Brain Anatomy Changes Associated with Persistent Neuropathic Pain Following Spinal Cord Injury

Persistent neuropathic pain commonly occurs following spinal cord injury (SCI). It remains one of the most challenging management problems in this condition. In order to develop more effective treatments, a better understanding of the neural changes associated with neuropathic SCI pain is required. The aim of this investigation was to use diffusion tensor imaging (DTI) to determine if persistent neuropathic pain following SCI is associated with changes in regional brain anatomy and connectivity. In 23 subjects with complete thoracic SCI, 12 with below-level neuropathic pain and 11 without pain, and 45 healthy control subjects, a series of whole-brain DTI scans were performed. The mean diffusivity (MD) of each voxel was calculated and values compared between groups. This analysis revealed that neuropathic pain following SCI is associated with significant differences in regional brain anatomy. These anatomical changes were located in pain-related regions as well as regions of the classic reward circuitry, that is, the nucleus accumbens and orbitofrontal, dorsolateral prefrontal, and posterior parietal cortices. The right posterior parietal cortex projected to most regions that displayed an anatomical change. Analysis of the fiber tracts connecting areas of MD differences revealed no significance differences in MD values between the SCI pain, SCI no pain, and control groups.

Keywords: diffusion tensor imaging, neuropathic pain, parietal cortex, spinal cord injury, thalamus

Introduction

Pain is a common and debilitating consequence of spinal cord injury (SCI). Although loss of mobility is often considered the most serious consequence of SCI, people with SCI consistently rate pain as one of the most difficult problems (Widerstrom-Noga et al. 1999). Several types of pain occur following SCI. However neuropathic pain, which occurs in almost 50% of people following SCI, is one of the most intractable (Siddall et al. 1999). Improvements in the management of neuropathic SCI pain remain hampered by our incomplete understanding of the pathophysiology underlying this condition. Much research to date has focused on the contribution of spinal pain mechanisms. However, attempts to relieve pain using intrathecal local anesthetic and even surgically excising damaged spinal cord segments have not resulted in consistent pain relief (Davis 1954; Melzack and Loeser 1978; Loubser and Donovan 1991). The inability to obtain consistent pain relief using treatments aimed at the spinal cord and periphery suggests that supraspinal mechanisms also play a role.

Evidence highlighting the presence of supraspinal changes in human subjects with neuropathic SCI pain include altered thalamic firing patterns (Lenz et al. 1989; Jeanmonod et al. 1993), biochemistry (Pattany et al. 2002), and blood flow (Ness et al. 1998). Neuropathic SCI pain is also associated with somatosensory cortical reorganization that correlates with pain intensity (Wrigley, Press, et al. 2009). Evidence for a link between brain anatomical changes and pain is starting to emerge in other persistent pain conditions. In subjects with persistent lumbar spinal pain, significant volume loss in the thalami and frontal cortices has been demonstrated (Apkarian et al. 2004). In rodent models of persistent neuropathic pain, neural death has been shown not only in the dorsal horn but also in higher brain centers (Eaton et al. 1998, Moore et al. 2002; Siniscalco et al. 2007; Jalalvand et al. 2008). These findings suggest that persistent pain is associated with alterations in neuronal activity that are linked to long-term structural changes in the brain.

Recent advances in imaging and analysis techniques enable detection of subtle changes in brain structure. For example, diffusion tensor imaging (DTI), which is capable of identifying extremely small changes in the molecular motion of water protons, may be used to detect fine alterations in neuronal morphology. We have recently used DTI to show that SCI results in significant anatomical changes within the primary motor cortex (in the region innervating the paralyzed lower body), as well as the cerebellar and medial prefrontal cortices (PFCs) (Wrigley, Gustin, et al. 2009). However, in the previous study, it was not possible to determine which changes were associated with the presence of pain.

The aim of this investigation was to use DTI to determine the regional changes in brain structure specifically associated with persistent neuropathic SCI pain. We hypothesized that persistent pain following SCI would be associated with a significant change in brain anatomy and that these changes will be located in brain regions involved in the processing of acute pain.

