Neural Connectivity in the Chronic Pain Human Brain Before and After Cognitive Behavioral Therapy: A Diffusion Tensor Imaging Study

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I. Specific Aims

Chronic pain is a medical condition in which pain states persist for prolonged periods of time, frequently interfering with quality of life and even leading to an increased risk of mortality. Chronic pain can result from a wide variety of biological and environmental causes ranging from simple bodily injury and disease to complex neuropathies that are still little understood. Frequently, chronic pain occurs because injuries are sustained that exceed the body's ability to heal, or else the nervous system itself is injured. While many therapeutic approaches to treating chronic pain exist, none seem to work universally. Cognitive Behavioral Therapy (CBT) for coping with chronic pain has been shown to effectively reduce the intensity of perceived pain, the negative emotions that often accompany pain, and the deleterious effects of pain on quality of life in some populations of chronic pain patients.

Strong evidence suggests the existence of a “pain matrix,” a series of gray matter loci and white matter circuits that encode the sensory, attentional, and affective components of the perception of pain. The existing literature demonstrates that there are differences in both gray matter structure and functional activity between the brains of healthy subjects and chronic pain patients. Further, clinical interventions such as CBT have been shown to partially reverse some of these differences. Previous work from our lab has supported both of these findings in a population of patients with chronic musculoskeletal pain, while also attempting to correlate the post-intervention structural and functional changes with long-term clinical outcomes. It is the goal of this proposal to investigate whether these observed differences in gray matter structure and functional activity are accompanied by variations in white matter fiber tract organization, as measured by Diffusion Tensor Magnetic Resonance Imaging (DT-MRI, DTI). Unlike functional and morphometric approaches, DTI has only been utilized in the study of pain to a very limited extent. Existing data shows that there are differences in the characteristics of pain matrix fiber connections in neuropathic pain, migraine with aura, and fibromyalgia, but no studies have been conducted in patients with musculoskeletal pain conditions such as chronic low back pain. There have also been no studies to date that investigate the ability of psychotherapeutic intervention to influence the connections between the pertinent regions of cortical and subcortical gray matter.

Specific Aim 1: To compare white matter connectivity in the brains of chronic low back pain patients with connectivity in the healthy brain. Reported changes in gray matter structure and functional activity in the brains of chronic pain patients suggest that there may also be pathology of the white matter tracts that connect regions of the pain matrix. To test this, we will compare diffusion tensor magnetic resonance imaging scans of healthy controls with scans of chronic low back pain patients. We will focus on specific seed regions of interest, as well as perform whole-brain analyses. We hypothesize that chronic pain patients will show decreased fractional anisotropy in white matter tracts between areas of the pain matrix that frequently demonstrate decreased gray matter density and altered functional activity in the chronic pain brain (e.g. cingulum bundle, sensory thalamocortical projections, limbic and sensory portions of internal capsule). Additionally, we predict that probabilistic tractography will reveal altered connectivity between gray matter regions of the pain matrix: we expect that connectivity will increase in some cases (e.g. fibers connecting prefrontal regions with insular cortex), and decrease in others.

Specific Aim 2: To determine whether Cognitive Behavioral Therapy beneficially influences white matter connectivity in patients with chronic low back pain. Cognitive Behavioral Therapy
geared toward coping with chronic pain improves clinical outcomes, alters neural function in regions of
the pain matrix, and begins to reverse decreases in gray matter density and cortical thickness in the
brains of chronic pain patients. Diffusion tensor magnetic resonance imaging scans of the brains of
chronic low back pain patients will be acquired prior to and after an 11-week regimen of cognitive
behavioral therapy for coping with pain. Seed regions of interest and whole brain analyses will be
conducted comparing pre- and post-CBT scans. We predict that, in addition to normalization of
structural and functional alterations assorted with chronic pain, pain-related differences in white matter
connectivity will also exist. Specifically, we expect that fractional anisotropy will increase in fiber tracts
linking gray matter regions of the pain matrix such as the cingulum bundle and that probabilistic
tractography will reveal normalization of connectivity and fiber characteristics after CBT in such a
manner that they begin to more closely approximate those observed in healthy controls.

Specific Aim 3: To investigate how CBT-related changes in white matter connectivity relate to
clinical outcomes. Just as many of the gray matter structural and functional changes observed after
CBT correlate with clinical outcomes, we expect that differences in white matter connectivity will also be
predicted by the efficacy of treatment and correlated with observed gray matter and functional changes.
The results of questionnaires aimed at assessing intensity of pain, negative affect associated with pain,
and the negative impact of pain on quality of life will be compared from pre- to post-CBT. This data will
be statistically analyzed to determine whether correlations exist between clinical outcomes, structural
and functional changes, and white matter connectivity. We hypothesize that decreased fractional
anisotropy in pain matrix fiber tracts will correlate with decreases in reported pain intensity, possibly
serving as a marker for treatment efficacy.

