STRUCTURAL BRAIN IMAGING IN PEOPLE WITH LOW BACK PAIN

A Cross-Sectional Study

BY

Zaid Mansour

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Neena Sharma, PT, PhD
(Chairperson)

_____
William Brooks, PhD

_____
Jeff Burns, MD

_____
Irina Smirnova, PhD

_____
Henry Yeh, PhD

4/29/2016
Date of Dissertation Defense

The Dissertation Committee for Zaid Mansour certifies that this is the approved version of the following dissertation:

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Neena Sharma, PT, PhD
(Chairperson)

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Abstract

Low back pain (LBP) is a common chronic pain condition affecting millions of people worldwide. Conventional methods of diagnosing LBP have provided limited guidance; consequently most patients get a general diagnosis of "nonspecific" LBP. Brain imaging has been proposed to be a method of studying LBP since all pain signals are processed in the brain. Up till today, the relationship between brain structure and LBP is not fully understood. A few studies have examined this relationship but reported inconsistent findings. Additionally, all of those studies examined the chronic LBP population and none have attempted to study acute/subacute LBP population. In this study we have acquired structural brain scans from participants with LBP (acute/subacute and chronic) and healthy controls. A total of 130 participants were included in this study (23 subacute LBP participants, 68 chronic LBP participants, and 39 healthy controls). We compared whole-brain volume between each 2 groups separately using volumetric measurements and using voxel-based morphometry (VBM). We also examined specific regions-of-interest (ROIs) of pain processing. Finally we conducted correlation analyses between brain volumes and clinical outcome measures we collected from the LBP participants in the 2 groups. Our results showed no difference in whole-brain volume between any of the groups measured by volumetric measurements or VBM after correcting for multiple comparisons. We noticed difference in 2 voxels (6.75 mm^3) in the cortical affective regions of the brain when comparing participants with chronic LBP to healthy controls. Normal

aging can lead to an annual loss of 4-6 mm^3 of brain volume; therefore the reduction we have noticed is not clinically significant. No differences were noticed in the other ROIs. Finally, no correlations were noticed between any of the clinical outcome measures and brain volumes. We calculated the effect size of LBP and found it to be <0.1, which is considered a minimal effect size. Our conclusion is that LBP has minimum to no-effect on brain structure regardless of its duration. This information is clinically important for patients, clinicians, and scientists for understanding the underlying neurophysiological consequences of LBP and therapeutic applications.

Acknowledgements

After working on this dissertation for almost a year, I feel like I ran out of words to say, yet there is a lot to be said. Also, this is the part that I've been looking forward to the most in this dissertation to be honest so I'm just going to say it!

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Chapter I

Introduction

1. Low Back Pain Prevalence and Economic Impact:

Low back pain (LBP) is one of the most common chronic pain conditions affecting millions of people worldwide (Hoy *et al.*, 2012; Meucci *et al.*, 2015). It is the second most common reason for visiting a primary care provider after upper respiratory tract infections (Hart *et al.*, 1995; Andersson, 1999). According to the European Guidelines for the Management of Acute Nonspecific LBP in Primary Care, it is defined as "pain or discomfort localized below the costal margin and above the inferior gluteal folds, with or without leg pain" (van Tulder *et al.*, 2006). Two national surveys conducted in the Unit States revealed that about one quarter of the entire population reported LBP in a period of 3 months (Deyo *et al.*, 2006). Due to its wide prevalence, LBP is a major economic burden on society. In the United Kingdom, the annual estimated cost of LBP exceeded $19 billion (Maniadakis and Gray, 2000). In the Netherlands, the direct annual cost of LBP exceeded $350 million (van Tulder *et al.*, 1995). In Australia, the total annual cost of LBP exceeded $6 billion (Walker *et al.*, 2003). Yet, the most alarming figure is from the most recently published study by Katz et al. where they estimated the annual total cost of LBP in the United States at more than $100 billion (Katz, 2006).

2. Low Back Pain Diagnosis and Phases:

LBP can be described according to its duration as acute, subacute, or chronic. There is no consistency in the literature regarding the exact timeline of each of these phases (Dionne *et al.*, 2008); however, most researchers would describe the "acute"

phase as pain for less than 3-4 weeks, and the "chronic" phase as pain for more than 3-6 months. There are no clear guidelines or regulations regarding the timeframe of the subacute phase, nonetheless, it is the transitional phase between the acute and chronic phases. Therefore it can be implied that the "subacute" phase of LBP is pain between roughly 4 weeks and 6 months. Additionally, LBP can also be described according to its cause; discogenic, arthrogenic, or myogenic. Yet, one of the biggest distresses related to LBP is that almost 85% of patients have no specific patho-anatomical diagnosis and rather have idiopathic or "nonspecific" LBP (Deyo and Weinstein, 2001). Nonspecific LBP has been defined as "tension, or soreness and/or stiffness in the lower back region for which it is not possible to identify a specific cause of the pain" (National Collaborating Centre for Primary, 2009). This indicates that patients visiting a physician will not be given a definitive diagnosis of why they are having back pain. Instead, they merely get a statement that indicates that their back pain has no specific known cause. From a healthcare provider's perspective, this can have drastic impacts on therapeutic practices due to the lack of a specific diagnosis leading to additional expenses and more time spent trying to treat this condition. From a patient's perspective, the potential stress of not having a definitive diagnosis may add to the psychosocial aspect of LBP, which can be a major contributor to the pain (Ramond-Roquin *et al.*, 2015).

Another major distress related to LBP is the fact that there is a big mismatch between radiographic findings (spine MRIs) and clinical presentation or symptoms of patients (Jensen *et al.*, 1994; Berg *et al.*, 2013). The study by Jensen et al. (1994)

found that 52% of asymptomatic individuals (individuals with no LBP) showed a disc bulge on their spine MRI on at least one level, 27% showed a protrusion, and 1% showed an extrusion. All those conditions are actual diagnoses of LBP-related conditions, yet none of those individuals have any pain. Berg et al. (2013) concluded that findings from spine MRIs are not related to the intensity or degree of disability caused by LBP. Due to all the aforementioned reasons, getting a specific diagnosis of LBP is a very intricate job.

Lack of a specific diagnosis may be one of the contributors to the progression of acute/subacute LBP into recurrent LBP, and eventually into chronic LBP. Studies show that up to 75% of people who suffer from an acute attack of LBP can sustain feeling pain for at least one year afterwards (Hestbaek *et al.*, 2003). As a chronic condition, other factors such as anxiety, depression, and fear of movement take place simultaneously and start to play a role in pain processing (Reme *et al.*, 2014). The longer the duration of the condition is, the harder it gets to disentangle all the factors that can lead to this complex pain experience, and eventually lead a reduction in quality of life for those patients. Therefore, trying to understand LBP starting from the acute phase, throughout the subacute phase, is very essential in an attempt to comprehend its progression towards "chronicity". This understanding eventually might affect clinical practice in manners where this seemingly unstoppable progression can be slowed down or even prevented. A number of clinical outcome measures are used to assess clinical components of this condition including pain intensity scales, fear of movement questionnaires, depression

measures, and disability scores. The main clinical outcome measures that were used in this study will be discussed in later sections of the introduction.

3. The Pain Phenomenon:

In order to understand LBP, one should take a step back and try to understand "pain" first. Pain is a very challenging phenomenon to study, especially since it is a purely subjective sensation, which makes an objective understanding of it complicated and problematic. In order to understand pain, one can imagine the difference in emotions felt when experiencing a *physically painful incident*, and the emotions felt when *seeing a painful incident*. This indicates that pain has two main components to it; a sensory-discriminative component and an affective-emotional component. The sensory component is similar to other feelings and senses we experience, such as thirst, hunger, or olfaction. In other words, it is the perception of a stimulus that is affecting a part of the human body (Craig, 2002). Nociceptors (pain receptors) are located in different parts of the body (cutaneous, visceral, muscular, and in different joints) and their main function is to alert us about damaging - or potential damaging - stimuli (Dubin and Patapoutian, 2010). Just as stimulating the olfactory receptors leads to smelling an odor, stimulating nociceptors (with high levels of pressure or heat) can lead to experiencing physical pain. Nonetheless, physical stimulation is not the only reason for experiencing pain. The affective component of pain is another main cause of this experience. Pain anticipation, fear of pain, and empathy of pain are all examples of the affective component of pain. In this case, there is no role of nociceptors in experiencing pain, yet pain is felt (Auvray

et al., 2010). This is mainly because pain has an anticipatory aspect to it (Machado *et al.*, 2014). The integration of both aspects, sensory and affective, leads to what is called "the pain phenomenon" (Craig, 2003).

The two components of pain are processed in different parts/regions of the brain (Figure 1.1). According to Borsook et al. (2010), the main regions processing the sensory aspect include the primary somatosensory cortex, thalamus, and posterior insula. The affective pain processing regions include the cingulate, orbitofrontal and medial prefrontal cortices, anterior insula, nucleus accumbens, amygdala, caudate, thalamus, and hippocampus (Borsook *et al.*, 2010).

The primary somatosensory cortex plays a number of roles in terms of brain function, yet it also plays a significant role in pain processing. It is one of the major sites within the brain for integration of afferent input, which leads to sensing the presence, intensity, and location of touch, non-painful thermal stimuli, and more importantly, pain (Vierck *et al.*, 2013).

The insula is divided into anterior and posterior portions. This distinction has been made based on the functional differences of the portions of the insula. The anterior insula is responsible for self-awareness and feeling different emotions such as happiness, anger, music enjoyment, and awareness of pain (Craig, 2002). On the other hand, the posterior insula is related to processing painful stimuli, mostly thermal noxious stimuli (Brooks *et al.*, 2002; Craig, 2003).

The cingulate cortex, and more specifically the anterior cingulate cortex, is also related to pain processing. Many researchers found that the anterior cingulate cortex is activated when painful stimuli were applied to healthy participants, which indicates its role in pain processing (Craig *et al.*, 1996; May *et al.*, 1998; Peyron *et al.*, 2000). The orbitofrontal cortex was also found to be activated in different emotional experiences, including both positive and negative emotions (Etkin *et al.*, 2011). Furthermore, the medial prefrontal cortex was found to be activated in painful experiences and in feeling empathy for others experiencing pain (Lamm *et al.*, 2011).

Not only cortical regions of the brain are involved in pain processing, but also subcortical regions are involved as well. The nucleus accumbens is related to multiple aspects of human behavior such as facilitating goal-directed behaviors (Goto and Grace, 2008) and mediating the rewarding process in the brain (Salamone *et al.*, 2005). Nonetheless, it also plays a role in pain processing, more specifically in mediating and suppressing pain (Altier and Stewart, 1999). The amygdala is another subcortical brain region that is associated with emotional processing, mainly fear emotions (Fernando *et al.*, 2013). Yet this is not the only function of the amygdala as research is pointing towards its role as a memory storage device, and moreover as a "hot spot" for pain control (Rouwette *et al.*, 2012). The caudate is one of the basal ganglia, and a recent literature review reported that it plays a role in emotional processing but only related to sad emotions (Meerwijk *et al.*, 2013). The hippocampus is yet another brain region involved in different functions such as

arousal and attention, memory, emotional processing and sensory-motor integration (Oddie and Bland, 1998; Bird and Burgess, 2008). Additionally, it is found to be involved in processing pain signals (Liu and Chen, 2009). Finally, the thalamus is considered a major center that receives multiple projections from different ascending pain pathways. It is not only a relay station for ascending pathways, but also a major role player in processing pain signals, both sensory and affective (Ab Aziz and Ahmad, 2006).

Pain is a very complex experience. It is affected not only by the amount of the noxious stimulus but also by all the emotions, memories, and cognitive factors that form this experience. Furthermore, it is not *linearly* related to the extent of nociceptive input, especially in cases of chronic pain (Tracey and Mantyh, 2007). Studies examining different pain populations showed that there are structural brain differences in populations with chronic pain. For instance, a number of studies reported significantly lower cortical thickness and brain volume in participants with fibromyalgia when compared to healthy controls (Burgmer *et al.*, 2009; Ceko *et al.*, 2013; Jensen *et al.*, 2013). In the complex regional pain syndrome population studies have found less gray matter volume in different pain-related regions such as the cingulate and orbitofrontal frontal cortices (Geha *et al.*, 2008; Pleger *et al.*, 2014). In general, such findings have been reported in almost all chronic pain conditions indicating that decrease in brain volume is applicable to most, if not all, pain conditions, including chronic LBP (Henry *et al.*, 2011).

It is very essential to understand that a painful experience can activate most, and in some cases all, of the previously mentioned brain regions. This wide involvement of multiple regions highlights the complexity of the pain phenomenon and suggests that pain is not merely a sensory process but rather a complex experience incorporating many regions of the brain. This is why all major regions involved in pain processing were selected to be a part of the regions-of-interest (ROI) analysis that was conducted in this study (*aim 2*). Based on their function, brain regions were assigned into a sensory mask, a cortical affective mask, a subcortical affective mask, and a separate mask for the thalamus since it is involved in both sensory and affective pain processing. Figure 1.2 shows the main masks that we created for this study.

4. Structural Brain Imaging:

Structural brain imaging is one of the major ways of analyzing the brain and examining its volume. Volumetric measurements are used for calculating gray matter (GM), white matter (WM), cerebro-spinal fluid (CSF), and total intra-cranial volumes (GM+WM+CSF). Such measurements are essential in terms of explaining how various brain matter volumes are different on a global level. However, volumetric measurements do not provide information on the location of any differences in brain volume. That is why Voxel-Based Morphometry (VBM) has become a commonly used method for examining brain volume. VBM generates statistical probability brain maps of the differences in volume between groups of subjects indicating the exact location of such differences (Ashburner and Friston,

2000) (*aim 1*). Both methods have been used vastly within the LBP research (Apkarian *et al.*, 2004; Schmidt-Wilcke, 2008; Baliki *et al.*, 2011; Ivo *et al.*, 2013; Ung *et al.*, 2014). Volumetric analyses, as aforementioned, provide a global view of difference in brain matter volume while VBM presents a more focused and cluster-like presentation of such differences. Any volumetric differences occurring in the brain that are not within a sufficiently large cluster (according to the cluster size threshold that is set for the analysis) will not be identified by VBM; however, they will be noticed in the volumetric analyses. Therefore a combination of both methods is the most comprehensive way of examining brain volume, which is what we included in this study.

5. Low Back Pain and Brain Imaging:

With advantages within *in vivo* imaging techniques, a better understanding of centrally mediated differences (within the brain) can be achieved. Brain imaging is considered a safe, noninvasive, relatively easy method of examining the brain, its volume, function, and neurochemistry. Specifically, magnetic resonance spectroscopy (MRS), functional magnetic resonance imaging (fMRI), and structural MRI studies have been conducted to examine central components of nociception within LBP and other various chronic pain conditions (Henry, Chiodo et al., 2011).

5.A. Magnetic Resonance Spectroscopy in LBP:

MRS studies examine the levels of different neurochemicals in the brain. Studies found decreased levels of N-acetyl aspartate (a neurochemical used as an indicator of neuronal health) in different parts of the brain in participants with chronic LBP (Grachev *et al.*, 2000; Sharma *et al.*, 2012). Others found altered levels of glutamate, glutamine, myo-insosytol, and choline in different regions of the brain that are associated with pain processing (Gussew *et al.*, 2011). Studies conducted in our lab demonstrated that such neurochemical differences were correlated with pain duration and pain severity (Sharma *et al.*, 2011). Such findings indicate abnormal brain neurochemistry in participants with chronic LBP.