Materials and Methods

Twenty-three subjects with SCI (19 males and 4 females, mean age = 43 ± 3 [± standard error of the mean (SEM)], range = 22–71 years) and 45 control subjects without SCI (28 males, mean age = 35 ± 2 [± SEM], range = 19–78 years) were recruited for the study. In order to focus our investigation on the underlying mechanisms of neuropathic pain, we employed a set of extremely strict inclusion criteria. Only those SCI subjects with complete (American Spinal Injury Association Impairment Scale grade A [Marino et al. 2003]) thoracic SCIs and below-level neuropathic pain or no neuropathic pain were included in the study. Below-level neuropathic pain was defined as constant shooting, electric, or burning pain in the region of sensory loss at least 3 segments below the neurological level of injury (Fig. 1) (Siddall et al. 2002). Subjects reporting pain immediately surrounding the neurological level of injury (at-level neuropathic pain) were excluded. These strict criteria reduced our subject pool dramatically. However, data were obtained from 11 SCI subjects with complete thoracic SCIs and below-level neuropathic pain or no neuropathic pain.
subjects without neuropathic pain and 12 SCI subjects with persistent below-level neuropathic pain (Table 1).

During the 7 days prior to the magnetic resonance imaging (MRI) session, each SCI subject kept a pain diary recording 3 times a day the intensity of their ongoing pain. Subjects rated the intensity of their pain using a 10-cm horizontal visual analogue scale with 0 indicating "no pain" and 10 indicating "the most intense imaginable pain." These pain intensity scores were then averaged over the 7-day period to create a mean pain intensity score. On the day of the MRI scanning, each subject drew the distribution of his/her ongoing pain and completed a short-form McGill Pain Questionnaire. Informed written consent was obtained for all procedures according to the Declaration of Helsinki, and the study was approved by our local institutional human research ethics committees.

Table 1

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<th>Years since injury</th>
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<th>Sensory level</th>
<th>Sensory ZPP</th>
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Note: Table indicating subject characteristics where neurological level of SCI = the most caudal segment of the spinal cord with normal sensory and motor function on both sides of the body; AIS = American Spinal Injury Association Impairment Scale where A = no motor or sensory function in the sacral segments S4–S5; motor/sensory level = the most caudal segment of the spinal cord with normal motor/sensory function; sensory zone of partial preservation (ZPP) = the most caudal spinal cord segment with partial sensory preservation.
MRI Acquisition

Subjects lay supine on the bed of a 3T MRI scanner (Achieva, Philips, Andover, MA) with their head immobilized in a head coil. DTI images were acquired with a whole-brain single-shot, spin-echo echo-planar pulse sequence (time repetition [TR] = 8788 ms, flip angle = 90°, 112 × 112 matrix size, 224 × 224 mm field of view, 2.5 mm slice thickness, 55 axial slices), with 4 image sets collected for each subject. For each slice, diffusion gradients were applied along 32 independent orientations with \( b = 1000 \, \text{s/mm}^2 \) after the acquisition of \( b = 0 \, \text{s/mm}^2 \) (b0) images. In each subject, 4 DTI scans were acquired, with repeated acquisitions to improve signal-to-noise ratios. A 3D \( T_1 \)-weighted anatomical image set, covering the entire brain, was also collected (turbo field echo; time echo = 2.5 ms, TR = 5600 ms, flip angle = 8°, voxel size = 0.8 × 0.8 × 0.8 mm).

MRI Analysis

Using SPM5 (Friston et al. 1995) and custom software, the 4 DTI sets were realigned and averaged. Using diffusion-weighted images collected from 32 directions and b0 images, the DT was calculated from the averaged images using a linear model (Basser and Pierpaoli 1996). Once the elements of DT were calculated, mean diffusivity (MD) maps were derived and the images spatially normalized and smoothed (full width at half maximum = 6 mm).

To determine regional changes in MD over the entire brain, a voxel-by-voxel analysis was performed to search for significant differences in MD values between SCI subjects with pain and SCI subjects without pain (analysis of covariance, uncorrected for multiple comparisons, \( P < 0.005 \), age and gender as nuisance variables, minimum clusters size = 20 voxels). Significant MD differences were overlaid onto an individual’s \( T_1 \)-weighted anatomical image for visualization. We understand that for population-based statistics, statistical thresholds corrected for multiple comparisons are desirable. However, given our strict inclusion criteria and thus relatively low subject numbers, only uncorrected statistical thresholds were possible. In order to reduce the likelihood of false positives, for the whole-brain analysis we have used only those clusters that were larger than 20 contiguous voxels in size. Furthermore, the mean ± SEM MD values of each cluster were calculated for all 3 groups (control, SCI pain, SCI no pain) and differences between all 3 groups determined (2-sample \( t \)-tests, 2 tailed, \( P < 0.05 \)). Correlations between ongoing pain and MD values and pain and pain duration were also determined for each cluster (\( P < 0.05 \)).