It is important to investigate this current gap in the pain literature because a greater knowledge
of the connectivity between the pain-processing centers of the brain may lead to a stronger
understanding of the mechanisms behind chronic low back pain (and other forms of chronic pain), and
may hopefully provide insight into future approaches toward the diagnosis and treatment of chronic
pain.

II. Research Strategy

A. Background and Significance

1. Epidemiology of Chronic Pain

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant
sensory and emotional experience associated with actual or potential tissue damage, or described in
terms of such damage” (Merskey and Bogduk, 1994). Chronic pain is typically defined as pain that
persists beyond the time that should usually pass for an injury to heal, or after a specific, set of period
of time (Loeser and Melzack, 1999; Apkarian et al, 2009). Chronic pain is usually classified by the type
and location of the injury responsible. Chronic pain may be caused by physical injury (e.g. chronic low
back pain), central nervous system injury (e.g. thalamic pain syndrome, stroke), peripheral nervous
system injury (e.g. allodynia, hyperalgesia), disease processes (e.g. diabetic pain, arthritis pain), or
even manifest for reasons that are not fully understood (e.g. complex regional pain syndrome,
fibromyalgia). However, one characteristic that most chronic pain conditions have in common is resistance to treatment.

Of the many types of chronic pain, the most common seem to be low back pain and arthritis (Elliott et al, 1999). In an elegant review article, Apkarian et al (2009) summarize the epidemiology of chronic low back pain: approximately three out of four adults will experience acute low back pain at some point in their lives, while chronic low back pain may affect up to one in three adults during their lives. Back pain is also reported to be the largest reason for decreased or limited activity in people younger than 45, and the second most common reason given for visits to the physician (Frymoyer, 1988; Praemer et al, 1992; Hart et al, 1995). Other sources suggest that chronic pain may be a problem for almost half of the general population (Elliott et al, 1999). Chronic pain has also been shown to frequently present comorbidly with depression (Romano and Turner, 1985; Banks and Kerns, 1996; Fishbain et al, 1997), anxiety disorders (McCracken et al, 1992; McWilliams et al, 2003), emotional decision-making impairments (Apkarian et al, 2004), and even a higher risk of mortality (Torrance et al, 2010). For a review, see (Gatchel, 2004). Differences in research methods used may result in slightly different epidemiological statistics across different review articles, but it remains abundantly clear that chronic pain is a major medical issue facing society today (Anderson, 1986; Olsen et al, 1992; Guo et al, 1995) and that treating chronic pain represents a major financial burden for countries all over the world (Maniadakis and Gray, 2000; Maetzel and Li, 2002; Walker et al, 2003; Ekman et al, 2005).

2. The Pain Matrix

Based loosely on his initial Gate Control Theory of pain (Melzack and Wall, 1965; Melzack and Wall, 1970) and subsequently published literature on the anatomical and functional correlates of pain, Melzack (Melzack and Wall, 1988; Melzack, 1990) first proposed the existence of a pain-related neuromatrix, or pain matrix (Ingvar, 1999), comprised of a number of spinal and supraspinal brain regions responsible for processing the perception of pain. More recent research has broken this pain matrix down into more specific components: a peripheral nociceptive system/pathway that carries the sensory aspects of pain and connects to somatosensory and limbic areas of the brain, a lateral pain system/pathway that processes the attentional and cognitive-evaluative components of pain, and a medial pain system/pathway that processes the affective components of pain (Melzack and Wall, 1988; Eccleston and Crombez, 1999; Brooks and Tracey, 2005; Kulkarni et al, 2005).
The nociceptive pathway begins with neurons whose endings are located in the periphery (e.g. nociceptors in the skin, viscera, and muscles that are sensitive to mechanical, thermal, and chemical tissue damage). These neurons enter the dorsal horns (DH) of the spinal cord as myelinated A\(\lambda\) and unmyelinated C fibers that synapse in nucleus proprius and the marginal nucleus. Second order nociceptive neurons cross to the contralateral spinal cord and ascend as parts of the lateral and ventral spinothalamic, spinotectal, and spinoreticular tracts, synapsing in specific nuclei of the thalamus (nearly all thalamic nuclei are implicated; see (Albe-Fessard, 1985) and brainstem. From the thalamus and brainstem, fiber tracts carrying pain-related somatosensory information project widely throughout the brain to a matrix of cortical and subcortical areas whose functional organization is still being widely researched.