5.B Functional Magnetic Resonance Imaging in LBP:

Functional MRI studies examine the blood-oxygen level-dependent signal in the brain, usually in response to a certain task. The assumption is that the areas showing more oxygenated blood are the areas that are being activated in response to the specific task. There have been a number of studies that examined brain activation patterns in response to different tasks and stimuli in participants with chronic LBP. Giescke et al. (2004) found that participants with chronic LBP have increased activation in pain-related regions such as primary and secondary somatosensory cortices when compared to healthy controls (Giesecke *et al.*, 2004). Kobayashi et al. (2009) had similar findings and reported increased brain activation patterns in response to mechanical pressure on the lumbar spine of participants with chronic LBP in similar brain regions (Kobayashi *et al.*, 2009). Tagliazucchi et al.

(2010) examined resting-state functional connectivity in participants with chronic LBP and found alterations in spontaneous brain activation patterns as compared to healthy controls (Tagliazucchi *et al.*, 2010). The previously mentioned fMRI studies suggest that there is potentially an altered state of the brain in participants with chronic LBP that affects brain activation patterns. Some authors interpreted those findings (mainly increased brain activation patterns in pain related regions) as a possible cause for decreased pain threshold in those participants and increased pain sensitivity (Kobayashi, Kurata *et al.*, 2009). It is noteworthy that interpreting such findings is difficult due to the complexity of the condition and the various study designs, yet it may indicate an abnormal pattern in brain activation compared to those without LBP.

5.C. Structural Brain Imaging in LBP:

As previously described, structural MRI studies examine the structure and volume of the brain, and eventually grant researchers a way to systematically compare volumes between groups/subjects. There have been only seven studies in this field that were conducted in the past 12 years (Table 1.1). The pioneering work of Apkarian et al. (2004) indicated a significant reduction of brain GM in participants with chronic LBP as compared to healthy controls. Their findings demonstrated a 5-11% reduction in neocortical GM volume, which (according to the authors) is the equivalent to GM loss due to 10-20 years of aging. This reduction was significantly negatively correlated with the duration of pain (Apkarian, Sosa *et al.*, 2004). As significant and alarming those findings might be, the study had a number

of limitations. The authors included a total of 52 participants (26 with chronic LBP and 26 healthy controls) aging from 19-70 years with pain duration ranging from 1 to 28 years. After matching their subjects (chronic LBP group to healthy controls) the authors conducted a paired *t*-test, which might not be considered the best approach for different participants in different groups. The authors also did not use corrections for multiple comparisons when they reported their results, when instead they did 1000 permutations for their analysis.

In an attempt to overcome some of these limitations a number of papers were published subsequently within this arena, but not without some inconsistencies. Baliki et al. (2011) and Ivo et al. (2013) had similar findings regarding decreased whole-brain GM volume in participants with chronic LBP compared to healthy controls. Baliki et al. (2011) had 4 groups in their study; chronic LBP (36 participants), knee osteoarthritis (20 participants), complex regional pain syndrome (28 participants), and healthy controls (46 participants). They detected GM volume differences only in the chronic LBP when compared to healthy controls; the other groups did not show volumetric differences. For their voxel-based analysis they split the brain into 82 ROIs and examined the correlation of brain volumes extracted from each of those regions with clinical outcome measures such as depression symptoms, anxiety, and medications. No correlations were noticed between those outcome measures and the brain volumes. This places a question mark on the validity of the differences they noticed before. If those volumetric differences were not correlated with the clinical symptoms of LBP then

they might not be related to LBP to start with. Another limitation of this study is that the authors mention using Bonferroni-Holm correction for multiple comparisons; however, throughout the article the *p*-value at which such corrections took place is not mentioned. Ivo et al. (2013) compared 2 groups of 14 participants in each; one with chronic LBP participants and the other with healthy controls. Their results show decreased GM volume in the middle cingulate, thalamus, and dorsolateral prefrontal cortex. They also detected a negative correlation between anxiety scores and GM volume in the anterior cingulate. Yet, their volumetric results were based on analyses conducted without correcting for multiple comparisons. Instead they used $p_{\text{uncorrected}} < 0.001$ and a threshold of 100 voxels. Many brain imaging studies have used this approach; however, it is not the recommended method to use with VBM, according to its creators (Ashburner and Friston, 2000). Other researchers found different results when conducting similar studies.

Schmidte-Wilcke et al. (2006), Buckalew et al. (2008), Ung et al. (2012), and Dolman et al. (2014) did not find differences in whole-brain GM volume when comparing participants with chronic LBP to healthy controls. Schmidte-Wilcke et al. (2006) had a total of 36 participants who were split into 2 groups, 18 with chronic LBP and 18 healthy controls. Their results showed no differences in overall GM volume. However, they did notice some differences when using VBM in the somatosensory cortex and brainstem. Yet those findings were also without using corrections for multiple comparisons. Moreover, they conducted correlation analyses between pain duration and intensity and brain volumes. No correlation

was noticed between pain duration and brain volume, but they noticed a negative correlation between pain intensity and brain volume. Nonetheless, they also noticed some increase in GM volume in the basal ganglia and the thalamus, which is the opposite of what has been reported about the thalamus in other studies (Apkarian, Sosa *et al.*, 2004; Gustin *et al.*, 2011). Buckalew et al. (2008) studied a total of 16 participants, 8 with chronic LBP and 8 healthy controls. They reported some trends of decreased GM volume; however, they also reported that none of those results survived corrections for multiple comparisons. Additionally, none of the correlations they conducted between clinical outcome measures and brain volumes were significant. Ung et al. (2012) examined 94 participants, 47 with chronic LBP and 47 healthy controls. The overall VBM analysis did not reveal any between-group differences. However, they also mentioned some trends showing differences in brain volume (exhibiting both increase and decrease in GM volume) in regions such as primary somatosensory and motor cortices and middle occipital lobe when corrections for multiple comparisons were not used. Finally, Dolman et al. (2014) in the most recently published study examined 28 participants, 14 with chronic LBP and 14 healthy controls. They found some volumetric differences between groups; however, none of those trends survived the corrections for multiple comparisons and controlling for other covariates. Their conclusion was that any volumetric differences that were noticed in the brain when comparing participants with LBP and healthy controls were reduced - or even eliminated - when controlling for other major contributing factors (such as age and sex), and after correcting for multiple

comparisons. As noticed, there is a lot of inconsistency in the literature regarding the effect of LBP on brain volume.

There is a number of reasons for such variations in results such as using 1) different magnitude of scanners (1.5 vs. 3 Tesla scanners), 2) different age ranges, 3) different inclusion/exclusion criteria of participants, 4) relatively small sample size (in most papers), and 5) various different data processing parameters. Thus, such inconsistent findings do not provide a clear understanding of possible structural brain differences associated with chronic LBP. Therefore, the **main goal of this study** was to determine whether there are any structural whole-brain differences in participants with subacute and chronic LBP compared to healthy controls. Furthermore, we aimed to examine ROIs that are related to pain processing which can provide a more focused view on those regions. Additionally, we wanted to determine whether there are any correlations between clinical outcome measures related to LBP and the normalized whole-brain volumes. In order to achieve those aims we utilized a larger sample size, used clearly defined inclusion/exclusion criteria, and used the strictest methods of data analyses and corrections for multiple comparisons.

6. Significance:

Up to 85% of LBP cases do not have a specific diagnosis, which ends up being diagnosed as "nonspecific" and eventually also treated "nonspecifically". Moreover, chronic pain conditions can be present due to structural brain differences without

the presence of peripheral causes (Gustin, Peck *et al.*, 2011). This indicates that as pain advances into a chronic case (like in chronic LBP) central differences in the brain can be related to experiencing pain. Therefore, in our study we aimed to determine the structural brain differences that may accompany LBP (in both subacute and chronic phases). Understanding such potential differences can have significant impacts on clinical practice. Findings from this study can be directed towards healthcare professionals in assisting patients suffering from LBP. If we were able to reject the null hypotheses (and detect volumetric differences in the brain) then that would indicate a major central role of brain structure in relation to LBP. At the moment, sensory pain modulation and approaches targeted to treat the lower back are mostly focused on the spine. Nonetheless, clinicians are starting to recognize the affective aspect of chronic pain and how important it is to address this component when it comes to treating patients. If our findings suggest central structural differences in the brain, whether in the chronic or the subacute phases, then clinicians could benefit from that information by modifying their treatment methods. This can lead to a new era of dealing with LBP from a perspective that is more inclined towards affective and emotional interventions. Two previous studies showed that with the appropriate intervention, differences in brain structure and function could be reversed (Baliki *et al.*, 2008; Seminowicz *et al.*, 2011). Given that such brain differences may be reversible, we might be able to provide people with chronic LBP with better treatment approaches. Moreover, clinicians can potentially intervene with aggressive treatment methods to control LBP during the subacute phase and possibly slow down its progression, or even prevent it from taking place.

On the other hand, if we fail to reject the null hypotheses (do not detect volumetric differences) such results can still add a lot to the body of knowledge related to this field. Not being able to detect any structural brain differences in participants with subacute or chronic LBP can be a very calming piece of information for the millions of people around the world suffering from LBP. This would indicate that maybe there are functional and neurochemical differences taking place in the brain, however not structural differences. This would give hope for patients with LBP that their condition might still be manageable and that there is hope for them to get rid of their chronic pain. Of course, this is only way down this path of research, a lot of further research will be required to get to the point where findings can have significant impacts on clinical practice.

7. Innovation:

This study was the first to examine LBP within the two main components of pain; the sensory and affective components. It is of paramount importance to understand that pain is a very complex phenomenon that is not only related to sensory input, but also to affective components. Memory and emotion play a crucial role in pain processing as well (Ploghaus *et al.*, 1999). Therefore understanding the complexity of this composite phenomenon can have significant impacts on rehabilitation in general, and physical therapy practice more specifically. Moreover, in this study we used strict inclusion/exclusion criteria for our participant recruitment (which was a limitation of the previous studies in this field).

Additionally, we examined the correlation of the Fear Avoidance Belief Questionnaire, which is an instrument developed for the assessment of patients' beliefs on how physical activity and work affect their LBP (Waddell *et al.*, 1993), with the normalized whole-brain volumes, which has not been done previously.

In terms of data analysis we created sensory and affective brain masks for the pain processing regions. This method of analysis has not been applied in any of the previous studies, which may present valuable insights into those pain regions. Finally, there have been no previous studies that examined the subacute LBP population. This was the first study to address this population and include it in a brain imaging study to examine the potential brain differences in this group of patients. Findings related to the subacute population will be very essential in terms of their effects on clinical practice (more details on this are presented in Chapter II).

8. Clinical Outcome Measures:

In this study we examined the clinical presentation of our participants. We were interested in 5 main measures: pain duration, pain intensity, fear of movement, depression, and disability. Those measures, since they are related to LBP, were only collected from participants with LBP and not from the healthy controls. The following section is a brief description of each one of the outcome measures.

8.A. Pain Duration:

Pain duration is the subjective duration of which participants have been complaining of LBP for. Unfortunately there is no objective method of measuring the duration of pain other than personal report from each participant, and this was how we collected this data. For the chronic LBP participants they were asked about the duration of their pain in years, for the subacute LBP participants they were asked about it in months. For data analyses purposes, all pain durations were converted into months for all participants.

8.B. Pain Intensity:

Pain intensity is the subjective rating of severity of pain measured by the Numeric Rating Scale (NRS). The NRS is a 0-10 scale that expresses the level of pain experienced by the participant, with 0 indicating no pain and 10 indicating the worst pain imaginable. The NRS is a widely used measure that has been utilized in many studies examining pain levels (Chapman *et al.*, 2011).

8.C. Fear Avoidance Belief Questionnaire:

Fear Avoidance Belief Questionnaire (FABQ) is an instrument used to measure the impact of LBP on work and physical activity (Waddell, Newton *et al.*, 1993). This instrument is a 16-item questionnaire with each item being scored from 0-6. Higher scores indicate higher levels of fear avoidance beliefs (Appendix 1). The questionnaire is made of 2 sub-scales: work subscale (7 items), and a physical

activity sub-scale (4 items). This instrument has been validated in different studies and found to be a valid and reliable instrument (Swinkels-Meewisse *et al.*, 2003).

8.D. Beck Depression Inventory-II:

Beck Depression Inventory-II (BDI-II) is an instrument used to measure the level of depressive symptoms. It is made of 21 questions with each being scored from 0-3. Higher scores indicate more depressive symptoms (Appendix 2). The BDI-II has been validated in many studies including studies examining LBP participants (Wang and Gorenstein, 2013).

8.E. Oswestry Disability Index:

The Oswestry Disability Index (ODI) is a tool that is used to quantify individual disability as a result of LBP (Fairbank *et al.*, 1980). The ODI is made of 10 questions with each being scored from 0-5. Higher scores indicate higher levels of disability (Fairbank and Pynsent, 2000; Joshi *et al.*, 2013). Each one of those questions addresses a different aspect of daily living such as personal care, lifting, walking, sitting, and social life (Appendix 3).

9. Aims and Hypotheses:

In conclusion, the main aims and hypotheses of this study were:

Aim 1: **To determine whether participants with subacute and chronic LBP have altered whole-brain volume compared to healthy controls.**

Hypothesis 1a: Volumetric measurements of normalized whole-brain volume will show less volume in the subacute and chronic LBP groups as compared to healthy controls, and less volume in the chronic group as compared to the subacute LBP group.

Hypothesis 1b:Voxel-wise whole-brain volume determined by VBM will show less GM volume in the subacute and chronic LBP groups as compared to healthy controls, and less volume in the chronic group as compared to the subacute LBP group.

Aim 2: **To determine whether participants with subacute and chronic LBP have altered regional brain volume compared to healthy controls.**

Hypothesis 2a: Regional VBM analysis will show less GM volume within the sensory regions (primary somatosensory cortex and posterior insula) in the subacute and chronic LBP groups compared to healthy controls, and less volume in the chronic group as compared to the subacute LBP group.

Hypothesis 2b: Regional VBM analysis will show less GM volume within the cortical affective regions (cingulate, orbitofrontal, and medial prefrontal cortices, and anterior insula) in the subacute and chronic LBP groups compared to healthy controls, and less volume in the chronic group as compared to the subacute LBP group.

Hypothesis 2c: Regional VBM analysis will show less GM volume within the subcortical affective regions (nucleus accumbens, amygdala, caudate, and hippocampus) in the

subacute and chronic LBP groups compared to healthy controls, and less volume in the chronic group as compared to the subacute LBP group.

Hypothesis 2d: Regional VBM analysis will show less GM volume within the thalamus in the subacute and chronic LBP groups compared to healthy controls, and less volume in the chronic group as compared to the subacute LBP group.

Aim 3: **To determine the relationship between clinical outcome measures and normalized whole-brain volume within both subacute and chronic LBP groups.**

In both the subacute and chronic LBP groups

Hypothesis 3a: Pain duration will be negatively correlated with normalized whole-brain volume.

Hypothesis 3b: Pain intensity will be negatively correlated with normalized whole-brain volume.