Tractography was performed using mrDiffusion software (Dougherty et al. 2005), based on the DT calculated as described above. Fibers were tracked from those clusters that displayed significant differences in MD between SCI pain and SCI no pain groups. For each subject, these clusters were “unnormalized” into their native space and the output fibers tracked from this seeding cluster using a minimum fractional anisotropy (FA) value of 0.15 and a maximum turning angle of 15°. The resulting fibers were then normalized into Montreal Neurological Institute space, binarized, and added to the output fibers from other subjects to provide an indication of the frequency of each fiber bundle in all 68 subjects (control, \( n = 45 \); SCI no pain, \( n = 12 \); SCI pain, \( n = 11 \)). In addition, fiber tracts that passed between 2 significant clusters were plotted for each subject. Frequency maps of these fibers were then calculated and the mean FA values of the fibers calculated in each subject. These FA values were then averaged for each of the 3 groups (control, SCI pain, SCI no pain) and differences between all 3 groups determined (2-sample \( t \)-tests, 2 tailed, \( P < 0.05 \)).

Results

The injury levels and distributions of ongoing pain in the 12 SCI pain subjects are shown in Figure 1. Consistent with the inclusion criteria, all subjects reported ongoing pain below the neurological level of their injury, and in most subjects the pain was perceived in both legs and feet. The mean pain intensity for the week prior to scanning was 4.3 ± 0.4 and was most commonly described as “sharp,” “shooting,” and “electric” in nature.

Whole-brain DTI analysis revealed significantly different MD values in SCI pain subjects in a number of brain regions when compared with SCI subjects without pain. Increased MD values (change in MD corrected for age; mean ± SEM × 10⁻³ mm²/s) occurred in the right posterior parietal cortex (PPC; SCI pain: 0.16 ± 0.07, SCI no pain: -0.17 ± 0.05, \( P = 0.0008 \)), right dorsolateral prefrontal cortex (DLPFC; SCI pain: 0.05 ± 0.02, SCI no pain: -0.05 ± 0.01, \( P = 0.0002 \)), left anterior insula (SCI pain: 0.02 ± 0.02, SCI no pain: -0.04 ± 0.01, \( P = 0.005 \)), medial orbitofrontal cortex (OFC; SCI pain: 0.13 ± 0.08, SCI no pain: -0.13 ± 0.06, \( P = 0.017 \)), and the premotor cortex (SCI pain: 0.17 ± 0.04, SCI no pain: -0.11 ± 0.03, \( P = 0.00002 \)). SCI pain subjects displayed decreased MD values in the ventral pons extending into the ventral midbrain (SCI pain: -0.16 ± 0.04, SCI no pain: -0.003 ± 0.05, \( P = 0.034 \)), left amygdala (SCI pain: -0.13 ± 0.02, SCI no pain: -0.03 ± 0.02, \( P = 0.0004 \)), and right ventroposterior (VP) thalamus (SCI pain: -0.15 ± 0.01, SCI no pain: -0.09 ± 0.01, \( P = 0.0002 \)) (Figs 2 and 3; Table 2). Apart from the ventral pons/midbrain cluster, all significant clusters were located either completely within gray matter or centered within gray matter and spreading into the immediately adjacent white matter. In no instance was the significant cluster located entirely within white matter.

The MD cluster values of the SCI pain group were also significantly different to the control group except in the nucleus accumbens (NA), anterior insula, and medial OFC. Significantly increased MD values in the SCI pain group occurred in the DLPFC, PPC, and premotor cortex, and significantly decreased MD values occurred in VP thalamus, amygdala, and ventral pons. In the SCI no neuropathic pain group, the anterior insula, PPC, and DLPCF, NA, VP thalamus, and premotor cortex had significantly lower MD values compared with control subjects.