While the exact circuitry of the “pain matrix” is still under investigation, several important regions of the brain are generally agreed to be involved in the processing of pain. The sensory components of pain are relayed from the spinal cord and brainstem pain processing centers such as the periaqueductal gray (PAG) to the primary and second somatosensory cortices (S1, S2), anterior cingulate cortex (ACC), regions of anterior and posterior insular cortex (AIC, PIC), several different circuits in the dorsolateral, ventrolateral, and medial prefrontal cortices (DLPFC, VLPFC, MPFC), and to limbic centers such as the orbitofrontal cortex (OFC) and basolateral amygdala (BLA). These brain regions then intricately interconnect with one another to modulate the affective and attentional components of pain perception and modulation. There is also less well-understood evidence that areas of the premotor cortex and the posterior parietal cortex (PCC) may also be involved in the perception of pain. (Davis et al, 1997; Davis et al, 1998; Bushnell et al, 1999; Coghill et al, 1999; Gelnar et al, 1999; Treede et al, 1999; Peyron et al, 2000; Ostrowsky et al, 2002; Jones et al, 2003; Lorenz et al, 2003; Tracey and Mantyh, 2007; Kim et al, 2008; Kang et al, 2010).
The complexity of the circuitry involved in processing pain and the large number of places where pathology may occur make it unsurprising that so many different types of chronic pain exist and that treating chronic pain is not always effective. One problem with these models is that even the complicated representation depicted in Figure 2A does not do the complexity of the circuitry justice. Evidence exists for connections not illustrated in this model. For example, connections from the somatosensory cortices to the insula and from prefrontal cortices to the basal ganglia (Schmidt-Wilcke et al, 2006; Geha et al, 2008) may also be important in modulating perception of chronic pain. Another weakness of these models is that much of the experimental evidence for these pathways was acquired by analyzing perception of different kinds of acute pain in healthy controls. The following section will address changes in the pain matrix observed in the brains of patients with various types of chronic pain. For thorough reviews of the literature that focuses on neural activity elicited by acute pain, see (Peyron et al, 2000) and (Peyron et al, 2000; Apkarian et al, 2005).

3. Structural and Functional Differences in the Chronic Pain Brain

Many studies have been conducted that analyze gray matter structure and neural function in the chronic pain brain. The majority of this literature suggests the chronic pain brain differs from the healthy brain in many ways, both structural and functional. Using cortical thickness analyses (CTA) and/or voxel-based morphometry (VBM) to compare the brains of healthy controls to patients with chronic back pain (Apkarian, 2004; Schmidt-Wilcke et al, 2006; Seminowicz et al, 2011), fibromyalgia (Kuchinad et al, 2007; Schmidt-Wilcke et al, 2007; Lutz et al, 2008), irritable bowel syndrome (Davis et al, 2008; Seminowicz et al, 2010), migraine (Rocca et al, 2006; Kim et al, 2008; Valfré et al, 2008), and
chronic tension-type headache (Schmidt-Wilcke et al, 2005), researchers have shown differences in cortical thickness, gray matter volume, and/or gray matter density in many regions of the pain matrix. Specifically, gray matter decreases are observed in thalamus, S1, ACC, Insula, DLPFC, VLPFC, MPFC, OFC, PPC, and amygdala. Interestingly, gray matter increases have also been shown in left OFC and basal ganglia. Gray matter density (GMD), which does not always correlate with cortical thickness/volume, is lower in ACC and OFC, and higher in the thalamus, ACC, insula, VLPFC, and MPFC in the brains of patients with irritable bowel syndrome (Seminowicz et al, 2010) and fibromyalgia (Kuchinad et al, 2007). For reviews of gray matter structural differences in the chronic pain brain, see (May, 2008). Additionally, chronic pain patients show increased activity in S1, ACC, Insula, and prefrontal cortical regions, as well as both increases and decreases in thalamic activity (Apkarian et al, 2001; Verne et al, 2003; Cook et al, 2004) when presented with painful stimuli, as compared to healthy subjects. For reviews of functional differences in the chronic pain brain, see (Tracey and Mantyh, 2007; Tracey and Bushnell, 2009; Lee and Tracey, 2010; Apkarian et al, 2011). In a unique approach to a within-subjects design comparing the chronic pain brain to the healthy brain, Witting et al (2006) examined functional activity in patients with unilateral peripheral nerve injuries. Compared to non-allodynic brushing of skin on the unaffected side of the body, brush-stroke allodynia resulted in increased activity in contralateral OFC, ipsilateral insula (as opposed to contralateral insula in non-allodynic stimulation) and ACC (in a subset of patients), as well as decreased activation in S1. Overall, it seems clear that there are significant differences in the brains of patients with chronic pain, leading to the question of whether clinical interventions that successfully treat pain also influence the neural function and anatomy behind pain perception.

4. Clinical Interventions for Chronic Pain – Reversal of Structural and Functional Pathology

Despite risks of serious side effects, two of the most common and most successful treatment approaches for chronic pain are surgery and pharmaceuticals, both techniques that are capable of alleviating pain and normalizing some of the structural and functional differences in chronic pain brains. Using EEG, Stern et al (2006) showed that neurogenic pain patients presented with persistent hyperactivation in S1, S2, ACC, IC, unspecified PFC, and PPC and that the observed hyperactivation in ACC and IC normalized after therapeutic thalamotomy. More recently, Seminowicz et al (2011) compared MRI data from healthy controls with those of chronic low back pain patients both before and after therapeutic spinal surgery or facet joint injections. The chronic low back pain patients initially differed from controls in that cortical thickness was lower in S1, ACC, IC, and DLPFC; and functional activity appeared abnormal during a cognitive/attentional task. After treatment, cortical thickness increased in both DLPFC and IC (significantly correlated with reports of reduced levels of pain). DLPFC during the cognitive task normalized after treatment, as well. Pharmaceutical treatment for chronic pain has also been shown to reverse some of the structural and functional differences in the chronic pain brain. For example, successful lidocaine administration has been shown to decrease functional activity associated with spontaneous pain in post-herpetic neuralgia in thalamus, S1, S2, ACC, basal ganglia, amygdala, and OFC; though right IC activity increased after treatment (Geha et al, 2007).

