asked to perform light exercise, while during the other two scans you will be asked to rest. The total time will be about 25 minutes in the scanner.
- Next, you will be removed from the scanner, but will be asked to turn onto your right side. The examiner will gently twist your low back until resistance is felt. If there is no increase in pain, the examiner will perform a gentle thrust to your low back. You will be asked to roll to your left side where this procedure will be performed again. You may or
may not hear and audible pop. The pop is not indicative of anything wrong and will not cause you any pain.

• After the manipulation, you will be placed in the scanner once more for the second series of scans. The second series of scans is identical to the first.

Group Two:

Subjects assigned to group two will undergo the exact procedures as subjects in group one; however, in lieu of receiving the spinal manipulation, you will be asked to rest on your side. If at the conclusion of the study, you decide you want a spinal manipulation one will be provided.

MRI ENVIRONMENT

Before you have your scan, we will ask you to remove all metal from your person, such as jewelry and rings. We will ask you to lie on your back on a small bed called a gantry. Then we will ask you to rest your head in a small cage called a “coil” that goes around your head. The bed will be moved into a large tube where you will undergo the scanning series. While you are in the scanner, you will periodically hear a banging sound. While the sound generated by the scanner is not loud enough to cause permanent damage to your hearing, you will be provided with earplugs, and headphones, that you will be required to wear to protect your hearing.

RISKS OF PARTICIPATION

Risks of MRI:

Because the MRI machine acts like a large magnet, it could move metallic objects in the room during your examination, which could harm you. To prevent such an event from happening; loose metal objects, like pocket knives or key chains, are not allowed in the MRI room. If you have a piece of metal in your body, such as a fragment in your eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, you will not be allowed into the MRI room and cannot have a MRI.

Having a MRI may mean some added discomfort to you. In particular, you may be bothered by feelings of claustrophobia and by the loud banging noise during the study. You will be asked to wear earplugs to avoid possible hearing impairment.

Risks of Spinal Manipulation:

Spinal manipulation treatments are safe if you have no medical problems such as osteoporosis or a recent fracture that may weaken your spine. As mentioned above, we will ask you questions to determine if you are at risk for the presence of those conditions. We will immediately stop treatment and/or testing during the study if you have pain or discomfort. There is a chance that you might have worse pain following the joint manipulation.

BENEFIT OF PARTICIPATION

Other studies that have used this same type of treatment have found participants often report improvement in pain levels and function; however, we are unable to know if you personally will
perceive an improvement following participation in this study. We do not know which of our treatments will provide the best result, but the information gained in this study will help our understanding of the application of treatment to people with back pain.

INCIDENTAL FINDINGS
MRI scans can detect medical conditions, such as cancer, brain injury, and abnormal blood vessels; however, this functional MRI is carried out purely for experimental purposes, and we will not be looking for brain disorders. Furthermore, we are not trained in diagnosing brain disorders; therefore, we are not qualified to offer any diagnostic opinions concerning your scan. It is possible that we will notice something in your scan that appears unusual and/or abnormal. If this occurs, we will inform you of the finding and provide you with a copy of your scan, which you may take to a medical expert for further review and diagnosis. Being told of such a finding may cause anxiety as well as the suggested need for additional tests and financial costs. Any costs associated with a clinical follow-up opinion will be your responsibility. If you do not wish to be informed of this type of finding, you should not participate in the study.

COSTS AND PAYMENTS
There are no costs to you for participating in this research study. You will be compensated for your time with $50.00 cash after both scans have been completed.

COMPENSATION FOR INJURY
In the unlikely event that you sustain an injury, the research team will assist you in obtaining appropriate medical care. All costs associated with such medical care are your responsibility.

CONFIDENTIALITY OF RECORDS
Your identity will be protected throughout this study. An ID number will be assigned to you to ensure that personal information is not disclosed to unauthorized individuals. All records will be kept in a locked file cabinet in the principal investigator's office. Every effort will be made to limit your personal research information to people who have a need to review this information; however, we cannot promise complete confidentiality. There are regulatory agencies (i.e., OHRP, NSF, NJI, etc.) that have a legal right to inspect and copy research records. In addition, the University of South Carolina’s Institutional Review Board can inspect research records for purposes of ensuring that the research study is being, or has been, conducted properly. Any information that is obtained in connection with this study and that could identify you will remain confidential and will not be released or disclosed without your further consent, except as specifically required by law. The results of this study may be presented at meetings, or in publications; however, your identity will not be disclosed.