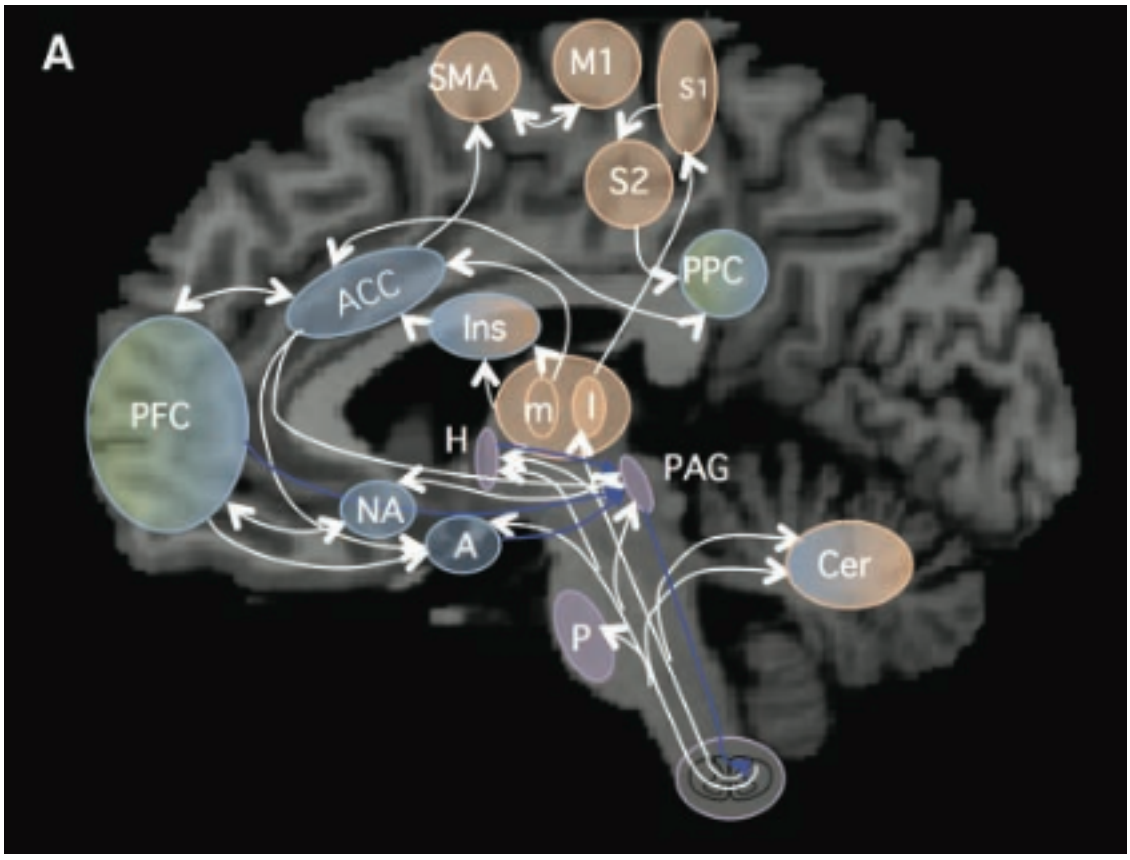
Hypothesis 3c: Fear avoidance (measured by the Fear Avoidance Belief Questionnaire) will be negatively correlated with normalized whole-brain volume.

Hypothesis 3d: Disability scores (measured by the Oswestery Disability Index) will be negatively correlated with normalized whole-brain volume.

Hypothesis 3e: Depressive symptoms (measured by Beck's Depression Inventory-II) will be negatively correlated with normalized whole-brain volume.

10. Figures:

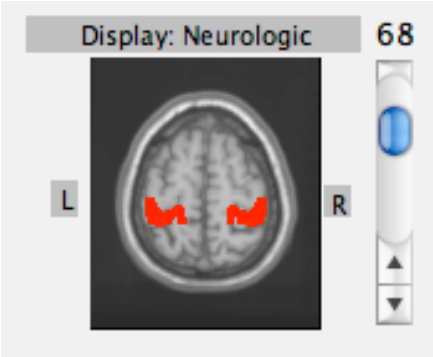
Figure 1.1: Brain regions involved in pain processing.



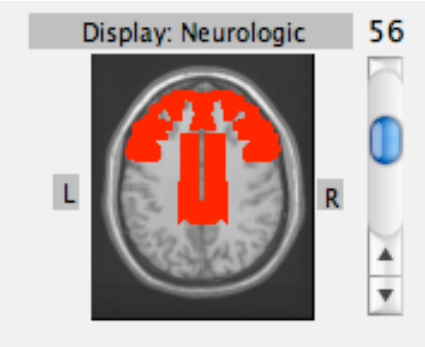
Borsook *et al*. 2010

A: Amygdala, ACC: Anterior cingulate cortex, Cer: cerebellum, H: Hypothalamus, Ins: Insula, l, m: lateral and medial thalamus, M1: Primary motor cortex, NA: Nucleus accumbens, PAG: Periaqueductal gray, PFC: prefrontal cortex, PPC: Posterior parietal cortex, S1 & S2: Primary & secondary somatosensory cortex, SMA: Supplementary motor area.

Figure 1.2: Brain masks created for specific ROIs.



1.2 a



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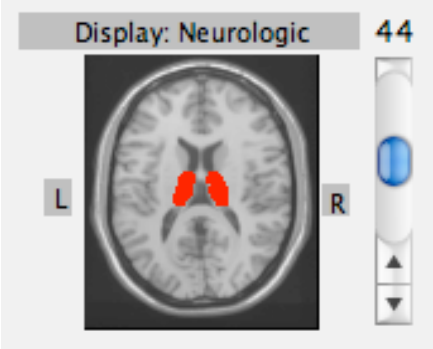
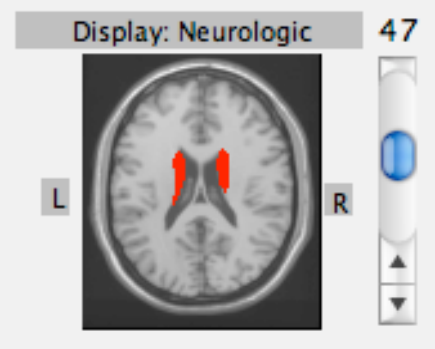


1.2 c



1.2

1.2 a: Sensory mask (somatosensory cortex and posterior Insula). 1.2 b: Cortical affective mask (Cingulate, Orbitofrontal, and Medial Prefrontal cortices, and anterior Insula). 1.3 c: Sub-cortical affective mask (Nucleus Accumbens, Amygdala, Caudate nucleus, and Hippocampus). 1.4 d: Thalamus mask.

11. Tables:

Table 1.1: Summary of previous structural brain imaging studies.

Study	Sample Size	NGM Differences	VBM Differences	Correlation with Pain Duration	Correlation with Pain Intensity
Apkarian et al., 2004	52 (26 cLBP, 26 HC)	Yes	Yes (DLPFC and Th)	Yes	No
Schmidte-Wilcke et al., 2006	36 (18 cLBP, 18 HC)	No	Yes (S1 and DLPFC)	No	Yes
Buckalew et al., 2006	16 (8 cLBP, 8 HC)	No	Yes (parietal cortex)	No	No
Baliki et al., 2010	82 (36 cLBP, 47 HC)	Yes	Yes (insula)	No	No
Ung et al., 2012	94 (47 cLBP, 47 HC)	No	No	No	No
Ivo et al., 2013	28 (14 cLBP, 14 HC)	Yes	Yes (DLPFC, CC, Th)	No	No
Dolman et al., 2014	28 (14 cLBP, 14 HC)	No	No	No	No

NGM: Normalized gray matter, VBM: Voxel-based morphometry, cLBP: Chronic low back pain, HC: Healthy controls, DLPFC: Dorsolateral Prefrontal cortex, Th: Thalamus, S1: Primary Somatosensory cortex, CC: Cingulate cortex.

Chapter II

Subacute Low Back Pain (Prospective Study)

1. Overview:

Low back pain (LBP) is one of the most common conditions worldwide (Hoy, Bain *et al.*, 2012; Meucci, Fassa *et al.*, 2015). Recent, brain imaging studies have found potential differences in brain function and neurochemistry in people with chronic LBP when compared to healthy controls. Although, findings related to structural brain differences are inconsistent in the literature, it is important to investigate if structure differences occur in LBP, and if so how soon following the initial episode of LBP. No previous brain imaging research has been conducted on LBP in acute and subacute phase (pain < 6 months). The subacute phase of LBP is essential to study since it is the transitional phase into chronic LBP. The lack of studies in this phase has been hindering physicians and clinicians' ability to implement effective treatments to patients. We do not know if any brain differences (structural, functional, or neurochemical) take place in acute/subacute phases of LBP. Therefore, we aimed to investigate this population and examine brain volumes in people with subacute LBP, and examine whether the clinical presentation of those participants correlate with their brain volume.

Not only brain imaging studies are lacking regarding the subacute population, even clinical studies are also very limited and scarce. There are a number of possible reasons for why such research is limited. First, there is still no clear definition of a timeline for subacute LBP. Researchers have defined it ranging from 3 weeks up to one year in some cases (Chanda *et al.*, 2011), which is a huge timeframe that adds a lot of heterogeneity to this population making it much more

harder to study. Second, as from our experience, subject recruitment can be very challenging and difficult. Given that subacute LBP has a relatively narrow window – an average of less than 6 months - recruiting participants can be a major challenge. Therefore, only 1 paper has discussed the clinical presentation of this population. In this paper by Chanda et al. (2011) explained the clinical characteristics of participants with subacute LBP as compared to participants with chronic LBP. Their conclusions were that participants with subacute LBP have less pain intensity on a visual analogue scale and less referral pain pattern (unilateral compared to bilateral leg pain) compared to participants with chronic LBP. All other outcome measures they examined (like depression and sensory and affective components of pain) were not significantly different between groups after correcting for pain intensity. With a total of 77 participants in this single study, more research is needed to have a better understanding of this population.

Subacute LBP is defined as pain lasting for 6 months or less following the initial episode of back pain. Understanding central mechanisms of pain during the subacute phase is important for the development of effective and individualized rehabilitation approaches that are currently lacking. A good understanding of such mechanisms might aid researchers in dissecting this progression and may help to slow down or prevent development of chronicity of LBP. To date most studies have explored pain-related neural differences in the chronic phase of LBP. Therefore, we intended to examine this population from a brain imaging perspective. The long-term goal of this project was to understand the neurophysiological factors within

the subacute phase that may lead to chronicity of LBP. The main objective was to determine whether there are any brain volumetric differences in participants with subacute LBP on the whole-brain level and within pain processing regions.

While clinical questionnaires and laboratory-based methods of testing pain provide patient perspective and self-reported pain threshold, these methods do not define the specific neurophysiology consequences of pain, more specifically within the brain. Non-invasive brain imaging methods can be used as a tool to examine such effects. Examining the relationship between patient-reported pain and functional outcomes and structural differences within the brain allows us to gain insights into the neurophysiological mechanisms of pain processing. Investigating pain-processing regions in an early timeframe of pathology may improve our understanding of how and why certain patients develop chronic pain. This information can be used in future studies to identify which individuals may respond to specific therapies, either rehabilitation-based or pharmacological, such that personalized treatments can be employed.

2. Background:

2.A. Low Back Pain:

LBP is a medical condition that affects almost 85% of the adult population (Freburger *et al.*, 2009). It accounts for substantial healthcare spending and is considered a socioeconomic burden to society (Katz, 2006; Juniper *et al.*, 2009). The

exact mechanisms and pain generators contributing to chronic pain are not well understood. Moreover, up to 85% of LBP cases do not have a specific diagnosis and are labeled as "non-specific", which results in lack of specificity in treatment options (Deyo and Weinstein, 2001). Spine radiographs do not correlate with clinical features of pain (Jensen, Brant-Zawadzki *et al.*, 1994; Berg, Hellum *et al.*, 2013) and play a limited role in terms of guiding clinical practice in subacute and chronic LBP phases. Non-invasive neuroimaging methods can be used to gain a better understanding of pain processing and associated differences within the brain.

2.B. LBP and Neuroimaging:

Recent neuroimaging studies suggest the involvement of the brain in chronic LBP. We have previously shown that people with chronic LBP have decreased levels of neurochemicals (specifically N-acetyl aspartate) in sensory and motor cortices that correlate with the duration and intensity of pain (Sharma, McCarson *et al.*, 2011; Sharma, Brooks *et al.*, 2012). Apkarian et al. (2003) reported similar results in affective brain regions, dorsolateral prefrontal cortex and cingulate cortex in people with chronic LBP (Apkarian, Sosa *et al.*, 2004). Decrease in N-acetyl aspartate can be attributed to neuronal degeneration of metabolic changes in sensory and affective pain regions. These neuro-metabolic changes are likely to accompany or lead to volumetric differences (mainly gray matter volume) in the brain. In fact, a number of studies (a total of 7 studies) have examined brain volumetric differences in people with chronic LBP when compared to healthy controls.

Apkarian et al. (2004) reported significant reduction of global brain gray matter (GM) volume (5-11%) in participants with chronic LBP as compared to healthy controls. They attributed this finding to be equivalent to GM loss due to 10-20 years of aging. This reduction was significantly correlated with the duration of pain, indicating that the longer the pain duration was the less brain volume participants had (Apkarian, Sosa *et al.*, 2004). Baliki et al. (Baliki, Schnitzer *et al.*, 2011), and Ivo et al. (Ivo, Nicklas *et al.*, 2013) reported similar findings in relation to decreased overall GM volume in participants with chronic LBP when compared to healthy controls. On the other hand, Schmidte-Wilcke et al. (Schmidt-Wilcke, 2008), Buckalew et al. (Buckalew *et al.*, 2008), Ung et al. (Ung, Brown *et al.*, 2014), and Dolman et al. (Dolman *et al.*, 2014), found no differences in GM volume when comparing participants with chronic LBP to healthy controls. Mao et al. (2013) examined voxel-based morphometry (VBM) in people with LBP and upper back pain. They reported a significant reduction in GM volume in multiple regions related to sensory and affective appraisal (Mao *et al.*, 2013). Although some of these studies were underpowered and presented inconsistent results, they provide initial evidence of potential differences in brain volume. A better understanding of pain-specific regions delineating sensory versus affective pain regions with well-powered study – as the one we conducted – is essential to get a clear understanding of the extent of brain volumetric differences in LBP.

3. Current Gap in Knowledge about Subacute LBP:

Our current knowledge about mechanisms and brain-related differences in subacute LBP is limited. No study has examined possible central nervous system differences in the subacute phase of LBP. LBP can become chronic and result in decreased quality of life and eventually elevated health care costs if it is not managed properly. People experiencing pain and impaired function at 6 weeks are less likely to undergo recovery with considerable percentage progressing to chronic LBP (Waddell, 1998). A systematic review of the prognosis of acute LBP showed that pain and disability are typically ongoing and 73% of patients have at least one recurrence of LBP within 12 months (Pengel *et al.*, 2003). Results from studies examining the long-term effects of an acute/subacute attack of LBP are complicated. Most of the time studies follow-up and report on patients going back to work rather than actual pain scores. Return to work does not necessarily indicate the absence of pain; therefore the results from most published studies are thought to be underestimating the percentage of patients who continue to have LBP after an initial attack of pain (Pengel, Herbert *et al.*, 2003).

