Brief Report

Differences in resting cerebellar and prefrontal cortical blood flow in spinal cord injury-related neuropathic pain: A brief report

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Context: Little is understood about differences in resting neural activity among those with spinal cord injury (SCI)-related neuropathic pain. The purpose of this pilot study was to determine resting cerebral blood flow differences in persons with SCI-related neuropathic pain compared to healthy, pain-free able-bodied controls. **Methods:** Five persons with paraplegia and ten able-bodied participants were included in this study. Resting blood flow, as measured by a continuous arterial spin labeling (ASL) method of fMRI, was analyzed via statistical parametric mapping.

Results: Persons with SCI-related neuropathic pain had significantly lower resting blood flow in the cerebellum (Crus I/II), rostral ventromedial medulla and left insular cortex. In contrast, greater resting blood flow occurred in the medial orbitofrontal cortex among those with SCI-related neuropathic pain compared to controls.

Conclusion: Differences in resting blood flow were observed among those with SCI-related pain, particularly in regions that may be involved in affective-motivational and cognitive-evaluative aspects of pain. Larger ASL studies in addition to functional connectivity studies using fMRI are needed to clarify unique neural patterns in this complex and often intractable form of pain.

Keywords: Spinal cord injuries, Neuropathic pain, Resting blood flow, Arterial spin labeling

Introduction

Individuals with spinal cord injury (SCI) experience multiple secondary complications, with chronic pain as one of the most common and debilitating. Over two-third of patients with SCI report pain,¹ and often more than one form of pain.² Neuropathic pain following SCI (SCI-NP) is one type experienced around or below the level of injury. It is often intractable, showing only modest improvement with available treatments.³ This is unfortunate, as SCI-related pain results in lower quality of life,⁴⁻⁶ reduced mood and psychosocial functioning,^{7,8} interference with sexuality⁹ and

sleep.^{10,11} Finding effective pain management strategies for SCI-NP has been precluded by limited understanding of supraspinal mechanisms that underlie its onset and maintenance.

Pain is no longer understood as a simple function of a noxious stimulus; rather, central processing of pain involves an interconnected matrix of brain regions that impact the pain experience.¹² There are predictable cortical activations in the perception of pain generally, including activation of the thalamus, prefrontal, anterior cingulate, insular and somatosensory cortices.¹³ Similar patterns emerge in persons with chronic pain, with notable increased activation in the prefrontal cortex (PFC).¹³ The PFC has anatomical subregions involved in a number of cognitive functions, though increased activity in the PFC in chronic pain may reflect increased cognitive-affective aspects of the pain experience.¹⁴

Clinical implications from broader chronic pain populations are often generalized to those with SCI-

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NP, which is arguably tenuous and may contribute to reliance on suboptimal approaches to the management of SCI-NP. There is potentially a different pathophysiology to SCI-NP in that the pain may arise from a disruption in the dynamic between cortical activity and afferent, sensory processes.¹⁵ The somatosensory cortex of those with SCI-NP is functionally reorganized relative to a typical homunculus pattern of activity.¹⁶ When structural integrity of various anatomical regions have been investigated, those with SCI-NP show differences in the posterior parietal cortices, the nucleus accumbens and PFC.¹⁷

There is increased interest in investigating patterns of activity when the brain is not engaged in specific tasks. SCI impairs the default mode network,¹⁸ an activity pattern between interacting brain regions outside of engaging in specific tasks. Specifically, cortical networks associated with processing sensory input as well as cognitive and executive functions are altered in SCI,¹⁸ and such areas may also be involved in processing sensory and cognitive components of pain.^{13,14} However, differences related to pain in SCI have not been considered. Therefore, using five cases with SCI-NP, we sought to explore differences in resting activity compared to healthy, pain-free individuals.

Methods

Subjects: Five persons with SCI who were non-ambulatory, manual wheelchair users were recruited from an outpatient rehabilitation center (Table 1). We recruited individuals with paraplegia who were able to independently transfer to and from the scanner. Patients were excluded if they had tetraplegia, were unable to independently transfer, or had a current pressure wound precluding them from being supine in the scanner for an extended period of time. Four participants were recruited from our own center, and thus we could confirm their International Standards for Classification of Spinal Cord Injury Classification of

motor score via clinic charts (all four were classified as having a grade of A). The remaining participant, with L1 level SCI, was recruited from a neighboring model system of care and therefore we relied on self-report for his injury grade. Without a full neurological examination, we simply designated his injury as incomplete, given self-reported sparing of some motor and sensory function (though this individual was still reliant on a manual wheelchair for ambulation). The presence of neuropathic pain was confirmed via the Bryce Ragnarsson Pain Classification Scheme¹⁹ by agreement of two independent raters. Two out of ten items from the Neuropathic Pain Scale (NPS)²⁰ were completed the day of scanning, which assessed SCI-NP intensity and unpleasantness on a scale of 0–10. We chose these two items to measure overall intensity and unpleasantness of neuropathic pain rather than its quality, which is assessed by the other NPS items. Mean intensity was 5.0 ($SD = 2.4$) and mean unpleasantness was 6.6 ($SD = 2.1$). Data from ten able-bodied, pain-free individuals recruited for another study were used for comparison. Controls included seven men and three women; nine were Caucasian and one was African American. Control participants were excluded if, upon screening, they endorsed a history of or current experience of chronic pain conditions. The able-bodied control participants were between 23 and 43 years old ($M = 28.5$ years, $SD = 6.4$). Informed consent was obtained from all participants and the protocol was approved by the institution's IRB.