Because most forms of chronic pain are likely caused by a combination of complex factors involving somatosensory, attentional, and emotional circuitry (Naylor et al, unpublished observations), psychotherapeutic approaches like CBT that address all of these underlying functions are highly appealing options for treating chronic pain. CBT also carries none of the risks of serious side effects.
that are common with surgical and pharmaceutical interventions. While plenty of evidence exists that supports CBT as an effective treatment for chronic pain (Vlaeyen et al, 1995; Basler et al, 1997; Morley et al, 1999), there are currently no published studies that compare the clinical outcomes of CBT for chronic pain with changes in structure and function. Preliminary data from our lab shows that chronic pain patients exhibit decreased functional activity in right IC, amygdala, and prefrontal cortices, as well as increased activity in thalamus and left IC when viewing salient negative emotional images after 11 weeks of CBT. Preliminary cortical thickness analyses also reveal that chronic pain patients have thicker cortices in several regions (analysis ongoing) after the completion of therapy (Naylor et al, in preparation for publication).

5. Diffusion Tensor Imaging in Chronic Pain

Correlations between clinical outcomes and post-CBT normalization of gray matter structure and function provide promising evidence that ties chronic pain to abnormal physiology within the brain, suggesting that white matter pathology in tracts that connect pain-processing centers may also be involved in dysfunction of pain perception. The literature shows, for example, that FA is lower in the left cingulum-callosum bundle (Geha et al, 2008) in patients with complex regional pain syndrome. Correlated with changes in gray matter density, the authors suggest that this finding likely represents neurodegeneration rather than cortical atrophy without cell death. Using probabilistic tractography, the same study demonstrated that VMPFC to IC activity was increased and VMPFC connectivity to the basal ganglia was decreased, suggesting that white matter reorganization may occur as a result of gray matter structural and functional changes associated with chronic pain. Interestingly, Gustin et al (2010) found some changes in mean diffusivity (MD) in regions of cortex (but not in the connecting fiber tracts) in patients with persistent neuropathic pain following spinal cord injury. Fibromyalgia patients have demonstrated increases in FA in projections originating in the thalamus and insula as well as decreases in FA in white matter associated with S1, amygdala, hippocampus, and ACC (Lutz et al, 2008). In central post-stroke pain, lateral thalamocortical fibers associated with nociceptive processing demonstrated decreased FA (Seghier et al, 2005), while lower FA was observed in corpus callosum, optic radiations, and a region that may include the posterior cingulum bundle in patients with migraine with aura (DaSilva et al, 2005). While the literature may be relatively sparse and not entirely consistent when it comes to white matter analyses of chronic pain brains, the data that has been reported supports our hypothesis that effective CBT for chronic pain may influence fiber tract characteristics and connectivity as well as gray matter structure and function.

B. Innovation

The experiments proposed in the following section represent a novel and innovative approach to the study of chronic pain in that the vast majority of the literature currently centers around differences in gray matter structure and functional activity involved with pain perception. White matter connectivity is not usually taken into consideration, likely because DTI has not been available as a research method for as long as many other imaging modalities. This series of experiments will seek to replicate the structural and functional findings reported in the literature regarding differences in the chronic pain brain and the ability of clinical interventions such as CBT to reverse some of these changes. We will also show that white matter connectivity between regions of the pain matrix is different in the chronic pain
brain and that pathological changes in connectivity may also be treated via a psychotherapeutic approach. Finally, we will also correlate white matter tract characteristics with clinical outcomes in an attempt to demonstrate that the integrity of the connections between regions of the pain matrix is intricately related to healthy and pathological processing and perception of pain.

C. Approach

Experiment 1.

Strategy. Our initial pilot study was designed to investigate whether CBT for coping with chronic pain could alter gray matter structure and patterns of neural activity in the brains of patients with chronic pain in a manner that would correlate with clinical outcomes (Specific Aim 2). To test this, we compared baseline pre-CBT fMRI and DTI scans of chronic pain patients to post-CBT scans.