During the transitional period of acute/subacute LBP into chronic LBP, recruitment of additional signaling mechanisms beyond acute mechanisms is likely to occur. Understanding these differences and implementing targeted interventions during the subacute phase of LBP is important to improve current clinical practice and reduce healthcare cost. No studies have examined the transitional phase of LBP from a brain imaging perspective, whether structurally, functionally, or in relation

to neurochemistry. We examined brain structure within this phase in this study and its relation to clinical symptoms of LBP.

4. Specific Aim of the Current Study:

The main specific aim of this prospective study was:

> To determine the relationship between clinical outcome measures and normalized brain volumes in participants with subacute LBP.

Hypothesis a: We hypothesize that whole-brain and regional brain volume will be lower in the subacute LBP group as compared to healthy controls.

Hypothesis a: We hypothesize that clinical outcome measures of pain duration, pain intensity, disability, fear of movement, and depression will be negatively correlated with normalized whole-brain volume.

Structural brain imaging measures were used to examine whole-brain and regional-brain volumes. Standard questionnaires of pain, disability, fear of movement, and depression were collected and correlated with the volumetric measurements.

5. Methods and Analysis:

5.A. Pilot work:

In 2014, I was able to run statistical testing on some of the data that we collected on participants with chronic LBP. Fourteen participants (7 with chronic LBP and 7 healthy controls) who were age and sex matched were included in the preliminary data analysis. I calculated the normalized brain volumes from both groups using volumetric measurements and then used the VBM toolbox to examine whole-brain and regional-brain differences between both groups. The preliminary results indicated some structural differences in brain volume between groups (while using an uncorrected $p < 0.001$ due to the small sample size). Using our findings we submitted and received a grant from the Orthopedic Section of the American Physical Therapy Association, specifically to study the subacute population (July 2015 – June 2017). We had already collected data on 17 participants with subacute LBP in our lab from previous studies, so we proposed to study 20 additional participants with subacute LBP. An IRB approval was received in October 2015 (Appendix 4) and data collection started later that month. Our main way of advertising was broadcast e-mails to all university staff, faculty, and students and electronic media (mainly Craigslist). At present we are collecting data towards this study. Figure 2.1 demonstrates the recruitment and screening process of this ongoing study.

After completing the screening process with those participants only 6 qualified and agreed to participate in our study. The clinical data and brain images

of those 6 participants have already been included in the analysis and the discussion of Chapter IV. We will continue to recruit participants for this study, and hope to recruit all 20 by the end of year 2016.

5.B. Inclusion and Exclusion Criteria:

Inclusion criteria for this study included 1) being male or female between the ages of 21 and 60, 2) having LBP for less than 6 months, and 3) having the ability to read and write English (in order to read and sign the consent form).

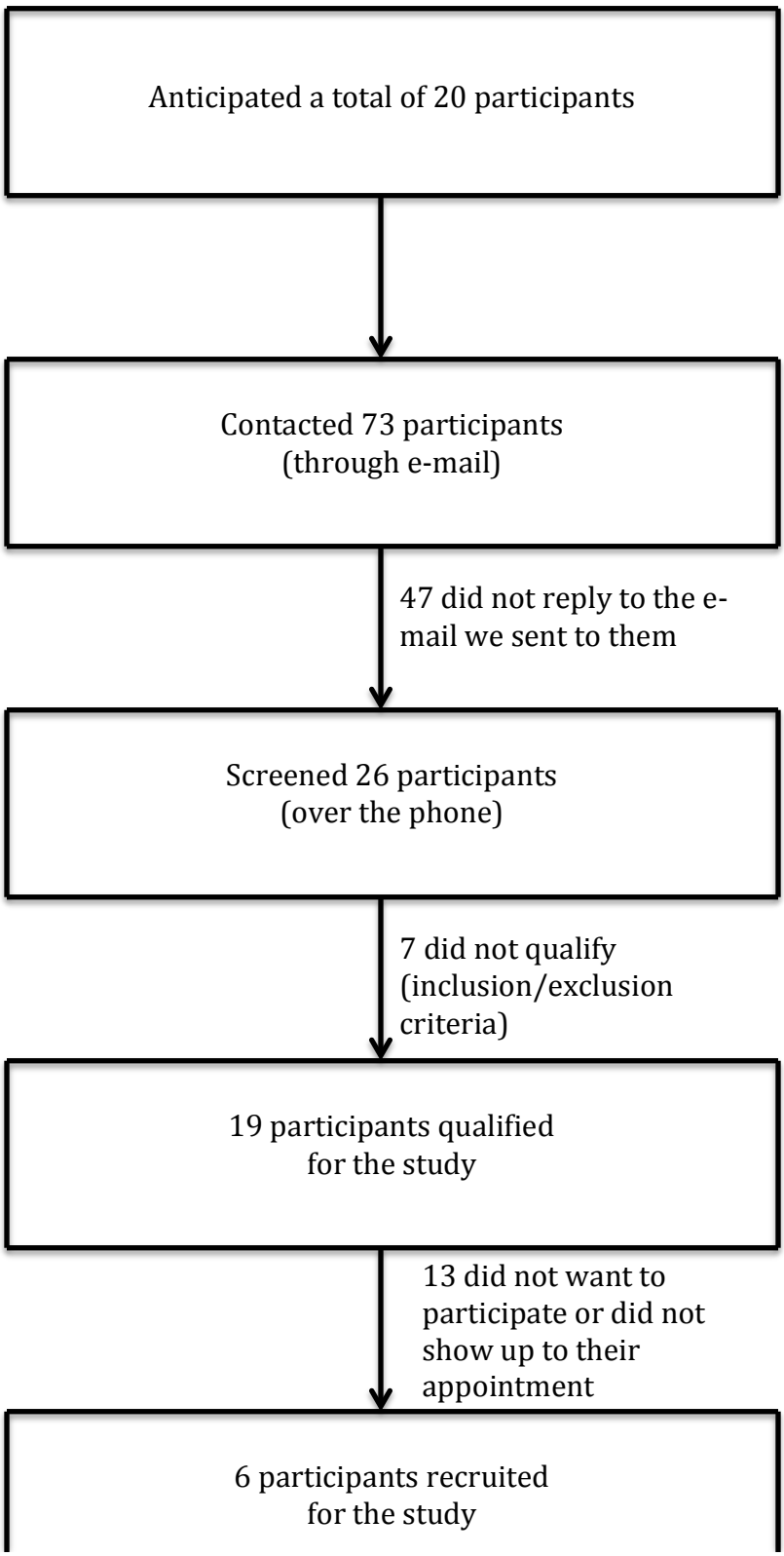
Exclusion criteria for this study included 1) having spinal cord compression, tumor, or infection, 2) any neurologic conditions such as stroke or Alzheimer's Disease, 3) history of spine surgery within one year, 4) head trauma, psychiatric, or cardiovascular disease, 5) use of drugs or alcohol abuse, 6) pregnancy, and 7) and MRI exclusion criteria: implanted metallic objects not compatible with MRI, epilepsy, claustrophobia etc..

6. Results:

The results of this current study are included in the following chapter. All demographic, clinical, and brain imaging data for the subacute LBP group are included in the group analysis in the experimental chapter (Chapter IV).

7. Figures:

Figure 2.1: Screening process and participant recruitment.



Chapter III

Brain Involvement in Low Back Pain

BRAIN INVOLVEMENT IN LOW BACK PAIN

Zaid M. Mansour[1], MS; Rebcca J. Lepping[2], PhD; Robyn A. Honea[3], DPhil; William M. Brooks[2], PhD; Hung-Wen Yeh[4], PhD; Jeffrey M. Burns[3,5], MD, MS; and Neena K. Sharma[1], PT, PhD

[1]Department of Physical Therapy and Rehabilitation Science, University of Kansas Medical Center, 3901 Rainbow Blvd, Kansas City, Kansas, 66160

[2]Hoglund Brian Imaging Center, University of Kansas Medical Center, 3901 Rainbow Blvd, Kansas City, Kansas, 66160

[3]Alzheimer's Research Disease Center, University of Kansas School of Medicine, Kansas City, Kansas, 66160

[4]Department of Biostatistics, University of Kansas Medical Center, Kansas City, Kansas, 66160

[5]Department of Neurology, University of Kansas School of Medicine, Kansas City, Kansas, 66160

Corresponding author:	Neena K. Sharma, PT, PhD
	Assistant Professor
Institution:	University of Kansas Medical Center
	Rainbow Blvd, Kansas City, Kansas, 66160
Phone:	(913) 588-4566
Fax:	(913) 588-4566
E-mail:	nsharma@kumc.edu

1. Abstract:

Low back pain is one of the most common pain conditions affecting millions of people worldwide. Low back pain has been associated with less brain volume in a few studies, yet this finding is inconsistent across studies. The aim of this study was to determine whether low back pain (subacute and chronic) is related to brain volume. Additionally we aimed to examine the relationship between brain volume and clinical presentation of pain. A total of 130 participants were included (23 with subacute low back pain, 68 with chronic low back pain, and 39 healthy controls). The main outcome measure was brain volume. Clinical outcome measures included pain duration, pain intensity, fear avoidance belief questionnaire, Oswestry disability index, and Beck's depression inventory. After correcting for multiple comparisons, no significant differences were detected between any of the 3 groups in whole-brain volume. However, regionally, we detected less gray matter volume in 2 voxels in the middle frontal gyrus in those with chronic low back pain compared to healthy controls. Without correcting for multiple comparisons some patterns of brain volume differences were observed. None of the clinical outcome measures were correlated with brain volume measurements. Low back pain (subacute or chronic) was not related to significant differences in brain volume. The effect size may have been too small to detect possible subtle changes unless much larger sample sizes are examined, or it is also possible that low back pain does not affect brain volume.

Keywords: low back pain, chronic, subacute, neuroimaging, voxel-based morphometry

2. Introduction:

Low Back Pain (LBP) is one of the most common pain conditions affecting millions of people worldwide (Flor *et al.*, 1997; Von Korff and Dunn, 2008), and can be a major cause of disability (Walker *et al.*, 2004; Verma and Pal, 2015), depression (Rush *et al.*, 2000; Pincus *et al.*, 2002; Ramond *et al.*, 2011), and loss of work (Rizzo *et al.*, 1998; Nguyen and Randolph, 2007). Consequently, its economic impacts are tremendous with an annual cost in the US exceeding $100 billion (Katz, 2006). One of the biggest mysteries of LBP is that almost 85% of patients have no specific patho-anatomical diagnosis but rather have idiopathic or "nonspecific" LBP (Deyo and Weinstein, 2001). Furthermore, there is a mismatch between radiographic findings from spine images and clinical symptoms (Berg, Hellum *et al.*, 2013; Jensen, Srinivasan *et al.*, 2013), making diagnosing - and even understanding - LBP much more intricate. Although underlying causes of LBP can be varied and difficult to determine, all pain sensations are processed similarly in the brain. Brain imaging methods can be used to determine the relationship between pain and brain function and structure.

Pain is subjective and idiosyncratic. In general, the pain experience incorporates two main components: sensory-discriminative and affective-emotional components. These components are processed in different brain regions, yet are integrated and influenced by each other (Borsook, Sava *et al.*, 2010). Although recent evidence suggests that people with LBP have altered brain neurochemistry (Grachev, Fredrickson *et al.*, 2000; Sharma, Brooks *et al.*, 2012) and function

(Giesecke, Gracely *et al.*, 2004; Tagliazucchi, Balenzuela *et al.*, 2010), similar structural brain changes have not been established.

Smaller brain volumes have been reported in such neurodegenerative diseases as multiple sclerosis (Cheriyan *et al.*, 2012; Koenig *et al.*, 2014; Radue *et al.*, 2015), Alzheimer's disease (Karas *et al.*, 2004; Ibrahim *et al.*, 2009; Gordon *et al.*, 2013), and schizophrenia (Shenton *et al.*, 2001; Cahn *et al.*, 2002; Kasparek *et al.*, 2009), and also in chronic pain conditions such as fibromyalgia (Kuchinad *et al.*, 2007; Diaz-Piedra *et al.*, 2015; McCrae *et al.*, 2015), complex regional-pain syndrome (Geha, Baliki *et al.*, 2008; Barad *et al.*, 2014), and chronic LBP (Apkarian, Sosa *et al.*, 2004; Baliki, Schnitzer *et al.*, 2011). To date, seven structural brain imaging studies examining volumetric brain measurements in people with chronic LBP (Apkarian, Sosa *et al.*, 2004; Schmidt-Wilcke *et al.*, 2006; Buckalew, Haut *et al.*, 2008; Baliki, Schnitzer *et al.*, 2011; Ivo, Nicklas *et al.*, 2013; Dolman, Loggia *et al.*, 2014; Ung, Brown *et al.*, 2014) have been completed. Findings from these studies were inconsistent, with some observing smaller volumes in participants with chronic LBP compared to healthy controls, and others finding no group differences in brain volume. Importantly, the sample sizes in these studies were modest and many of those that reported differences in brain volume based their conclusions on results uncorrected for multiple comparisons (Schmidt-Wilcke, Leinisch *et al.*, 2006; Buckalew, Haut *et al.*, 2008; Ivo, Nicklas *et al.*, 2013), drawing into question the significance of the observation. Moreover, no studies have addressed subacute LBP in terms of brain structure and whether such potential differences exist during

earlier stages of the disease. The relationship between possible volumetric differences and clinical presentation of LBP is also unclear.

The main aims of this study were to determine whether there are: 1) whole-brain volumetric differences in participants with subacute and chronic LBP compared to healthy controls, within a relatively large sample, measured by total volume measurements and voxel-based morphometry (VBM); 2) regional brain differences in participants with subacute and chronic LBP compared to healthy controls measured by VBM; and 3) relationships between clinical outcome measures and brain volumes in participants with subacute and chronic LBP. We hypothesized that participants with chronic LBP would have smaller whole-brain volumes as compared to subacute and healthy controls, and participants with subacute LBP would have smaller whole-brain volumes compared to healthy controls. Secondly, we hypothesized that we would find smaller brain volumes within sensory and affective pain processing regions in participants with LBP. Finally, we hypothesized a negative correlation between normalized whole-brain volumes and clinical outcome measures such as pain intensity, pain duration, depression, or fear avoidance.

3. Methods:

3.A. Study Population:

130 participants were included in this study: subacute (<6 months) LBP (n=23, 57% female), chronic (>6 months) LBP (n=68, 71% female), and healthy controls (n=39 participants, 44% female). Inclusion criteria for the LBP participants were: 1) male/female between 21 and 70 years, 2) having pain for less than 6 months (subacute group) and more than 6 moths (chronic group), and 3) being able to read and understand English. Exclusion criteria were: 1) spinal cord compression or spine surgery within the past year, 2) known injuries or arthritis to the hip, knee or ankle joints, 3) any neurologic condition (including head trauma, stroke, or Alzheimer's disease), 4) psychiatric or cardiovascular disease, tumor, or infection, 5) use of drugs or alcohol abuse, 6) pregnancy, and 7) MRI exclusion criteria (such as metallic object implants not compatible with MRI, epilepsy, or claustrophobia). The healthy controls self-reported no history of LBP within the last one year. Participants were recruited through broadcast e-mails to university staff and employees, and word-of-mouth. The study was approved by the Human Subject Committee at the University of Kansas Medical Center, and all participants provided informed consent prior to taking part in the study.