In SCI subjects, some regions also displayed significant correlations between pain intensity and MD values. There was a significant positive correlation between MD values in the DLPFC (\( P < 0.004 \)), PPC (\( P < 0.005 \)), anterior insula (\( P < 0.001 \)), and premotor cortex (\( P < 0.0001 \)) and a significant negative correlation between MD values and pain intensity in the amygdala (\( P < 0.0002 \)) and VP thalamus (\( P < 0.001 \)) (Fig. 3). In contrast, no cluster demonstrated a significant correlation between MD value and pain duration (ventral pons/midbrain: \( R = 0.35, P = 0.26 \); NA: \( R = 0.26, P = 0.41 \); DLPFC: \( R = 0.23, P = 0.48 \); medial OFC: \( R = 0.03, P = 0.92 \); VP thalamus: \( R = 0.30, P = 0.34 \); PPC: \( R = 0.16, P = 0.63 \); premotor: \( R = 0.14, P = 0.65 \); anterior insula: \( R = 0.03, P = 0.93 \); amygdala: \( R = 0.31, P = 0.33 \)).

Individual subject analysis revealed that for all clusters except the VP thalamus and amygdala, the SCI pain and SCI no pain MD values lay well within the range of MD values of the control subjects (Fig. 4). In contrast, for the amygdala, over 80% of the SCI pain subjects had MD values below the lowest MD value in control subjects, and for the VP thalamus, over 90% of the SCI pain subjects had MD values below the lowest MD value in control subjects.

Tractography revealed that fibers from the PPC cluster projected to most of the clusters demonstrating regional MD differences. That is, the PPC cluster projected to the DLPFC, medial OFC, thalamus, premotor area, and ventral pons/midbrain clusters (Fig. 5). Analysis of fibers passing from the PPC to these clusters revealed that the PPC cluster connected directly to the DLPFC in 51 subjects, medial OFC in 38 subjects, VP thalamus in 45 individuals, and ventral pons/midbrain in 51 individuals (Fig. 6). Despite significant differences in the MD
values of the clusters from which these tracks were derived, comparisons of the FA values of the fiber bundles revealed no significant difference in the fiber tract properties between the control and SCI pain groups. There was, however, a significant difference between the control and SCI no pain group in the fiber bundle connecting the PPC to the ventral pons/midbrain.

Discussion
The results of this investigation reveal that persistent neuropathic pain following SCI is associated with significant changes in the anatomy of a number of brain regions traditionally associated with nociceptive processing including the VP region of the thalamus, PFC, insular cortex, amygdala, and premotor cortex. The amount of change in all these regions significantly correlated with pain severity, further strengthening an association with pain perception. In addition, regions typically linked with reward behaviors also demonstrated regional anatomical changes including the NA, OFC, and associative cortices such as the PPC. Furthermore, tractography revealed that one of these regions, the PPC, projected to most regions that displayed an anatomical change.

Using DTI analysis, 2 measures of neuronal integrity can be derived, MD and FA. MD is the average degree of water diffusion in a region. It provides a general measure of tissue structure and cellular integrity. FA describes the degree of directional diffusivity or "anisotropy" of water. FA values range from 0 to 1 indicating free water diffusion and unidirectional diffusion, respectively. FA can be used to compute the pathways and connections of tracts ("tractography"). Changes in MD reflect changes in the ease of water movement in neural tissues. Water movement is determined by the structural properties of neurons including cellular size, shape, and integrity (Pierpaoli and Basser 1996). A reduction in MD indicates less water movement suggesting more restrictive tissue barriers. Changes that may decrease MD include neuronal sprouting, cellular proliferation, and tumor formation (without pronounced edema). An increase in MD indicates greater water movement suggesting decreased tissue barriers and can occur with edema, demyelination, cell death, and axonal loss (Stevenson et al. 2000; Iannucci et al. 2001).

Although some persistent pain conditions appear to result from neural activity in the primary afferent fiber and dorsal horn, it is clear that neural changes in sites well above the level of the primary synapse contribute to the experience of persistent pain. Several voxel-based morphometry (VBM) studies have shown that persistent pain is associated with differences in regional brain structure, including decreased gray matter volume in the thalamus, PPC, DLPFC, thalamus, and NA (Apkarian et al. 2004; Kuchinad et al. 2007; Buckalew et al. 2008; DaSilva et al. 2008; Kim et al. 2008; Lutz et al. 2008). In the present study, DTI revealed that neuropathic pain following SCI is also associated with MD differences in each of these regions.

The widespread and bidirectional changes found in this study are consistent with those one would expect following such a major insult to the nervous system. It is known that SCI results in "upstream" changes including activation of microglia that are possibly linked to the presence of pain (Hains and Waxman 2006). However, microglial activation is known to be associated with a range of functional and structural changes including both cell death and sprouting, both of which could result in opposite changes in water diffusivity. It is very likely
that SCI results in a complex mixture of changes including both neuronal loss and sprouting even within the same region.