Methodology: Nine female chronic pain patients were recruited to participate in this study. Patients were evaluated for study eligibility, provided informed consent, and underwent an initial clinical assessment of chronic pain conditions. Patients deemed eligible to participate underwent anatomical, functional, and diffusion tensor imaging scans both prior to and after the completion of 11 weeks of cognitive behavioral therapy geared toward coping with chronic pain. Clinical Assessment. Beck Depression Inventory (Beck et al, 1978), McGill Pain Questionnaire (Melzack, 1975), and a Coping Strategies Questionnaire (Keefe et al, 1991) that includes a measure of pain catastrophizing were administered both before and after CBT. Clinical data was scored according to the instructions for each questionnaire (see previous three references) and compared using SPSS statistical software.

Functional Magnetic Resonance Imaging. fMRI data was acquired in a 3T Philips Achieva TX high field MRI scanner with the following scan parameters: 28 slices, 5mm slice thickness, 2466ms TR, 80ms TE, 3.0 NSA, and 230mm FOV. Functional data was preprocessed and analyzed using region of interest and whole brain analyses with BrainVoyager QX (Brain Innovation, Maastricht, Netherlands). Functional data was mapped to anatomical data based on mean and peak voxel coordinates in Talairach Daemon. VBM and CTA analyses of gray matter characteristics were analyzed using CIVET Pipeline v1.1.9. Diffusion Tensor Imaging. DTI data was acquired via an axial 2D spin echo EPI sequence with 6 diffusion directions and the following scan parameters: 30 slices, 5mm slice thickness, 5400ms TR, 56ms TE, 2x2mm in-plane resolution, 1000 s/mm² B-value, and 45 EPI factor. Seed regions of interest were used to calculate fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values in the anterior cingulum bundle, anterior arm of internal capsule, posterior arm of internal capsule as well as in areas where DTI differences were not expected to serve as a control (genu and splenium of corpus callosum). DTI data was analyzed using PRIDE V4.1 FiberTracker 6.5 (Philips Healthcare) on the IDL Virtual Machine (RSI/ITT Visual Information Solutions). Statistical comparisons of DTI data were done using PASW Statistics 18.

Expected Outcomes and Implications. Specific Aim 2: We predict that fiber tracts connecting the regions of the pain matrix will exhibit altered fiber characteristics after the completion of CBT. Specifically, we expect to see increased FA values in the anterior cingulum bundle, limbic and sensory portions of the internal capsule, projections from the somatotopic regions of S1 and S2 that correspond to the somatic locations of pain origin, and in fibers connecting the insula to other regions of interest.
These findings would be indicative of a more normal/intact pain matrix. We expect to see decreased post-CBT FA values in fiber tracts that connect prefrontal cognitive/evaluative centers with sensory and emotional regions of the pain matrix, reflecting lower levels of attention to and/or preoccupation with pain intensity.

**Preliminary Data.** Structural and functional data from this study are summarized in Background and Significance (Part 4, Clinical Interventions for Chronic Pain). Preliminary analysis of DTI data revealed a post-CBT increase in FA in the right anterior cingulum bundle ($t=-3.994, p=0.007$), as well as post-CBT increases in ADC in the left anterior cingulum bundle ($t=-2.795, p=0.023$), the anterior arm of the left internal capsule ($t=-3.010, p=0.017$), and the posterior arm of the left internal capsule ($t=-3.332, p=0.010$). While we have not yet demonstrated that connectivity in these white matter tracts is decreased in chronic pain patients at baseline, it is still promising to observe such significant changes in fiber pathways known to be involved in the perception of pain after completion of CBT. These results support our hypothesis that the integrity of connections between regions of the pain matrix likely plays a role in modulating perception of pathological pain.

**Table 1. Mean values of fractional anisotropy (FA) and apparent diffusion coefficient (ADC) in chronic pain patients before and after 11 weeks of CBT.**