3.B. Imaging Procedures:

High-resolution T1-weighted magnetization prepared rapid acquisition gradient echo (MP-RAGE) brain images were collected at 3-Tesla (matrix=256x256;

208 slices; voxels=1.0 mm x 1 mm x 0.97 mm; TE=3.05 ms; and TR=2300 ms on Siemens Allegra and Skyra, Siemens Medical Solutions, Germany) at the University of Kansas Medical Center Hoglund Brain Imaging Center. Standard preprocessing was performed for all images using VBM8 toolbox(Ashburner and Friston, 2000) through Statistical Parametric Mapping software SPM8 (Welcome Department of Cognitive Neurology, London, UK) that operates under MATLAB (Mathworks, Sherborn, MA, USA). Preprocessing included spatial normalization of all acquired images into the same stereotactic space, to account for head size differences between participants. DARTEL segmentation into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF), and Gaussian spatial smoothing (8 mm full-width at half-maximum) as determined by previous studies was performed. Image quality and sample homogeneity were verified through visual inspection using the VBM8 tools (Ashburner and Friston, 2000). We used volumetric outputs from the VBM8 stream to calculate individual normalized whole-brain volume, which is the sum of GM volume and WM volume divided by total intracranial volume. Further, we used VBM analysis to generate smoothed, modulated, warped statistical brain maps of the probability of difference in brain volume between groups of participants (Ashburner and Friston, 2000).

For region-of-interest (ROI) analysis we used the Wake-Forest PickAtlas (Maldjian *et al.*, 2003; Maldjian *et al.*, 2004) to create masks of pain-related brain regions (Borsook, Sava *et al.*, 2010). Four ROI masks were created; a sensory mask, which included the primary somatosensory cortex and the posterior insula; a

cortical affective mask which included the cingulate, orbitofrontal, and medial prefrontal cortices and the anterior insula; a subcortical affective mask which included nucleus accumbens, amygdala, caudate, and hippocampus; and a mask of the thalamus. The thalamus was created as a separate mask, as both sensory and affective pain experiences are processed via thalamus (Borsook, Sava *et al.*, 2010).

3.C. Clinical Outcome Measures:

The clinical outcome measures included pain duration, pain intensity, fear avoidance, disability, and depression. Pain duration was measured in months. Pain intensity was measured as the subjective rating of pain severity over the previous week measured by the Numeric Rating Scale (NRS) (Chapman, Norvell *et al.*, 2011). The NRS is a 0-10 scale that represents pain level, with 0 as having no pain and 10 as having the worst pain imaginable. Fear avoidance was measured by the Fear Avoidance Belief Questionnaire (FABQ), which quantifies the subjective impact of work and physical activity on pain level (Waddell, Newton *et al.*, 1993). This instrument is a 16-item questionnaire with each item scored from 0-6. Higher scores indicate higher levels of fear avoidance. Disability was measured by the Oswestry Disability Index (ODI (Fairbank, Couper *et al.*, 1980)), which quantifies individual disability due to LBP. ODI scores greater than 60% indicate severe disability (Fairbank and Pynsent, 2000; Joshi, Raiturker *et al.*, 2013; Mohan *et al.*, 2015). Finally, depression symptoms were measured using the Beck Depression Inventory (BDI–II), which has been validated in multiple studies (Wang and

Gorenstein, 2013). BDI–II scores greater than 17 indicate borderline depressive symptoms.

3.D. Statistical Analysis:

To investigate difference in age between the groups, we conducted an analysis-of-variance (ANOVA) test, followed by Tukey's post-hoc testing using SPSS 22.0 software (IBM Corp. Released 2013. IBM SPSS Statistics for Macintosh, Version 22.0. Armonk, NY: IBM Corp). Then, we conducted Chi-square testing to investigate differences in sex and scanner between groups. Age, sex, and scanner difference were then used as covariates in each of the brain volume analyses.

- Normalized Whole-Brain Volumes:

To determine whether there were overall brain volume differences between the three groups, we conducted a univariate one-way ANOVA test using SPSS for the normalized whole-brain volumes as the dependent variable, and group (subacute, chronic, healthy) as the independent variable controlling for age, sex, and scanner as covariates.

- Voxel-Based Analysis (whole-brain and ROI):

We examined GM volume differences between the groups using SPM8. We conducted two sample *t*-tests between each pair of groups (healthy-subacute, healthy-chronic, subacute-chronic) over the whole brain and then within the four

regional masks, correcting for multiple comparisons in each test. Age, sex, and scanner were controlled for in each test.

- Correlation Analysis:

In order to detect relationships between clinical outcome measures and brain volume, we conducted partial correlations between the normalized whole-brain volumes and each clinical outcome measure in the subacute and chronic LBP groups separately using SPSS 22.0 software, while controlling for age, sex, and scanner in each test.

4. Results:

The ANOVA test revealed a significant age difference between the groups ($F(2,127)=3.99$, $p=0.021$, $\eta^2=0.06$), with the chronic group being significantly older than the subacute group ($p=0.025$, $M_{difference}$ *=-8.39, std. error=3.18*) and no difference between the healthy and subacute ($p=0.527$, $M_{difference}$*=3.74, std. error=3.46)* or healthy and chronic groups ($p=0.189$, $M_{difference}$ *=-4.64, std. error=2.65*). The Chi-square test showed that the ratio of males/females was different across the groups ($\chi^2(2)=7.67$, $p=0.022$) with a greater proportion of females in the chronic LBP group. The ratio of participants scanned on the two scanners was not significantly different across groups ($\chi^2(2)=5.40$, $p=0.067$) with more participants scanned on the Allegra scanner in all 3 groups (healthy 84.6%, subacute 60.8%, and chronic 66.2%). Therefore, throughout this study we included age, sex, and scanner as covariates in our analyses.

4.A. Clinical Features:

Demographic and clinical data are presented in Table 3.1. The clinical outcomes were collected only from participants with LBP (subacute and chronic). There was no statistical difference between both LBP groups in any of the outcome measures except for pain duration and disability scores. Participants in the chronic LBP group had experienced pain longer than the subacute LBP group ($t(86)=-5.63$, $p<0.001$). Moreover, the same group showed greater levels of disability compared to the subacute LBP group ($t(87)=-2.47$, $p=0.016$).

4.B. Brain Volume Differences:

- Normalized Whole-Brain Volumes:

There was no overall difference in normalized whole-brain volume between groups after controlling for age, sex, and scanner ($F(2,124)=1.63$, $p=0.20$, $\eta^2=0.03$). Figure 3.1 presents the mean and standard deviation of the normalized whole-brain volumes for each group. Additionally we determined the effect size of this aim using G-Power software (Faul *et al.*, 2007; Faul *et al.*, 2009). Through calculating the means and standard deviations of the normalized whole-brain volumes for each of our groups we detected an effect size of 0.07, which is considered a small effect size. We then calculated the sample size required to detect this effect size (0.07) at a power of 80% and it was a total of 1722 participants.

- Voxel-Based Analysis (whole-brain and ROI):

Following correction for multiple comparisons (family-wise error corrected $p<0.05$), we found no differences between any inter-group comparisons on the whole-brain level. All comparisons tested both contrasts of each set (for example, subacute>healthy and healthy>subacute). However, to verify whether previously reported trends were also observed in this large sample, we repeated the comparisons using uncorrected $p<0.001$ and a threshold of 100 contiguous voxels. At this less stringent threshold we observed evidence of volume differences in some regions: middle frontal gyrus, superior frontal gyrus, parahippocampal gyrus, and cerebellum (Table 3.2).

The ROI analysis of the cortical affective mask indicated that the chronic LBP group have less GM volume in 2 voxels (6.75 mm^3) within the middle frontal gyrus (MNI-coordinates: -34/51/15) compared with healthy controls (corrected $p<0.05$; Figure 3.2). No other ROI comparisons showed any differences in GM volume.

- Correlation Analysis:

The clinical outcome measures were not correlated with the normalized whole-brain volumes in either subacute or chronic LBP groups after controlling for age, sex, and scanner (all $r<0.18$ Table 3.3).

5. Discussion:

To our knowledge this is the largest study (total of 130 participants) that has examined brain volume in participants with LBP. Although several studies have investigated chronic LBP, none have addressed the subacute population. This is the first to examine such brain volume effects within the subacute LBP population.

Our results are consistent with previous reports that found no difference in whole-brain volumes in chronic LBP (Schmidt-Wilcke, Leinisch *et al.*, 2006; Buckalew, Haut *et al.*, 2008; Dolman, Loggia *et al.*, 2014; Ung, Brown *et al.*, 2014), and suggest that chronic LBP is not associated with robust differences in brain structure and volume. Consistent with this theoretical argument, we also found no difference in brain volume in participants in the earlier (subacute) stages of the disease. Additionally, when examining sensory and affective pain-related ROIs we found evidence of lower middle frontal gyral (cortical affective mask) volume in 2 voxels in participants with chronic LBP compared to healthy controls. If structural brain changes were occurring during persistent LBP, they must therefore be very subtle and would require a very large sample size (about 1700 subjects) to detect with current structural brain imaging techniques. Dolman et al. reported needing up to 1616 participants per group to detect such differences in the chronic LBP population (Dolman, Loggia *et al.*, 2014).

We conducted partial correlations (controlling for age, sex, and scanner) and did not find any correlation between clinical measures and normalized whole-brain

volume. These findings did not support our original hypothesis. Although within the broad pain literature, findings suggest a correlation between clinical outcome measures and brain volume (Kuchinad, Schweinhardt *et al.*, 2007; Kim *et al.*, 2008; Blankstein *et al.*, 2010), studies specifically examining LBP reported no correlations between such outcomes and brain volume even in the presence of brain volume differences (Baliki, Schnitzer *et al.*, 2011; Ivo, Nicklas *et al.*, 2013). Such findings question the clinical relevance of the differences in brain volume reported in previous pilot studies.

Brain imaging results can be influenced by many factors. We employed rigorous methods to avoid type 1 errors. We corrected for multiple comparisons as recommended by the creators of VBM (Ashburner and Friston, 2000). Other studies either did not correct for multiple comparisons (Schmidt-Wilcke, Leinisch *et al.*, 2006; Buckalew, Haut *et al.*, 2008; Ivo, Nicklas *et al.*, 2013) or used a different method (such as permutation testing (Apkarian, Sosa *et al.*, 2004)). Another difference is related to the methodology and subject recruitment. We recruited participants with LBP and then healthy controls and conducted ANOVA, controlled for age and sex, to compare our groups as suggested by Dolman et al. (Dolman, Loggia *et al.*, 2014) We also used two-sample *t*-tests, unlike some of the methodology used by other researchers. The latest study published on this topic by Dolman et al. concluded that controlling for the main covariates (such as age and pain levels) could reduce - or even potentially eliminate - the previously reported findings of differences in brain volume (Dolman, Loggia *et al.*, 2014). Mover, it is

well known that aging is associated with decreases in GM and WM volumes (Good *et al.*, 2001). This loss is not homogeneously distributed across the brain, with some regions demonstrating more decline in GM volume with aging than others. This includes regions that are related to pain processing such as the orbitofrontal, cingulate, and insular cortices (Resnick *et al.*, 2003) that might explain our failure to detect volume differences after we carefully controlled for age effects.

Several theoretical models have been proposed as mechanisms for brain volume changes in chronic LBP; however, these models account for both theoretical decreases and increases in brain volume, making interpretation of brain volumes from MR images difficult. Increased levels of glutamate have been reported in chronic pain (Mullins *et al.*, 2005; Harris *et al.*, 2009; Valdes *et al.*, 2010; Gerstner *et al.*, 2012; Fayed *et al.*, 2014). Prolonged exposure to high levels of glutamate is neurotoxic, and this neurotoxicity could result in loss of neurons via neurodegeneration or neuronal apoptosis (Rothstein, 1996). Conversely, some have argued that increased glutamate might lead to tissue scarring and therefore increasing cortical thickness (Dolman, Loggia *et al.*, 2014). Moreover, after tissue injury cells hypertrophy in response to increased levels of glutamate (Buffo *et al.*, 2008), potentially reversing cell volume loss. In addition to neurochemical hypotheses, some researchers credit volumetric differences to changes in lifestyle, since chronic pain leads to decreased mobility and activity (Tracey and Mantyh, 2007). Exercise has been shown to assist in increasing brain volume (Gondoh *et al.*, 2009; Erickson *et al.*, 2011), suggesting that less mobility might be related to

decreased brain volume. More research is needed to confirm or refute these theories.

Our results suggest that brain volume is not severely affected by LBP, with other factors (such as age) having a larger impact on brain volume. Nonetheless, the brain cytoarchitecture might be affected by pain. Such differences require other methods of detection. For example, this might explain why other studies (Grachev, Fredrickson *et al.*, 2000; Giesecke, Gracely *et al.*, 2004; Kobayashi, Kurata *et al.*, 2009; Tagliazucchi, Balenzuela *et al.*, 2010; Gussew, Rzanny *et al.*, 2011; Boendermaker *et al.*, 2014) (including those conducted in our laboratory (Sharma, McCarson *et al.*, 2011; Sharma, Brooks *et al.*, 2012)) have observed differences in brain function and neurochemistry in people with chronic LBP and yet we did not detect gross structural differences with VBM. It may also be possible that LBP people with higher pain intensity than reported by our cohort and greater level of depression and disability may have greater effect on brain structure. Our subject experienced moderate pain intensity and minimum depression and disability.

Although we used a large sample size and stringent data analysis methods available we acknowledge some limitations. First, there was a significant difference in age between groups. This was anticipated since our LBP groups are defined by duration of their pain, and hence we expected the chronic group to have older participants than those in the subacute group. Also, there was a significant difference in sex proportion within our sample. Again this was also anticipated since

chronic pain is more prevalent in females than males (Mogil, 2012). Finally, although we collected data on different scanners, all acquisition parameters were identical. Moreover, since we are comparing calculated volumes that are based on careful scanner calibrations completed during routine quality assurance procedures, this is unlikely to contribute to false findings. Nonetheless, we added each of these factors as a covariate in our analyses to minimize their potential effects on our results.

6. Conclusion:

Clinical interpretation of this line of research can be challenging. However, we conclude that there is a minimum- to no-effect of LBP (subacute or chronic) on brain volume and structure. LBP might have effects on brain function and brain neurochemistry. However, our study did not find any significant differences in brain volume after controlling for age, sex, and scanner differences, and after correcting for multiple comparisons in participants with LBP (subacute and chronic) as compared to healthy controls. Moreover, none of the clinical outcome measures that we collected showed any significant correlation with brain volumes. Our findings can be calming to physicians, therapists, and even patients given the alarming findings of the first study in this field (Apkarian, Sosa *et al.*, 2004) that suggested participants with chronic LBP had a 5-11% decrease in GM volume. Also researchers can expand this field of research by examining the brain using different imaging modalities like functional MRI, magnetic resonance spectroscopy, or even diffusion tensor imaging. Structural brain imaging, provide insights into brain volume; however, it cannot inform researchers about any of the cyto-architectural differences of brain tissue that may occur when comparing people with LBP to healthy controls.