CONTACT INFORMATION
For information concerning this research study, or if you believe, you have suffered a research-related injury contact, Dr. Max Jordon, at (803) 777-5028 for further instructions.

Questions about your rights as a research subject are to be directed to, Lisa Marie Johnson, IRB Manager, Office of Research Compliance, University of South Carolina, 1600 Hampton Street, Suite 414D, Columbia, SC 29208, phone: (803) 777-7095 or email: LisaJ@mailbox.sc.edu. The
Office of Research Compliance is an administrative office that supports the University of South Carolina Institutional Review Board (USC IRB). The Institutional Review Board consists of representatives from a variety of scientific disciplines, non-scientists, and community members for the primary purpose of protecting the rights and welfare of human subjects enrolled in research studies.

**VOLUNTARY PARTICIPATION**

Participation in this study is voluntary. You are free not to participate or to withdraw at any time for whatever reason without negative consequence. In the event that you do withdraw from this study, the information that you have provided will be kept in a confidential manner.

**SIGNATURES/DATES**

I have read the contents of this consent form and have been encouraged to ask questions. I have received answers to my questions. I give my consent to participate in this study.

I have received (or will receive) a copy of this consent form for my records and future reference.

Subject (print name) ___________________________ Signature ___________________________ Date________

Person obtaining consent_____________________ Signature ___________________________ Date_______
APPENDIX D

BLAND ALTMANN PLOTS

Provided below is a series of supplemental Bland Altmann Plots that were generated to further describe individual responses to spinal manipulation. They represent the change in the magnitude of activation for each individual in the Regions of Interest where the manipulation groups experienced a significant change in mean activation. Red bars represent the 90% confidence intervals for the mean of the control groups.
APPENDIX E

GLOSSARY OF TERMS

**Blood Oxygen Level Dependent (BOLD)** – The BOLD signal is a measure of the difference between the magnetic properties of oxygenated and deoxygenated blood during different conditions. Hemoglobin, the protein molecule found within blood that transports oxygen, demonstrates different magnetic properties depending on the presence of oxygen. When carrying oxygen, hemoglobin has no unpaired electrons making it diamagnetic (meaning it has little effect on the surrounding magnetic field). However, once depleted of oxygen, deoxygenated hemoglobin can have up to four unpaired electrons making it paramagnetic (meaning it can exert an effect on the surrounding magnetic field). This change in the magnetism of the hemoglobin results in a measurable change in the magnetic resonance signal that is quantified as the BOLD change. It is not a direct measure of neuronal activity, but instead a measure of metabolic demand (a.k.a. oxygen consumption).

**Parameter Estimate (PE)** – The PE is an estimation of the amplitude of activation. A common analysis approach to detect the BOLD response to a task is through the use of the general linear model (GLM). The equation used for GLM in fMRI data is:

\[ y = X\beta + e \]
Where $Y$ is the observed time series of data points, $X$ is the design matrix of our study (signal changes that we expect to observe based on our study design), $e$ is the residual error, and $\beta$ (or parameter estimate) is the magnitude of $X$ as a fit to the measured data, $y$.

**False Discovery Rate** – A method of correcting data that controls for the fraction of detected voxels or clusters that are false positives.

**Family Wise Error** – Probability of one or more false positive voxels in the entire image. A generally more conservative method to correct for false positives than FDR and results in low power. Assumes that the activation is zero everywhere, therefore when you reject the null hypothesis (state that a voxel is active) you are rejecting the family-wise null hypothesis. It controls the probability of any false positives.

**Functional Connectivity** – Functional connectivity is the correlation of the observed BOLD signal over time in separate regions of the brain. Task-based functional connectivity is the correlation of the observed BOLD signal during the performance of a task. The correlation of the BOLD signal between the different regions is calculated into an $r$ value.

**Z-Score** – The $z$-score is the number of standard deviations from the mean an observed data point is. SPM converts the parameter estimates into a $t$-statistic then into a $z$-score. Following this, SPM then creates colored maps to represent where the signal is the highest in the brain. The brighter color is given to the higher $z$-score, allowing for better interpretation of the signal. The CONN toolbox correlates the signal between two
regions, creating an r value. In seed-to-voxel analysis, this r-value undergoes a Fisher’s Z transformation to create the z-map.