**Regional Brain Anatomy Changes in Below-Level Neuropathic SCI Pain**

**Thalamus**
The differences in thalamic MD values found in this study are consistent with previous research involving a variety of acute and persistent pain states. A number of electrophysiological (Lenz et al. 1989), biochemical (Pattany et al. 2002), and morphological studies (Draganski et al. 2006) have demonstrated changes in the thalamus following deafferentation. Despite these reports, the link between thalamic changes and persistent neuropathic pain remains in dispute (Radhakrishnan et al. 1999; Draganski et al. 2006). In the present study, changes in MD were significantly greater in the pain group, and the magnitude of change was highly correlated with the intensity of ongoing pain.

**Ventral Pons and Amygdala**
MD changes in the ventral pons and amygdala contrast with those found in the thalamus. SCI subjects with neuropathic
pain demonstrated significant decreases in MD values compared with control and SCI no pain subjects (Figs 2 and 3).

Several studies implicate the amygdala in pain processing, including a role in both pain inhibition and facilitation and in regulating the affective component of pain (Manning and Mayer 1995; Tershner and Helmstetter 2000). The amygdala may regulate pain intensity and affect via its outputs to the brain stem or to the medial PFC, OFC, and mediodorsal thalamus (Bushbaum and Fields 1984; Price 2003). A recent rodent investigation has revealed that persistent neuropathic pain is associated with signs of significantly altered affective control and an associated increase in amygdala volume (Goncalves et al. 2008). Surprisingly, the authors found that the amygdala hypertrophy associated with persistent pain did not result from alterations in the dendritic arborization of amygdala neurons, but instead the authors suggested that it was associated with increased cellular proliferation. Although this observation needs further confirmation, such a change would be consistent with the decrease in MD in the amygdala of neuropathic SCI pain subjects reported here.

**PPC, Anterior Insula, DLPFC, and Premotor Cortex**

A number of other brain regions demonstrated a significant difference between pain and no pain groups. However, the pattern of change was different to those described above. In the PPC, anterior insula, DLPFC, and premotor cortex, subjects without neuropathic pain demonstrated MD values significantly less than those in the pain group with a significant correlation between the extent of change and pain intensity (Figs 2 and 3). Changes in several of these brain regions have been demonstrated in morphological studies using VBM (Apkarian et al. 2004; Buckalew et al. 2008; Kim et al. 2008).

Although commonly considered part of the associative cortex rather than the classical pain pathway, the PPC has been implicated in pain processing (Tracey and Mantyh 2007). Recently, Amario et al. (2002) reported that central pain can result from expansive parietal lobe tumors that encompass the PPC. PPC neurons are activated by both noxious and non-noxious stimuli (Dong et al. 1994), and it is thought that the PPC receives this sensory information directly from areas such as the primary and secondary somatosensory cortices. It has been suggested that the integration of noxious and nonnoxious information in the PPC provides an indication of the overall threat of the noxious stimulus (Price 2002). Human neuroimaging studies indicate that the PPC is active when an individual is required to attend to a specified stimulus (Corbetta et al. 1993, 1995; Gitelman et al. 1996), and electrophysiological investigations in monkeys have revealed that the activity of PPC neurons is often correlated with attention to behaviorally relevant stimuli (Robinson et al. 1978; Bushnell et al. 1981; Colly et al. 1996). It has been proposed that the PPC relays information to other associative cortices such as the anterior cingulate and insula where a second-order appraisal of the stimulus is processed (Price 2002).

Our data suggest that the role of the PPC in pain processing may be lateralized as we found only right PPC changes. Lateralized functioning of the parietal cortex has been well described. For example, it has been shown that strokes involving the right PPC result in hemispatial neglect (Mort et al. 2003), and Posner and Petersen (1990) suggested, in their seminal review, that the right PPC is involved in maintaining an alert state. During a noxious event, an adequate appraisal of the degree of threat posed by the stimulus and a heightened state of alertness are critical for an animal to make relevant and potentially life-preserving behavioral changes. These behaviors may be mediated by the right PPC.