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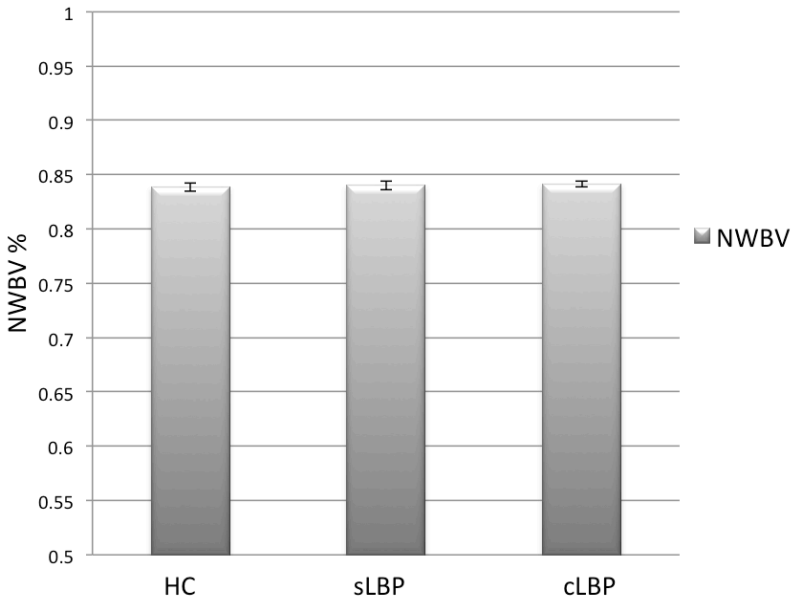
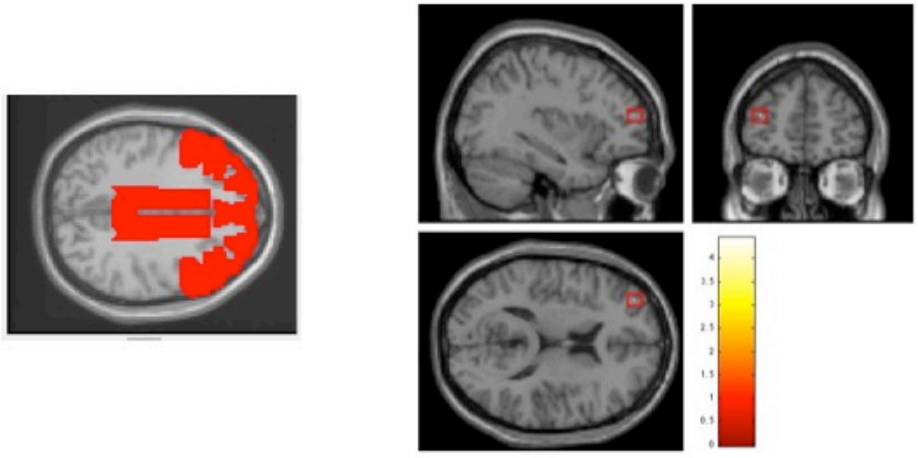
9. Figures:

Figure 3.1: Normalized whole-brain volumes for each group



HC: Healthy controls, sLBP: subacute low back pain group, cLBP: chronic low back pain group, NWBV: normalized whole-brain volume.

Figure 3.2: Cortical affective mask and the presentation of chronic LBP participants showing less GM volume within that mask.



3.2 a 3.2 b

3.2 a: Cortical affective mask, 3.2 b: Affective cortical ROI, $p_{corrected} < 0.05$.

10. Tables:

Table 3.1: Demographic and clinical outcome measures.

Characteristic	**sLBP**	**cLBP**	**HC**	**Statistic**	***p***
Sex (Female/Male)†	13/10	48/20	17/22	χ^2=7.67	0.022*
Age ǂ	36±11	45±12	40±16	*F*=3.99	0.021*
Pain Duration §	3.16±2.17	98.58±81.18	-	*t=-5.63*	<0.001**
Pain Intensity §	4.18±2.19	4.28±1.89	-	*t=-0.21*	0.834
FABQ-w §	13.63±13.28	12.55±12.01	-	*t=0.36*	0.723
FABQ-p §	11.77±6.22	13.81±5.08	-	*t=-1.54*	0.127
ODI §	19±14.97%	29.88±18.79%	-	*t=-2.47*	0.016*
BDI §	8.45±7.88	10.36±9.91	-	*t=-0.82*	0.414

Age is measured in years, pain duration is measured in months, pain intensity is measured using a 0-10 pain scale, FABQ-w: Fear-avoidance belief questionnaire – work component, FABQ-p: Fear-avoidance belief questionnaire – physical component, ODI: Oswestery disability index, BDI: Beck depression inventory.

† Chi-square

ǂ One-way ANOVA

§ Independent 2-sample *t*-test

Table 3.2: Non-significant trends ($p_{uncorrected}$ < 0.001, 100 voxels) showing overall gray matter volume differences.

Contrast	Location	Size
Healthy>cLBP	Middle frontal gyrus	603
	Precuneus	352
	Fusiform	264
	Middle temporal gyrus	234
	Parahippocampal gyrus	208
	Postcentral gyrus	205
	Superior frontal gyrus	196
	Medial frontal gyrus	181
	Cerebellum	123
	Parahippocampal gyrus	122
	Lingual gyrus	101
	Superior frontal gyrus	100
cLBP>Healthy	Cerebellum	342
	Cerebellum	195
Healthy>sLBP	Middle temporal gyrus	1506
	Cingulate gyrus	530
	Inferior frontal gyrus	351
	Occipito-temporal gyrus	266
	Caudate	241

	Superior frontal gyrus	224
	Inferior frontal gyrus	182
	Precuneus	122
	Middle frontal gyrus	119
	Parahippocampal gyrus	110
	Middle temporal gyrus	106
sLBP>Healthy	*No differences*	-
sLBP>cLBP	Pons	123
cLBP>sLBP	Cingulate gyrus	123

cLBP: Chronic LBP, sLBP: Subacute low back pain. Size is in voxels. All the contrasts indicate more gray matter in the first group as compared to the second group.

Table 3.3: Correlation of clinical outcome measures and normalized whole-brain volume.

Characteristic	**Statistic**	**NWBV**	***p***
Pain Duration	Partial correlation	0.179	0.109
Pain Intensity	Partial correlation	0.098	0.382
FABQ-w	Partial correlation	0.068	0.546
FABQ-p	Partial correlation	0.167	0.136
ODI	Partial correlation	0.091	0.418
BDI	Partial correlation	-0.059	0.600

FABQ-w: Fear-avoidance belief questionnaire – work component, FABQ-p: Fear-avoidance belief questionnaire – physical component, ODI: Oswestry disability index, BDI: Beck depression inventory, NWBV: normalized whole-bran volume.
All correlations are partial correlations after controlling for age, sex, and scanner.
The number of participants is 84 for all the outcome measures including participants from both the subacute and chronic LBP groups.

Chapter IV

Discussion and Conclusion

1. Overview:

Low back pain (LBP) is one of the most common chronic pain conditions worldwide (Andersson, 1999; Von Korff and Dunn, 2008). Up till today almost 85% of LBP cases have a diagnosis of "nonspecific LBP" which indicates that there is no actual known cause for the pain (Deyo and Weinstein, 2001). Consequently those cases end up being treated nonspecifically. This might be a reason for the common progression of LBP from an acute/subacute phase into recurrent, and then chronic LBP. Chronic LBP has major economic impacts on the society (Walker, Muller *et al.*, 2003; Katz, 2006) and is usually accompanied by other psychosocial aspects that make the case much more complicated and harder to treat (Ramond-Roquin, Bouton *et al.*, 2015). As a common pain phenomenon, and since pain is processed in the brain, brain imaging studies have immerged in attempt to understand how brain regions are involved in LBP. All previous studies that have examined the brain and studied its relationship to LBP have been conducted in the chronic population (Apkarian, Sosa *et al.*, 2004; Tagliazucchi, Balenzuela *et al.*, 2010; Sharma, McCarson *et al.*, 2011). It is very critical to understand brain involvement earlier in the pain stage to see if progression to chronic stage can be slowed down or even prevented.

There is a huge gap in the literature regarding understanding of LBP and its relation to the brain. Brain function has been examined by a number of researchers in response to different stimuli and during rest in the chronic LBP population. The general findings indicate an increased activation in the regions that are related to pain processing (Giesecke, Gracely *et al.*, 2004; Kobayashi, Kurata *et al.*, 2009;

Tagliazucchi, Balenzuela *et al.*, 2010). A possible explanation for such findings was that this increased activation might be a role player in relation to the chronicity of pain in this population. From a neurochemical perspective, studies have shown that people with chronic LBP have altered levels of neurochemicals in their brains (Grachev, Fredrickson *et al.*, 2000; Gussew, Rzanny *et al.*, 2011; Sharma, McCarson *et al.*, 2011; Sharma, Brooks *et al.*, 2012). Also, studies have reported, including studies conducted in our lab, that altered levels of neurochemicals correlate with the clinical presentation of LBP. Those findings indicate that the brain might be functioning differently in people with LBP. Nonetheless, those findings are not limited to chronic LBP. Alterations in brain function and neurochemistry have also been reported in multiple pain conditions such as fibromyalgia (Cagnie *et al.*, 2014), complex regional pain syndrome (Schwenkreis *et al.*, 2009), and migraine (Schwedt and Chong, 2015).

Examining brain volume is another way to study the relationship between the brain and any medical condition. This method has been explored in several conditions such as Alzheimer's disease (Karas, Scheltens *et al.*, 2004; Ibrahim, Horacek *et al.*, 2009; Gordon, Blazey *et al.*, 2013), schizophrenia (Cahn, Hulshoff Pol *et al.*, 2002; Kasparek, Prikryl *et al.*, 2009), and multiple sclerosis (Cheriyan, Kim *et al.*, 2012; Koenig, Sakaie *et al.*, 2014; Radue, Barkhof *et al.*, 2015). It has also been studied in a number of pain conditions including fibromyalgia (Kuchinad, Schweinhardt *et al.*, 2007; Diaz-Piedra, Guzman *et al.*, 2015; McCrae, O'Shea *et al.*, 2015), complex regional pain syndrome (Geha, Baliki *et al.*, 2008; Barad, Ueno *et al.*,

2014), and chronic LBP (Apkarian, Sosa *et al.*, 2004; Ivo, Nicklas *et al.*, 2013; Dolman, Loggia *et al.*, 2014). Within the LBP arena only 7 studies have examined brain volume. Their results were inconsistent. Three studies reported volumetric differences while the other four reported no differences when comparing brain volume between participants with chronic LBP and healthy controls. Such inconsistencies indicate the lack of our knowledge in this field, and this is why we decided to create the current study with the largest sample size and the strictest methods to determine whether or not there is a relationship between LBP (subacute and chronic) and brain volume.

Brain volume can be measured overall using volumetric measurements, or it can be measured in a cluster-based method, which is voxel-based morphometry (VBM). Volumetric measurements indicate the overall differences in brain volume (gray matter, white matter, and cerebro-spinal fluid) but without indicating the location of any potential differences. It is of paramount importance to understand the importance of "location" when examining brain volume differences. Therefore, VBM is a tool that is used to create brain probability maps that show where potential differences of brain volume exist when comparing different groups of participants. We used both methods in our study. However, given that pain is a complex phenomenon and is composed of two main components (sensory and affective pain) we also wanted to examine the specific regions in the brain that process the different components of pain. Therefore, we created brain masks for all the pain processing regions and we extracted the brain volumes from those regions

and compared them across our groups. It is important to mention that while running all of our analyses, we included age, sex, and scanner differences (since we had data collected on 2 scanners) as covariates. Age and sex are major contributors to differences in brain volume (Gur *et al.*, 2002; Cowell *et al.*, 2007; Nordenskjold *et al.*, 2013). Also, different scanner types may cause some differences in results; however, we used the exact same image acquisition parameters from both scanners (for image parameters please refer to Chapter III). Yet, we included all 3 factors as covariates in our analyses in an attempt to control for as many variables as we can and to make our results as close to what LBP would *truly* affect the brain.

We have been conducting brain imaging studies in our lab for the past 6 years, mainly examining the LBP population (both subacute and chronic LBP). I have utilized the data collected previously and added a prospective study that allowed us to continue to collect data about the subacute LBP participants. The total number of participants included in this study was 130, 23 with subacute LBP, 68 with chronic LBP, and 39 healthy controls. We acquired structural brain scans from all participants, and collected clinical outcome measures from both LBP groups (those measures included pain duration, pain intensity, fear avoidance, disability, and depression symptoms). We then extracted the data from the preprocessed brain images and calculated the normalized whole-brain volumes (*aim 1*). Afterwards, using the VBM8 toolbox, we conducted statistical testing on a voxel-by-voxel level to examine volumetric differences between groups on a whole-brain level (*aim* 1) and in specific ROIs (*aim* 2) that were related to pain processing. Finally, we ran partial

correlation analyses between the clinical outcome measures and the normalized whole-brain volumes in order to determine whether there is a relationship between those measures and brain volume (*aim 3*). Again, for all the previous analyses we included age, sex, and scanner as covariates.

2. Summary of Findings:

Aim 1: **To determine whether subjects with subacute and chronic LBP have altered whole-brain volume compared to healthy controls.**

Hypothesis 1a: Volumetric measurements of normalized whole-brain volume will show less volume in the subacute and chronic LBP groups as compared to healthy controls, and less volume in the chronic group as compared to the subacute LBP group.
Hypothesis 1b:Voxel-wise whole-brain volume determined by VBM will show less GM volume in the subacute and chronic LBP groups as compared to healthy controls, and less volume in the chronic group as compared to the subacute LBP group.

Hypothesis 1a: After running an overall ANOVA comparing normalized whole-brain volumes between our groups no significant differences were noticed ($F(2,124)=1.63$, $p=0.20$, $\eta^2=0.03$). This indicates that we could not detect a significant difference in normalized whole-brain volumes between the 3 groups. We conclude that there is a minimum to no-effect of LBP on normalized whole-brain volume regardless of its duration.

Hypothesis 1b: After running whole-brain voxel-wise comparison we also did not notice any differences in brain volume between groups after correcting for multiple comparisons (all $p > 0.05$). Again this indicates that we could not detect a significant effect of LBP on brain volume while using VBM as a measurement method. For both those tests we used age, sex, and scanner as covariates.

Aim 2: **To determine whether subjects with subacute and chronic LBP have altered regional brain volume compared to healthy controls.**

Hypothesis 2a: Regional VBM analysis will show less GM volume within the sensory regions (primary somatosensory cortex and posterior insula) in the subacute and chronic LBP groups compared to healthy controls, and less volume in the chronic group as compared to the subacute LBP group.

Hypothesis 2b: Regional VBM analysis will show less GM volume within the cortical affective regions (cingulate, orbitofrontal, and medial prefrontal cortices, and anterior insula) in the subacute and chronic LBP groups compared to healthy controls, and less volume in the chronic group as compared to the subacute LBP group.

Hypothesis 2c: Regional VBM analysis will show less GM volume within the subcortical affective regions (nucleus accumbens, amygdala, caudate, and hippocampus) in the subacute and chronic LBP groups compared to healthy controls, and less volume in the chronic group as compared to the subacute LBP group.

Hypothesis 2d: Regional VBM analysis will show less GM volume within the thalamus in the subacute and chronic LBP groups compared to healthy controls, and less volume in the chronic group as compared to the subacute LBP group.