<table>
<thead>
<tr>
<th>Fiber Tract</th>
<th>Pre-CBT</th>
<th>Post-CBT</th>
<th>Paired Samples T-Test</th>
<th>Sig. (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean FA ± SD</td>
<td>Mean FA ± SD</td>
<td>t</td>
<td>Sig. (2-tailed)</td>
</tr>
<tr>
<td>Corpus Callosum, Genu</td>
<td>0.484 ± 0.019</td>
<td>0.481 ± 0.021</td>
<td>0.813</td>
<td>0.440</td>
</tr>
<tr>
<td>Corpus Callosum, Splenium</td>
<td>0.550 ± 0.012</td>
<td>0.557 ± 0.021</td>
<td>-1.002</td>
<td>0.345</td>
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<tr>
<td>Cingulum Bundle, Anterior, Left</td>
<td>0.449 ± 0.030</td>
<td>0.447 ± 0.036</td>
<td>0.130</td>
<td>0.894</td>
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<tr>
<td>Cingulum Bundle, Anterior, Right</td>
<td>0.390 ± 0.032</td>
<td>0.441 ± 0.033</td>
<td>-3.994 *</td>
<td>0.007 *</td>
</tr>
<tr>
<td>Internal Capsule, Anterior Arm, Left</td>
<td>0.480 ± 0.019</td>
<td>0.482 ± 0.030</td>
<td>-0.208</td>
<td>0.841</td>
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<tr>
<td>Internal Capsule, Anterior Arm, Right</td>
<td>0.463 ± 0.016</td>
<td>0.467 ± 0.028</td>
<td>-0.490</td>
<td>0.637</td>
</tr>
<tr>
<td>Internal Capsule, Posterior Arm, Left</td>
<td>0.517 ± 0.011</td>
<td>0.520 ± 0.011</td>
<td>-0.713</td>
<td>0.496</td>
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<tr>
<td>Internal Capsule, Posterior Arm, Right</td>
<td>0.512 ± 0.015</td>
<td>0.513 ± 0.017</td>
<td>-0.250</td>
<td>0.809</td>
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<table>
<thead>
<tr>
<th>Fiber Tract</th>
<th>Pre-CBT</th>
<th>Post-CBT</th>
<th>Paired Samples T-Test</th>
<th>Sig. (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ADC ± SD</td>
<td>Mean ADC ± SD</td>
<td>t</td>
<td>Sig. (2-tailed)</td>
</tr>
<tr>
<td>Corpus Callosum, Genu</td>
<td>0.855 ± 0.068</td>
<td>0.864 ± 0.053</td>
<td>-0.910</td>
<td>0.369</td>
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<tr>
<td>Corpus Callosum, Splenium</td>
<td>0.876 ± 0.053</td>
<td>0.890 ± 0.049</td>
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<td>0.233</td>
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<tr>
<td>Cingulum Bundle, Anterior, Left</td>
<td>0.777 ± 0.031</td>
<td>0.810 ± 0.024</td>
<td>-2.795 *</td>
<td>0.023 *</td>
</tr>
<tr>
<td>Cingulum Bundle, Anterior, Right</td>
<td>0.776 ± 0.026</td>
<td>0.780 ± 0.021</td>
<td>-1.794</td>
<td>0.123</td>
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<tr>
<td>Internal Capsule, Anterior Arm, Left</td>
<td>0.716 ± 0.046</td>
<td>0.750 ± 0.025</td>
<td>-3.010 *</td>
<td>0.017 *</td>
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<tr>
<td>Internal Capsule, Anterior Arm, Right</td>
<td>0.728 ± 0.038</td>
<td>0.738 ± 0.038</td>
<td>-1.321</td>
<td>0.223</td>
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<tr>
<td>Internal Capsule, Posterior Arm, Left</td>
<td>0.756 ± 0.023</td>
<td>0.777 ± 0.020</td>
<td>-3.332 *</td>
<td>0.010 *</td>
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<tr>
<td>Internal Capsule, Posterior Arm, Right</td>
<td>0.733 ± 0.020</td>
<td>0.744 ± 0.024</td>
<td>-1.635</td>
<td>0.141</td>
</tr>
</tbody>
</table>

**Experiment 2.**

**Strategy.** Our second experiment was designed to further investigate whether CBT for coping with chronic pain could alter gray matter structure and patterns of neural activity in the brains of patients with chronic pain in a manner that would correlate with clinical outcomes (Specific Aim 2) while at the same time comparing pre- and post-CBT data with age-matched healthy controls (Specific Aim 1). To test this, we plan to compare baseline pre-CBT fMRI and DTI scans of chronic pain patients to post-CBT
scans and scans of healthy volunteers. We also plan to correlate clinical outcomes, gray matter structural differences, and changes in neural activity with DTI data (Specific Aim 3).

**Methodology:** Forty chronic pain patients were recruited to participate in this study. Patients were evaluated for study eligibility, provided informed consent, and underwent an initial clinical assessment of chronic pain conditions. Patients deemed eligible to participate will undergo anatomical, functional, and diffusion tensor imaging scans both prior to and after the completion of 11 weeks of cognitive behavioral therapy geared toward coping with chronic pain. The final patients to participate in this experiment will receive their post-CBT scans during the next several weeks. Scans from ten age-matched healthy controls (recruited for a different experiment but scanned using the same tasks and parameters) will also be analyzed. **Clinical Assessment.** Beck Depression Inventory (Beck et al., 1978), McGill Pain Questionnaire (Melzack, 1975), and a Coping Strategies Questionnaire (Keefe et al., 1991) that includes a measure of pain catastrophizing will be administered both before and after CBT. Clinical data will be scored according to the instructions for each questionnaire (see previous three references) and compared using PASW Statistics 18. **Functional Magnetic Resonance Imaging.** fMRI data was acquired in a 3T Philips Achieva TX high field MRI scanner with the following scan parameters: 28 slices, 5mm slice thickness, 2466ms TR, 80ms TE, 3.0 NSA, and 230mm FOV. Functional data will be preprocessed and analyzed using region of interest and whole brain analyses with FSL (FMRIB, Oxford, UK). Functional data will be mapped to anatomical data based on mean and peak voxel coordinates in Talairach Daemon. VBM and CTA analyses of gray matter characteristics will be analyzed using SPM5. **Diffusion Tensor Imaging.** DTI data was acquired via an axial 2D spin echo EPI sequence with 15 diffusion directions and the following scan parameters: 30 slices, 5mm slice thickness, 5400ms TR, 56ms TE, 2x2mm in-plane resolution, 1000 s/mm² B-value, and 45 EPI factor. Seed regions of interest will be used to calculate fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values in the anterior cingulum bundle, anterior arm of internal capsule, posterior arm of internal capsule as well as in areas where DTI differences are not expected (to serve as controls. Whole-brain group comparisons will also be performed. DTI data will be analyzed using FSL. **Tract-Based Spatial Statistics (TBSS).** Our higher number of diffusion directionality allows for more complex analyses of DTI data than in experiment 1, including looking at deterministic tractography. TBSS data will be acquired by selecting gray matter regions of interest (S1, S2, thalamus, ACC, AIC, PIC, DLPFC, VLPFC, MPFC, OFC, and amygdala) and utilizing deterministic tractographical fiber tracing to measure connectivity and fiber characteristics, also using FSL software.