Table 2

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<th>Montreal Neurological Institute (MNI) coordinates of significant differences in MD between SCI pain and SCI no pain groups</th>
<th>t</th>
<th>Cluster size</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain &gt; no pain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial orbitofrontal cortex</td>
<td>–2</td>
<td>14</td>
</tr>
<tr>
<td>Right DLPFC</td>
<td>44</td>
<td>33</td>
</tr>
<tr>
<td>NA</td>
<td>26</td>
<td>43</td>
</tr>
<tr>
<td>Left anterior insula</td>
<td>29</td>
<td>18</td>
</tr>
<tr>
<td>Right PFC</td>
<td>54</td>
<td>27</td>
</tr>
<tr>
<td>Premotor cortex</td>
<td>42</td>
<td>–26</td>
</tr>
<tr>
<td>Right</td>
<td>42</td>
<td>–5</td>
</tr>
<tr>
<td><strong>No pain &gt; pain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventral pons/midbrain</td>
<td>2</td>
<td>–17</td>
</tr>
<tr>
<td>Left amygdala</td>
<td>–27</td>
<td>–5</td>
</tr>
<tr>
<td>Right thalamus</td>
<td>14</td>
<td>–21</td>
</tr>
</tbody>
</table>

Figure 4. Graphs of individual subjects’ MD for each significant cluster. Note that for each cluster except for the VP thalamus and amygdala, the individual SCI subjects’ MD values lay within the range of MD values for control subjects. In contrast, in the amygdala, the MD values of more than 80% of the SCI pain subjects were less than the lowest control MD value. Similarly, for the VP thalamus over 90% of the SCI pain subjects were also lower than the lowest control MD value. The horizontal dashed lines indicate the highest and lowest MD value for control subjects.
Given its proposed integrative role, we decided to track the output pathways originating in the area of anatomical difference within the PPC. This analysis revealed direct connections between the PPC and the other regions displaying anatomical changes including the DLPFC, OFC, and VP thalamus (Figs 4 and 5). The PPC has a central role in determining the threat value of noxious inputs. Through its connection to other higher order processing cortical regions, it is possible that the PPC plays a role in some of the psychological aspects of pain processing such as catastrophizing. In addition, its direct connection to the thalamus raises the possibility that the PPC could modulate thalamic output and influence the overall activity of pain-related brain regions.

In contrast to the PPC, the insular cortex is consistently activated by acute noxious stimuli (Craig 2002; Henderson et al. 2007). It has been suggested that the anterior insula encodes the unpleasantness of noxious stimuli (Dunckley et al. 2005; Schreckenberger et al. 2005) and may also code the unpleasantness of nonnoxious stimuli such as olfactory and visual disgust (Heining et al. 2003; Wright et al. 2004). A recent case study has revealed that the persistent pain condition fibromyalgia is associated with metabolic hypoactivity within the left insular cortex (Wood et al. 2008), further emphasizing a role for the insula in pain processing and the possibility of structural and functional abnormalities associated with persistent pain. Anatomical changes in the DLPFC have also been linked with persistent pain by a previously demonstrated association between reduced gray matter volume and the presence of pain (Apkarian et al. 2004).

**Nucleus Accumbens**

The pattern of water movement in the NA is different again. Although there was a significant decrease in MD in subjects without pain, there was no significant difference between subjects with pain compared with control subjects. Immunohistochemical, tract tracing, and functional studies have revealed that the NA is comprised of several structurally distinct regions of which the most prominent are the core and shell (for review, see Heimer et al. 1997). Although we do not have the spatial resolution to determine precisely where in the NA our MD changes are located, the medial positioning of the cluster suggests that it is located within the medial part of the accumbens shell. Accumbens shell inputs include the medial PFC, amygdala, and VTA (i.e., regions that also display significant anatomical changes in the SCI pain subjects) with outputs to the ventral pallidum, lateral hypothalamus, and VTA (see Carelli 2002 for review). Recently, Ikemoto (2007) proposed 2 distinct shell pathways: the mesoventromedial and the mesoventrolateral pathways, which differentially mediate the behavioral selection associated with reward and aversion. The mesoventromedial system involves the medial accumbens shell and is thought to mediate behavioral implementation of reward aversion, for...
example, to procure biologically salient stimuli or to avoid danger. Activation of the mesoventromedial striatal system has been associated with increased positive affect, whereas inhibition of this system has been associated with negative reinforcement and avoidance learning.