Hypotheses 2a, c, and d: After creating masks for specific pain processing regions and examining regional brain volumes we were not able to detect any significant differences (after correcting for multiple comparisons) in brain volume between our groups (all $p > 0.05$). This indicates that LBP has minimum to no effect on brain volume in pain processing regions within the brain regardless of its duration.

Hypothesis 2b: While examining the cortical affective mask (somatosensory cortex and posterior insula) we were able to detect 2 voxels (6.75 mm^3) that showed less GM volume in the chronic LBP group as compared to healthy controls. This indicates a minimum effect of chronic LBP on brain volume in the somatosensory cortex. No differences were noticed regarding the subacute group.

It is worth mentioning here that this method of examining the different pain related regions and creating affective and sensory masks is a new method that has not been employed by any of the previous studies examining the LBP population. It allowed us to gain a focused view on those pain processing regions, and yet we only noticed differences in 2 voxels in one of those masks indicating how minimal the effect of LBP is on brain structure.

Aim 3: **To determine the relationship between clinical outcome measures and normalized whole-brain volume within both LBP groups.**

Hypothesis 3a: Pain duration (measured in months) will be negatively correlated with normalized whole-brain volume.

Hypothesis 3b: Pain intensity (measured with 0-10 pain scale) will be negatively correlated with normalized whole-brain volume.

Hypothesis 3c: Fear avoidance (measured by the Fear Avoidance Belief Questionnaire) will be negatively correlated with normalized whole-brain volume.

Hypothesis 3d: Disability scores (measured by the Oswestry Disability Index) will be negatively correlated with normalized whole-brain volume.

Hypothesis 3e: Depressive symptoms (measured by Beck's Depression Inventory-II) will be negatively correlated with normalized whole-brain volume.

Hypotheses 3a, b, c, d, and e: After running the partial correlations between clinical outcome measures and normalized whole-brain volumes we were not able to detect any significant correlation (negative or positive). This indicates the clinical presentation of LBP (subacute or chronic) including pain duration, pain intensity, fear of movement, disability, and depressive symptoms are not correlated with normalized whole-brain volume. All those partial correlations included age, sex, and scanner as covariates.

3. Clinical Implications:

Clinical implications from brain imaging studies can be challenging. This is mainly due to the fact that we have limited understanding of the real meanings of "volumetric brain differences". Yet, our findings indicate that there is minimum to no effect of LBP on brain volume. To gain a better understanding of clinically meaningful differences of volumetric changes, we calculated the effect size from our study and the previous studies. We found that the effect size of LBP within our study was 0.07, which is a very small effect size. At this effect size, and in order to see a *true* effect of LBP on brain structure we will need a total of 1722 participants. None of the previous studies, including our own, were remotely close to this sample size. This is in agreement with the conclusion of the most recently published paper in this field. Dolman et al. (2014) indicated that most of the previously published results indicating volumetric differences in people with LBP might have been overestimated. They suggested that controlling for the main covariates that may affect brain volume (as age, sex, and pain descriptors) might diminish or even eliminate the volumetric differences, which would indicate that such differences are not related to LBP directly. On the other hand, we were able to detect some minor differences within the affective cortical brain mask in 2 voxels after controlling for covariates and correcting for multiple comparisons. This finding is statistically significant; however, clinically it is not. A difference of 2 voxels (6.75 mm^3) at best might be described as a pattern, especially that the threshold for cluster-based analysis is usually higher than that within VBM. Therefore, if there was an effect of LBP on brain volume it is very minimal, according to our results. Studies have

demonstrated that there is a 5% decrease of brain volume per decade due to normal aging (Resnick, Pham *et al.*, 2003). According to our healthy controls, this diminishment is equal to 4-6 mm^3 a year. The 6.75 mm^3 that we have noticed in our chronic LBP group was due to an average of 9 years of pain, which means that it has an effect of <1 mm^3 on average every year. Therefore it can be seen that the effect of normal aging is much bigger than the effect of chronic LBP in our cohort, indicating that this decrease is not clinically significant.

The common explanation from previous studies that have noticed volumetric differences was related to glutamate neurotoxicity. Glutamate levels are increased in pain related regions in the brain when experiencing pain (Mullins, Rowland *et al.*, 2005), and increased levels of glutamate can be neurotoxic and cause neuronal degeneration (Rothstein, 1996). Nonetheless, neuronal degeneration can also be accompanied by tissue scarring and cortical thickening (Buffo, Rite *et al.*, 2008; Dolman, Loggia *et al.*, 2014). It is possible that glutamate is causing neuronal degeneration, but also leading to cell hypertrophy. Current brain imaging technology is not sophisticated enough to pick up a single neuron and examine it's volume, therefore from a brain imaging perspective we cannot examine single cell volume. Such questions can be answered with histology studies. Therefore, there is a possibility that neuronal degeneration is taking place in the brain, yet using structural brain imaging we cannot truly detect it. This might be an explanation of why functional and neurochemical studies have much less inconsistencies when it comes to examining participants with LBP compared to healthy controls. It also may

explain the two studies that have noticed increased brain volumes in pain processing regions in participants with chronic LBP when compared to healthy controls (Schmidt-Wilcke, Leinisch *et al.*, 2006; Dolman, Loggia *et al.*, 2014).

Our findings, exemplified by not being able to detect volumetric differences in participants with LBP, deliver good news to those patients. Previous studies indicated that LBP has a significant impact on brain volume and such findings can be very alarming and frightening to patients. However, we noticed after conducting this study with a large sample size and the most stringent methodology, that those previous findings may have been overestimated. LBP might have an effect on brain function and neurochemistry; nonetheless we were not able to detect any volumetric differences related to it. LBP and the accompanying psychosocial aspects can be very limiting to patients, and letting patients understand that their pain is not affecting their brain structure can be a great relief. Potentially, it can help patients overcome their fears and gain hope for getting better.

Clinicians can use those findings and explain to their patients that there might be some changes in their brain function or neurochemistry related to their pain; however, it is not represented in brain volume. Many practices can be used in order to encourage patients to get better, such as exercise and physical therapy. With this knowledge in mind patients might feel encouraged to adhere to practices recommended by clinicians and therefore help improve their condition.

4. Limitations:

As with any other study, we acknowledge that we have a number of limitations to our current study, and those limitations are:

1. Retrospective analysis:

Most of the data used in this study has been collected previously for studies conducted in our lab, yet we added a prospective arm to recruit more participants with subacute LBP. This indicates that the inclusion/exclusion criteria were made for other studies rather than specifically for this current one which could potentially be a limitation.

2. Significant age difference between groups:

Participants who were in the chronic LBP group were significantly older than those in the subacute group. This finding was expected since the way those groups were designed was based on the duration of their pain, thus participants with chronic LBP were older than those with subacute LBP. Yet we included age as a covariate in all our analyses.

3. Significant sex difference between groups:

Again, the chronic group had more female participants in it than males, which was also expected. Chronic pain is more common in females than in males (Mogil, 2012) and that was represented in our sample. We included sex as a covariate in all our analyses.

4. Using two scanners:

All data were collected at the Hoglund Brain Imaging Center over the past 6 years. Through those 6 years the brain imaging center has replaced its old Allegra scanner with a Skyra scanner. Our results were a compilation of data collected on both scanners. This might have affected our results, yet all the imaging parameters were exactly the same. In addition we added scanner as a covariate in all our analyses.

5. Inclusion/exclusion criteria:

We have excluded participants with higher levels of pain (more than 8 on a 0-10 pain scale) because this was the criteria for the previous studies since they had an exercise component to them. This indicates that we were not able to include subjects with extreme amounts of pain. Such a subset of the population would be interesting to examine, yet recruiting them would be hard and asking them to lay in the scanner flat on their backs will be very challenging. We also excluded participants with any hip, knee, or ankle joint conditions. LBP is common in people who have pain in other joints; yet again this was part of the exclusion criteria for the previous studies.

5. Future Directions:

There are many future directions for this line of research, especially since brain imaging in people with LBP is a relatively new and emerging field.

1. Longitudinal study design:

Longitudinal studies are necessary to address the question of "the chicken or the egg". Given that our findings did not indicate any potential structural brain differences in people with LBP from a cross-sectional aspect, it would be interesting to examine brain differences before and after being affected by LBP. Certain populations are more prone to developing LBP than others (such as labor workers). Those populations can be targeted, scanned, and followed-up on in an attempt to get a longitudinal view on LBP. This would be a better study design and would grant us a better understanding of the true effects of LBP on brain structure. Such studies are very expensive, time consuming, and really hard to conduct (with the follow up scans); however, they are definitely needed.

2. Different inclusion/exclusion criteria:

Another option for a future study design would include classifying participants based on their pain duration, intensity, or type of pain (for example, neuropathic vs. non-neuropathic pain). We could not detect brain volumetric differences in a general population of LBP participants; however, maybe the effect of pain can be magnified in people with higher vs. lower intensities of pain, or longer duration vs, shorter duration of pain. We did not see any correlation with pain duration or pain intensity, but that still does not necessarily indicate that they cannot be split based on those clinical measures.

3. Using other brain imaging modalities:

We examined brain volume using structural brain imaging; however, other studies (including studies conducted in our lab) have used functional and spectroscopy imaging methods in people with LBP. A future study may use a large sample size (similar to the one in this current study) and examine the differences in brain function and neurochemistry between people with LBP and healthy controls. Resting state analysis can be a very interesting topic to explore in this population as well (research on it being conducted currently in our lab). Another proposed study design is looking at white matter volume in the brain, potentially using diffusion tensor imaging. By using this methodology researchers can examine the white matter tracts and try to examine any volumetric differences between participants with LBP and healthy controls.

4. No more VBM studies:

One of the future directions would be not to conduct more VBM studies, specifically in LBP population without involvement of other secondary effects i.e. high psychological involvement or depression. The results of our study indicate that the effects of LBP on brain volume are minimal, if not nonexistent. Therefore we do not recommend conducting any further studies that would use the same methodology to answer the same question. This finding is essential because it will save researchers' time, effort, and resources to investigate different topics.

6. Conclusions:

In conclusion we believe that LBP, regardless of its duration, has a minimum to no effect on brain volume. Also, given the findings from previous structural brain imaging studies in LBP that indicated decreased brain volume in LBP participants, we believe that those findings were overestimated. Multiple limitations may have led to those conclusions from the previous studies including sample size, methodology issues, or subject inclusion/exclusion criteria. Nonetheless, studies examining brain function and neurochemistry (including studies conducted in our lab) have found differences between participants with chronic LBP and healthy controls. This might indicate that LBP may affect brain function and neurochemistry; however, not brain volume and structure.

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Appendices:

Appendix 1: Fear Avoidance Belief Questionnaire.

FEAR AVOIDANCE BELIEFS QUESTIONNAIRE (FABQ)

Purpose: The FABQ was developed by Waddell to investigate fear-avoidance beliefs among LBP patients in the clinical setting.[3] This survey can help predict those that have a high pain avoidance behavior. Clinically, these people may need to be supervised more than those that confront their pain.

Scoring: The FABQ consists of 2 subscales, which are reflected in the division of the outcome form into 2 separate sections. The first subscale (items 1-5) is the Physical Activity subscale (FABQPA), and the second subscale (items 6-16) is the Work subscale (FABQW). Interestingly, not all items contribute to the score for each subscale; however the patient should still complete all items as these items were included when the reliability and validity of the scale was initially established. A low FABQW score (less than 19) was one of 5 variables in a clinical prediction rule that increased the probability of success from SI region manipulation in individuals with low back pain.[1] Each subscale is graded separately by summing the responses respective scale items (0 – 6 for each item); for scoring purposes, only 4 of the physical activity scale items are scored (24 possible points) and only 7 of the work items (42 possible points). The method to score each subscale is outlined below. (Note: It is extremely important to ensure all items are completed, as there is no procedure to adjust for incomplete items.)

Scoring the Physical Activity subscale (FABQPA)
Sum items 2, 3, 4, and 5 (the score circled by the patient for these items).

Scoring the Work subscale (FABQW)
Sum items 6, 7, 9, 10, 11, 12, and 15.

Measurement Characteristics: The FABQ has been demonstrated to be valid and reliable in a chronic LBP population[3] and appears to be a useful screening tool for identifying acute LBP patients who will not return to work by 4wks.[2]

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Name: _____ Date: _____

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

	COMPLETELY DISAGREE			UNSURE			COMPLETELY AGREE
1. My pain was caused by physical activity	0	1	2	3	4	5	6
2. Physical activity makes my pain worse	0	1	2	3	4	5	6
3. Physical activity might harm my back	0	1	2	3	4	5	6
4. I should not do physical activities which (might) make my pain worse	0	1	2	3	4	5	6
5. I cannot do physical activities which (might) make my pain worse	0	1	2	3	4	5	6

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

	COMPLETELY DISAGREE			UNSURE			COMPLETELY AGREE
6. My pain was caused by my work or by an accident at work	0	1	2	3	4	5	6
7. My work aggravated my pain	0	1	2	3	4	5	6
8. I have a claim for compensation for my pain	0	1	2	3	4	5	6
9. My work is too heavy for me	0	1	2	3	4	5	6
10. My work makes or would make my pain worse	0	1	2	3	4	5	6
11. My work might harm my back	0	1	2	3	4	5	6
12. I should not do my normal work with my present pain	0	1	2	3	4	5	6
13. I cannot do my normal work with my present pain	0	1	2	3	4	5	6
14. I cannot do my normal work until my pain is treated	0	1	2	3	4	5	6
15. I do not think that I will be back to my normal work within 3 months	0	1	2	3	4	5	6
16. I do not think that I will ever be able to go back to that work	0	1	2	3	4	5	6

Appendix 2: Beck Depression Inventory-II.

Roche

V 0477

Beck Depression Inventory

CRTN: _____ CRF number: _____

Baseline

Page 14 patient inits: _____

BDI-II

Date:

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4. Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike

0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness

0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying

0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

Subtotal Page 1

Continued on Back

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11. Agitation

0 I am no more restless or wound up than usual.

1 I feel more restless or wound up than usual.

2 I am so restless or agitated that it's hard to stay still.

3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.

1 I am less interested in other people or things than before.

2 I have lost most of my interest in other people or things.

3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.

1 I find it more difficult to make decisions than usual.

2 I have much greater difficulty in making decisions than I used to.

3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.

1 I don't consider myself as worthwhile and useful as I used to.

2 I feel more worthless as compared to other people.

3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.

1 I have less energy than I used to have.

2 I don't have enough energy to do very much.

3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.

1a I sleep somewhat more than usual.

1b I sleep somewhat less than usual.

2a I sleep a lot more than usual.

2b I sleep a lot less than usual.

3a I sleep most of the day.

3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.

1 I am more irritable than usual.

2 I am much more irritable than usual.

3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.

1a My appetite is somewhat less than usual.

1b My appetite is somewhat greater than usual.

2a My appetite is much less than before.

2b My appetite is much greater than usual.

3a I have no appetite at all.

3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.

1 I can't concentrate as well as usual.

2 It's hard to keep my mind on anything for very long.

3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.

1 I get more tired or fatigued more easily than usual.

2 I am too tired or fatigued to do a lot of the things I used to do.

3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.

2 I am much less interested in sex now.

3 I have lost interest in sex completely.

3456789101112 ABCDE

_____ Subtotal Page 2

_____ Subtotal Page 1

_____ Total Score

Appendix 3: Oswestery Disability Index.