**Expected Outcomes and Implications.** **Specific Aim 1:** We expect that chronic pain patients (as compared to healthy controls) will show higher levels of FA in the anterior cingulum bundle, limbic and sensory portions of the internal capsule, projections from the somatotopic regions of S1 and S2 that correspond to the somatic locations of pain origin, and in fibers connecting the insula to other regions of interest. We also expect that deterministic tractographical analyses will show increased connectivity between pain-modulating areas and decreased connectivity between prefrontal regions and limbic centers in chronic pain patients. **Specific Aim 2:** Further, we hypothesize that post-CBT scans will show changes in fiber characteristics that will begin to more closely resemble those observed in healthy controls. **Specific Aim 3:** Finally, we expect that reversal of the white matter changes associated with chronic pain will be positively correlated with improved clinical outcomes. These three hypotheses, when considered together, may help paint a picture of precisely how white matter connectivity in the brain may contribute to modulation of pain perception in chronic pain patients.
Experiment 3.

Strategy. Our third and final experiment was designed to further investigate whether CBT for coping with chronic pain could alter gray matter structure and patterns of neural activity in the brains of patients with chronic pain in a manner that would correlate with clinical outcomes (Specific Aim 2) while at the same time comparing pre- and post-CBT data with age-matched healthy controls (Specific Aim 1). To test this, we plan to compare baseline pre-CBT fMRI and DTI scans of chronic pain patients to post-CBT scans and scans of healthy volunteers. We also plan to correlate clinical outcomes, gray matter structural differences, and changes in neural activity with DTI data (Specific Aim 3). This experiment is intended as a follow-up to experiment 2 in that many of the parameters remain the same, but we plan to recruit up to 150 patients over the course of five years (as opposed to 40 in experiment 2 and 9 in experiment 1). We also intend to recruit healthy controls directly for this study rather than analyzing data from healthy controls recruited for unrelated experiments. Experiment 3 will also be less restrictive in regards to types of chronic pain to be analyzed, and pre- and post-CBT assessments will include additional emotional questionnaires as well as tasks designed to test cognitive performance. Finally, as this is our first experiment designed with high quality DTI data acquisition in mind, we are drastically increasing the parameters of our DTI scans (e.g. to 46 diffusion directions). We are still in the process of deciding upon our precise scanning protocols. The final addition to this experiment will be a regimen of prolonged daily Therapeutic Interactive Voice Response therapy (essentially automated CBT over the phone), though TIVR data will not be addressed in this proposal.

Methodology: 150 chronic pain patients will be recruited to participate in this study. Patients will be evaluated for study eligibility, provide informed consent, and undergo an initial clinical assessment of chronic pain conditions. Patients deemed eligible to participate will undergo anatomical, functional, and diffusion tensor imaging scans both prior to and after the completion of 11 weeks of cognitive behavioral therapy geared toward coping with chronic pain, as well as after a prolonged period of Therapeutic Interactive Voice Response treatment. Scans from age-matched healthy controls will also be analyzed. Clinical Assessment. Beck Depression Inventory (Beck et al, 1978), McGill Pain Questionnaire (Melzack, 1975), Treatment Outcomes in Pain Survey (Rogers et al, 2000), and a Coping Strategies Questionnaire (Keefe et al, 1991) that includes a measure of pain catastrophizing will be administered both before and after CBT, and after completion of TIVR. Clinical data will be scored according to the instructions for each questionnaire (see previous four references) and compared using PASW Statistics 18. Functional Magnetic Resonance Imaging. fMRI data will be acquired in a 3T Philips Achieva TX high field MRI scanner with the following scan parameters: 28 slices, 5mm slice thickness, 2466ms TR, 80ms TE, 3.0 NSA, and 230mm FOV. Functional data will be preprocessed and analyzed using region of interest and whole brain analyses with FSL (FMRIB, Oxford, UK). Functional data will be mapped to anatomical data based on mean and peak voxel coordinates in Talairach Daemon. VBM and CTA analyses of gray matter characteristics will be analyzed using SPM5. Diffusion Tensor Imaging. DTI data will be acquired via an axial 2D spin echo EPI sequence with 46 diffusion directions and the following scan parameters: 30 slices, 5mm slice thickness, 5400ms TR, 56ms TE, 1.75x1.75mm in-plane resolution, 1000 s/mm² B-value, and 45 EPI factor. Seed regions of interest will be used to calculate fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values in the anterior cingulum bundle, anterior arm of internal capsule, posterior arm of internal capsule as well as in areas where DTI differences are not expected (to serve as controls. Whole-brain group comparisons will also be performed. DTI data will be analyzed using FSL. Tract-Based Spatial
Statistics (TBSS). Our higher number of diffusion directionality and improved scan resolution will allow for more complex analyses of DTI data than in experiment 1 or 2, including looking at probabilistic tractography. TBSS data will be acquired by selecting gray matter regions of interest (S1, S2, thalamus, ACC, AIC, PIC, DLPFC, VLPFC, MPFC, OFC, and amygdala) and utilizing probabilistic tractographical fiber tracing to measure connectivity and fiber characteristics, also using FSL software.