Activity in the NA has also been directly implicated in pain intensity modulation (Becerra et al. 2001). For example, Saadé et al. (1997) reported that in rats lesions of the accumbens increased pain sensitivity. Furthermore, dopamine transmission has been reported to be altered in persistent pain conditions such as burning mouth syndrome and fibromyalgia (Jaaskelainen et al. 2001; Wood et al. 2007). The reason for the MD values found in the accumbens in this study remains unclear. It may be that in subjects with neuropathic pain, increased water movement due to neuronal loss, or atrophy is counterbalanced by axonal sprouting following injury. Alternatively, subjects with neuropathic pain may not experience any structural change, but factors such as sprouting may occur in subjects without pain, possibly serving as a protective effect against pain. Either of these situations could be consistent with the role of the NA in reward circuitry.

Do Changes in Structure Predispose or Precipitate Pain?

Whereas it is possible that differences in the anatomy of areas of the parietal cortex and PFC may result in changes in activity

Figure 6. Overlay showing individual output pathways of the right PPC to other clusters displaying significantly different MD values in SCI pain compared with SCI no pain subjects. The hot color scale represents the frequency of subjects displaying an output fiber originating in the PPC. The green shading represents the clusters of significant MD differences derived from the whole-brain analysis. For each fiber pathway, the FA (mean ± SEM) is plotted as a bar graph in the left side of each panel.
Pain is a complex perceptual experience that consists of ongoing pain following injury, it is also possible that the anatomy of areas such as the PPC or NA prior to injury predispose an individual to develop persistent pain and/or exacerbate a persistent pain state.

Interestingly, except for the amygdala and VP thalamus, we found that in all brain regions that displayed significant mean MD differences, the individual MD values lay well within the range of MD values of healthy control subjects (Fig. 4). This included both SCI subjects with and without pain. However, in the VP thalamus, over 90% and in the amygdala over 80% of subjects with neuropathic SCI pain had MD values below the lowest value recorded from all 44 control subjects. Although not conclusive, these results suggest that thalamic and amygdala anatomical differences reflect changes as a consequence of the injury itself. In contrast, anatomical differences in regions such as the PPC, DLPFC, and NA may not reflect an injury-induced change but instead reflect preinjury values that predispose an individual to the development of persistent pain following a traumatic event such as a SCI.

Furthermore, our data suggest that the properties of the projection pathways between the PPC and various limbic structures are similar in control, SCI no pain, and SCI pain subjects. Although we have not assessed the properties of other fiber tracts such as those connecting the VP thalamus and somatosensory cortices, these results suggest that changes within the cortical regions rather than the output projection fibers are responsible for the differences noted. It may be the case that chronic pain following SCI results from discrete, localized changes such as the loss of γ-aminobutyric acid-mediated interneurons instead of changes within pathways such as the spinothalamic tracts. Future investigations exploring the biochemistry of areas such as the VP thalamus may shed further light on this possibility.

Methodological Considerations

It is worth noting several issues that may have influenced the results. First, the mean age of the control subjects was significantly lower than those with SCI. Nevertheless, there was no significant age difference between the SCI pain and SCI no pain groups \( (P = 0.06, \text{2-tailed test}) \), and furthermore, in all analysis, the effects of age were removed by including it as a nuisance variable. Therefore, the demonstrated differences between these groups are likely to be due to the presence of pain. Second, even though all subjects were assessed as having clinically complete injuries, electrophysiological testing was not performed, and it may be that some subjects have some residual sparing of spinal pathways. Finally, it is possible that MD may have been influenced by confounds such as partial volume effects, gray/white matter edge misregistration, and head motion artifacts. Although this is possible, we suggest that it is highly unlikely that the regional significant differences presented in this investigation were significantly influenced by these factors as all subjects’ images were analyzed in an identical manner. For the MD differences to result from these confounds, one would have to assume that there was a consistent difference in the motion correction and normalization procedures between the SCI pain and SCI no pain groups.

Conclusions

Pain is a complex perceptual experience that consists of multiple aspects including distinct sensory and affective dimensions that can be influenced by a number of psychological variables. Part of the affective dimension of pain is the moment-to-moment unpleasantness of the stimulus that is linked closely to perceived pain intensity. Persistent pain is also characterized by a secondary affective component relating to the long-term implications of the pain, that is, suffering (Price 2002). It is becoming increasingly clear that although the various aspects of the pain experience are closely related, they are most likely coded by different neuroanatomical pathways. Although these different pathways can be independently modulated (Rainville et al. 1997), the current study provides further support for the strong interconnections that link somatosensory cortices to limbic structures such as medial OFC and DLPFC through the PPC (Friedman et al. 1986) and their involvement in the experience of pain.

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