Oswestry Low Back Pain Disability Questionnaire

Instructions

This questionnaire has been designed to give us information as to how your back or leg pain is affecting your ability to manage in everyday life. Please answer by checking ONE box in each section for the statement which best applies to you. We realise you may consider that two or more statements in any one section apply but please just shade out the spot that indicates the statement which most clearly describes your problem.

Section 1 – Pain intensity

- ☐ I have no pain at the moment
- ☐ The pain is very mild at the moment
- ☐ The pain is moderate at the moment
- ☐ The pain is fairly severe at the moment
- ☐ The pain is very severe at the moment
- ☐ The pain is the worst imaginable at the moment

Section 2 – Personal care (washing, dressing etc)

- ☐ I can look after myself normally without causing extra pain
- ☐ I can look after myself normally but it causes extra pain
- ☐ It is painful to look after myself and I am slow and careful
- ☐ I need some help but manage most of my personal care
- ☐ I need help every day in most aspects of self-care
- ☐ I do not get dressed, I wash with difficulty and stay in bed

Section 3 – Lifting

- ☐ I can lift heavy weights without extra pain
- ☐ I can lift heavy weights but it gives extra pain
- ☐ Pain prevents me from lifting heavy weights off the floor, but I can manage if they are conveniently placed eg. on a table
- ☐ Pain prevents me from lifting heavy weights, but I can manage light to medium weights if they are conveniently positioned
- ☐ I can lift very light weights
- ☐ I cannot lift or carry anything at all

Section 4 – Walking*

- ☐ Pain does not prevent me walking any distance
- ☐ Pain prevents me from walking more than 1 mile
- ☐ Pain prevents me from walking more than 1/2 mile
- ☐ Pain prevents me from walking more than 100 yards
- ☐ I can only walk using a stick or crutches
- ☐ I am in bed most of the time

Section 5 – Sitting

- ☐ I can sit in any chair as long as I like
- ☐ I can only sit in my favourite chair as long as I like
- ☐ Pain prevents me sitting more than one hour
- ☐ Pain prevents me from sitting more than 30 minutes
- ☐ Pain prevents me from sitting more than 10 minutes
- ☐ Pain prevents me from sitting at all

Section 6 – Standing

- ☐ I can stand as long as I want without extra pain
- ☐ I can stand as long as I want but it gives me extra pain
- ☐ Pain prevents me from standing for more than 1 hour
- ☐ Pain prevents me from standing for more than 30 minutes
- ☐ Pain prevents me from standing for more than 10 minutes
- ☐ Pain prevents me from standing at all

Section 7 – Sleeping

- ☐ My sleep is never disturbed by pain
- ☐ My sleep is occasionally disturbed by pain
- ☐ Because of pain I have less than 6 hours sleep
- ☐ Because of pain I have less than 4 hours sleep
- ☐ Because of pain I have less than 2 hours sleep
- ☐ Pain prevents me from sleeping at all

Section 8 – Sex life (if applicable)

- ☐ My sex life is normal and causes no extra pain
- ☐ My sex life is normal but causes some extra pain
- ☐ My sex life is nearly normal but is very painful
- ☐ My sex life is severely restricted by pain
- ☐ My sex life is nearly absent because of pain
- ☐ Pain prevents any sex life at all

Section 9 – Social life

- ☐ My social life is normal and gives me no extra pain
- ☐ My social life is normal but increases the degree of pain
- ☐ Pain has no significant effect on my social life apart from limiting my more energetic interests eg, sport
- ☐ Pain has restricted my social life and I do not go out as often
- ☐ Pain has restricted my social life to my home
- ☐ I have no social life because of pain

Section 10 – Travelling

- ☐ I can travel anywhere without pain
- ☐ I can travel anywhere but it gives me extra pain
- ☐ Pain is bad but I manage journeys over two hours
- ☐ Pain restricts me to journeys of less than one hour
- ☐ Pain restricts me to short necessary journeys under 30 minutes
- ☐ Pain prevents me from travelling except to receive treatment

.

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Appendix 4: Institutional Review Board approved consent form for the subacute low back pain study.

RESEARCH CONSENT FORM
Brain Imaging in People with Subacute Low Back Pain

You are being asked to join a research study. You are being asked to take part in this study because you have subacute low back pain. You do not have to participate in this research study. The main purpose of research is to create new knowledge for the benefit of future patients and society in general. Research studies may or may not benefit the people who participate.

Research is voluntary, and you may change your mind at any time. There will be no penalty to you if you decide not to participate, or if you start the study and decide to stop early. Either way, you can still get medical care and services at the University of Kansas Medical Center (KUMC).

This consent form explains what you have to do if you are in the study. It also describes the possible risks and benefits. Please read the form carefully and ask as many questions as you need to, before deciding about this research.

You can ask questions now or anytime during the study. The researchers will tell you if they receive any new information that might cause you to change your mind about participating.

This research study will take place at the University of Kansas Medical Center (KUMC) with Dr. Neena Sharma as the researcher. About 20 people will be in the study at KUMC.

BACKGROUND
Low back pain (LBP) is one of the most common pain conditions worldwide. LBP can be in the lower back region and/or the buttocks. LBP can also cause radiating pain down in one or both legs. Subacute LBP is defined as continuous or on-and-off pain up to 6 months after the first episode of pain. Brain imaging studies help researchers understand the pain processing regions within the brain. Previous research has found differences in brain volume, function, and chemicals in people with chronic LBP. No studies have examined the subacute LBP population. In this study we are interested in examining brain volume, brain blood flow, and brain chemicals within the subacute LBP population.

PURPOSE
By doing this study, researchers hope to learn whether individuals with subacute LBP have altered brain structure, blood flow, or chemical concentration. Moreover, we hope to learn whether any of those brain changes relate to clinical symptoms (such as pain intensity, pain duration, and fear of movement).

PROCEDURES
If you are eligible and decide to participate in this study, your participation will last

approximately 2 hours in total. Your participation will involve a clinical testing session (physical exam and few standard surveys) and a brain scan (magnetic resonance imaging: MRI).

- Clinical testing: Research personnel will do a physical examination on your back. Physical exam includes range of motion of your back, sensory and muscle testing. Another part of the examination will be the pain pressure threshold testing, which includes applying a pressure device to your back while you are lying on your stomach and then asking you to click a button once the pressure starts becoming uncomfortable (just about to cause pain). You will be asked to fill out questionnaires related to pain, physical activity, disability, and depression. This may take up to 60 minutes of your time.

  Any medications you are taking will need to be indicated.

- Neuroimaging evaluation: you will have one MRI exam of your brain (a standard procedure). The total time for the MRI session will be about 30 minutes. Throughout this scan we will be collecting three different types of images. First, we will collect structural brain images to look at brain volume. Second, we will collect functional brain images to look at the blood flow in the brain. Finally, we will collect spectroscopy images to look at the levels of different chemicals in the brain. These different types of imaging will be collected during the same session. You will lie down on a bed and the researcher will make you as comfortable as possible with padding and blankets. Your head and shoulders will be placed in a tunnel. As the MRI examination is performed, you will hear loud knocking noises. You will be provided ear protection including earplugs or earmuffs or both. You might also feel warm during this procedure. This is all normal for an MRI exam. You will lie in the tunnel for about one hour. During the functional MRI portion, you will be asked to keep your eyes open and look at a "+" sign presented in front of you. For the other 2 portions of the scan you can keep your eyes open or closed.
- After 3 and 6 months we will send you an e-mail with an electronic link to a webpage that has a survey on it for you to fill up. If you wish we can also send you the questionnaires via mail, or we can meet in person and fill up the questionnaires. The survey will have the exact same questionnaires you filled up on your first visit.

RISKS

There are potential discomforts and risks to your health and wellbeing if you agree to be a subject in this research. Generally, these procedures are considered to be noninvasive and safe. However, Dr. Sharma or her associates have discussed this research with you and have described them as follows:

Neuroimaging evaluation: MRI studies are among the safest of all non-invasive medical procedures, but certain risks and discomforts may be associated with this procedure. You will complete a ***MRI Safety Screening Form*** before your participation in this study.

You understand that the following risks are most common and should be considered:

- An MRI machine acts like a large magnet. If you have a pacemaker or any metal, such as an aneurysm clip, ear implant, or nerve stimulator in your body, you cannot have an MRI. If a piece of metal, a device made of metal, or an electronic device was on or in your body, especially in your eye, heart, or brain, you could be seriously injured by the magnetic field. Precautions have been taken to prevent any such event from happening and injuring you. These precautions include asking you to identify if you have any of these items in or on your body before you participate in the study, and removing all iron-containing objects from the room.
- If a piece of metal (such as a tool, keys, or watch) is released into the scanner room, you could be injured. This chance is minimized by careful screening and by having only trained technicians or assistants in the immediate area, which is otherwise restricted.
- If you have a serious medical condition, your heart rate and blood oxygen level will be monitored electronically while you are in the magnet. In addition, you will have an emergency call button placed in your arm. If you become unconscious the study will be stopped immediately and you will be given aid.
- If you do not wear ear protection, the noise could potentially injure your hearing. Ear protection will be offered and you should use it to minimize this possibility.
- If you bring credit cards, other magnetic media, or fine electronics or devices (such as a watch) into the MRI scanner room, they may be damaged by the strong magnetic field; you should remove these objects prior to the procedure.
- Individuals who are claustrophobic may become anxious during the MRI. During screening, you will be asked if you have difficulties with enclosed spaces or claustrophobia to determine if this is a risk factor for you. Additionally, you understand that if you begin to feel anxious during the procedure, you can ask the researchers to stop the MRI and discontinue your participation in the study
- Pregnancy Related Risk: It is not known how magnets will affect an unborn child. If you are a woman who is pregnant you may not enter this study.

Clinical evaluation: There are some discomforts that may be associated with clinical evaluation. You may become tired or feel pain during physical exam and the pressure pain testing. The researcher will stop the testing and will give you rest, as needed. If after the rest, you continue to have difficulties completing the testing, the researcher will stop the evaluation. In this case, you may withdraw from the study. You might also become anxious if you are having difficulty completing these tests. This is normal even in people without low back pain. If you wish you could tell the researcher and they will let you rest for a while and then restart the evaluation. Some questions may be embarrassing or frustrating. You can choose to not answer these questions if they make you uncomfortable.

Possibility of unknown risks: there may be other risks of the study that are not yet known.

NEW FINDINGS STATEMENT
You will be told about anything new that might change your decision to be in this study. You may be asked to sign a new consent form if this occurs.

BENEFITS
You may or may not benefit from this study. Researchers hope that the information from this research study may be useful in understanding brain structural, functional, and chemical differences in individuals with subacute LBP. Moreover, how do such differences relate to clinical presentation of LBP such as pain duration, pain intensity, disability, and fear of movement.

ALTERNATIVES
Participation in this study is voluntary. Deciding not to participate will have no effect on the care or services you receive at the University of Kansas Medical Center. This study does not involve providing you with any medical treatments or medical diagnosis. You can get any medical treatments or tests you might need, including MRI testing, without having to participate in this study.

COSTS
There is no cost for being in the study.

PAYMENT TO SUBJECTS
You will be paid for your participation. You will be offered a stipend of $30 (with a check) after the completion of both the clinical examination and the brain scan. If you decide to withdraw from the study before the completion of both components (clinical examination and brain scan) you will not receive the payment. After the completion of both surveys (after 3 and 6 months) you will be compensated with an additional $10.

The KUMC Research Institute will be given your name, address, social security number, and the title of this study to allow them to write checks for your study payments. Study payments are taxable income. A Form 1099 will be sent to you and to the Internal Revenue Service if your payments are $600 or more in a calendar year.

IN THE EVENT OF INJURY
If you have a serious side effect or other problem during this study, you should immediately contact Dr. Sharma at (913) 588-4566. If it is after 5:00 p.m., a holiday or a weekend, you should call the emergency room. A member of the research team will decide what type of treatment, if any, is best for you at that time.

If you have a bodily injury as a result of participating in this study, treatment will be provided for you at the usual charge. Treatment may include first aid, emergency care and follow-up care, as needed. Claims will be submitted to your health insurance policy, your government program, or other third party, but you will be billed for the costs

that are not covered by the insurance. You do not give up any legal rights by signing this form.

INSTITUTIONAL DISCLAIMER STATEMENT

If you think you have been harmed as a result of participating in research at the University of Kansas Medical Center (KUMC), you should contact the Director, Human Research Protection Program, Mail Stop #1032, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160. Under certain conditions, Kansas state law or the Kansas Tort Claims Act may allow for payment to persons who are injured in research at KUMC.

CONFIDENTIALITY AND PRIVACY AUTHORIZATION

The researchers will protect your information, as required by law. Absolute confidentiality cannot be guaranteed because persons outside the study team may need to look at your study records. The researchers may publish the results of the study. If they do, they will only discuss group results. Your name will not be used in any publication or presentation about the study.

Your health information is protected by a federal privacy law called HIPAA. By signing this consent form, you are giving permission for KUMC to use and share your health information. If you decide not to sign the form, you cannot be in the study.

The researchers will only use and share information that is needed for the study. The information collected during this research study may also be used for other future projects and analyses. To do the study, they will collect health information from the study activities. You may be identified by information such as name, address, phone, date of birth, social security number, or other identifiers. Your health information will be used at KU Medical Center by Dr. Sharma, members of the research team, the KUMC Research Institute, the KUMC Human Subjects Committee and other committees and offices that review and monitor research studies. Study records might be reviewed by government officials who oversee research, if a regulatory review takes place.

All study information that is sent outside KU Medical Center will have your name and other identifying characteristics removed, so that your identity will not be known. Because identifiers will be removed, your health information will not be re-disclosed by outside persons or groups and will not lose its federal privacy protection.

Your permission to use and share your health information will not expire unless you cancel it.

QUESTIONS

Before you sign this form, Dr. Sharma or other members of the study team should answer all your questions. You can talk to the researchers if you have any more questions, suggestions, concerns or complaints after signing this form. If you have any questions about your rights as a research subject, or if you want to talk with someone

who is not involved in the study, you may call the Human Subjects Committee at (913) 588-1240. You may also write the Human Subjects Committee at Mail Stop #1032, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160.

SUBJECT RIGHTS AND WITHDRAWAL FROM THE STUDY

You may stop being in the study at any time. Your decision to stop will not prevent you from getting treatment or services at KUMC. The entire study may be discontinued for any reason without your consent by the investigator conducting the study.

You have the right to cancel your permission for researchers to use your health information. If you want to cancel your permission, please write to Dr. Sharma. The mailing address is Neena Sharma, PT, PhD, University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, KS 66160. If you cancel permission to use your health information, you will be withdrawn from the study. The research team will stop collecting any additional information about you. The research team may use and share information that was gathered before they received your cancellation.

CONSENT

Dr. Neena Sharma or the research team has given you information about this research study. They have explained what will be done and how long it will take. They explained any inconvenience, discomfort or risks that may be experienced during this study.

By signing this form, you say that you freely and voluntarily consent to participate in this research study. You have read the information and had your questions answered.
You will be given a signed copy of the consent form to keep for your records.

_____
Print Participant's Name

_____	_____	_____
Signature of Participant	Time	Date

_____
Print Name of Person Obtaining Consent

_____	_____
Signature of Person Obtaining Consent	Date