Expected Outcomes and Implications. As experiment 3 is really just a more powerful (higher n, more clinical measures) than experiment 2, most of our hypotheses remain unchanged. We do expect that our higher number of diffusion directions and improved scan resolution, which make probabilistic tractography possible, will allow for more precise and accurate quantifications of white matter characteristics and connectivity. As a result, it is likely that we may notice more subtle changes in the chronic pain brain. It is also likely that we will be able to analyze smaller and harder to find white matter tracts within the brain.


DTI can be a fickle measure. Successful DTI data acquisition depends upon adequate diffusion directionality, multiple scans using different B-values, signal strength, and signal-to-noise ratio. In an ideal world, all of these parameters would be set to their hypothetical ideal or maximum values. In reality, improving scan parameters drastically increases the time required to complete the scan. Since DTI measures diffusion (movement) of water, it is highly sensitive to patient movement within the scanner. Longer scan times are more likely to result in patient movement. As a result, it requires empirical evaluation of the data to achieve optimal scanning parameters that can be utilized within a realistic window of scanning time. It is possible that our data from experiment 2 will be inadequate to perform TBSS analyses. It is also possible that data from experiments 1 and 2 will not be of high enough resolution to visualize smaller fiber tracts in the brain. These concerns are our primary motivation for improving the DTI scan parameters that will be utilized in experiment 3.

No DTI differences between healthy controls and chronic pain patients, or between pre- and post-CBT scans of chronic pain patients. With all of the inconsistencies in the literature, it is possible that we will observe no white differences between the brains of chronic pain patients and healthy controls. What little data has been published and our own preliminary data make this an unlikely possibility, but it is still one that must be considered. Fortunately, finding that white matter characteristics are not different between chronic pain patients and healthy controls would almost be an even more interesting than having our hypotheses confirmed. This would suggest that the cortical thinning and altered functional activity seen in the chronic pain brain are due to a mechanism other than neurodegeneration and altered functional connectivity. Similarly, lack of significant DTI findings in the pre- to post-CBT comparisons or lack of significant correlations to clinical outcomes would suggest that CBT treats chronic pain by influencing gray matter in the brain without involving related fiber tracts.

Gender differences in DTI. Our pilot study investigated DTI in nine women with chronic pain. Experiments 2 and 3 will analyze DTI information in patients of both genders. This may present a problem in that there is evidence that suggests the existence of fiber tract differences between the male brain and the female brain (Menzler et al, 2010). This issue will be addressed by analyzing the data
with gender as a covariate to determine whether any significant gender differences exist. A similar analysis will be performed to rule out confounding properties of white matter specific to individual types of chronic pain.

5. Future Directions: Several obvious future directions for this research to take include

- **Comparing the white matter characteristics between patients with different types of chronic pain.** Apkarian et al (2011) suggest that different types of chronic pain exhibit different patterns of neural activity and that these functional patterns might even be useful in diagnosing different pain disorders. If this is actually the case, it is possible that fiber tract characteristics and connectivity may also be useful in this regard, especially for any pain disorders that turn out to be more dependent on white matter organization than on gray matter structure.

- **Correlating DTI data with changes in cognitive performance.** Evaluation of cognitive performance (and any changes that follow CBT) is beyond the scope of this proposal. That said, chronic pain patients show impaired performance in some cognitive and emotional decision-making tasks. DTI analysis of pathways linking regions of prefrontal cortex to limbic and attentional areas may very well correlate with cognitive ability, as well.

- **Investigating more long-term DTI changes after a prolonged regimen of TIVR.** The main motivation for utilizing TIVR in experiment 3 is that TIVR should have comparable effects to in-person CBT on chronic pain. If this is the case, any reversal of white matter pathology observed after 11 weeks of CBT should be even more pronounced after months of TIVR.

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V. References