Image parameters and processing: Whole brain images were acquired using a Philips Achieva 3 Tesla MRI system. A continuous arterial spin labeling (ASL) method previously reported²¹ was used to measure resting cerebral blood flow (CBF). ASL is an MRI method that quantifies absolute regional CBF as opposed to indirect and non-quantitative change indicated by fMRI BOLD. A T1-weighted 3D MPRAGE sequence with $TR/TI/TE = 1620/950/3$ msec, flip angle = 30° , matrix = $192 \times 256 \times 160$, and voxel size = $0.98 \times 0.98 \times 1$ mm³ was used for structural images. The following parameters for ASL imaging were used: 1600 Hanning window shaped pulses for total labeling time = 2.4 s, post-labeling delay = 1.4 s, FOV = 230 mm, matrix = 128×128 , bandwidth = 3 kHz/pixel, $TR/TE = 5000/56$ ms, 13 slices with thickness of 7 mm plus 1.25 mm gap, mean Gz of 0.6 mT/m, with labeling placed at 80 mm below the center of imaging region. Thirty dynamics of ASL (label/unlabeled) were acquired over 330 s. Individuals were instructed to lay still with eyes open during the acquisition. Images underwent motion correction,

Table 1 Age and injury characteristics of participants with SCI-NP.

Age	Sex/ race	Injury duration (in years)	Injury cause	Level of injury	Impairment level
41	F/AA	22.6	GSW	T10	Complete
56	M/C	22.8	Fall	L1	Incomplete
32	M/C	7.1	MVC	T3	Complete
30	M/C	0.7	MVC	T10	Complete
43	M/C	8.8	Crush injury	T1	Complete

Notes: F = female; M = male; AA = African American, C = Caucasian, GSW = gunshot wound; MVC = motor vehicle crash.

residual motion effect removing, denoising, registration, CBF calculation, CBF map spatial normalization and smoothing. A threshold of 2 mm was used for motion, above which control and label scans were discarded so as to keep the same number used to average the signal. T1-weighted images were used to create subject-specific brain masks to remove all signals outside of the brain. An 8 mm kernel size was used for smoothing.

Quantitative CBF maps were calculated from the control-tag perfusion signal difference using a modified two-compartment ASL perfusion model:²²

$$f = \Delta M \cdot \lambda \cdot R_{1\alpha} \cdot \exp(\omega \cdot R_{1\alpha}) [1 - \exp(-\tau \cdot R_{1\alpha})]^{-1} \text{Eq. 1} \cdot 2 \cdot M_0 \alpha$$

where f is CBF, ΔM is the difference signal between the control and label acquisitions, $R_{1\alpha}$ is the longitudinal relaxation rate of blood, τ is the labeling time, ω is the post-labeling delay time, α is the labeling efficiency, λ is the blood/ tissue water partition coefficient and M_0 is approximated by the control image intensity. The processing parameters used in the study were $R_{1\alpha} = 1/1664$ s, $\tau = 1.5$ s, $\omega = 1.5$ s. These signal averages during control and tag are used to improve the signal to noise ratio of the computed rCBF map. The CBF maps were transformed to the standard Montreal Neurology Institute (MNI) template for comparison across subjects. The group analysis was performed on transformed rCBF maps using SPM8²³ second level analysis to determine the regions of brain that show significant differences. The regions were not selected *a priori*, but were highlighted as the centers of activity using the whole brain as the input for our model. A statistical threshold of $P \leq .05$ was used.

Results

Contrasting resting activity (control minus SCI-NP) revealed differences. Among those with SCI-NP, there was reduced resting activity in the cerebellum, with statistical parametric mapping (SPM) analysis indicating most significant reductions in bilateral Crus I/II regions (left > right), and to a lesser extent, rostral ventromedial medulla and left insular cortex (Figure 1). When the contrast was opposed (SCI-NP minus controls), SPM analysis revealed significant increased activity within the medial orbitofrontal cortex (mOFC) among those with SCI-NP (Figure 2).

Discussion

The resting activity among individuals with SCI-NP revealed differences relative to healthy, pain-free

individuals. One of the more striking differences found was lower resting cerebellar activity in those with SCI-NP, most notably within the Crus I/II regions. The cerebellum is involved with guiding/adjusting execution of movement, but is it becoming increasingly clear that the cerebellum also plays a role in higher order cognitive functions.²⁴ Motor and cognitive functions of the cerebellum correlate with distinct regions, with Crus I/II cerebellar regions forming a separate non-motor afferent/efferent circuit with the PFC.²⁵ Crus I/II of the cerebellum appears to be exclusively activated in higher order cognitive functions, regardless of whether those cognitive processes involve executing a motor response.²⁶ Using fMRI, Salmi and others²⁷ showed that activity in the Crus I/II regions of the cerebellum was associated with cognitive performance, with the lower Crus I/II activity associated with increased speed of processing as cognitive demands increase. At least in experimental pain, the actual experience of pain and expectation of pain appear to differentially activate the cerebellum, with the former producing a more somatotopical pattern of activation and the latter resulting in an area of activation that included Crus I.²⁸

The unique association between cerebellar Crus I/II and the PFC complements distinct dimensions of pain, particularly the affective-motivational and cognitive-evaluative aspects of the pain experience.¹² The PFC is heavily involved in decision-making and planning. In situations where there are conflicting motivational states, such as the co-occurrence of an opportunity to engage in a rewarding activity simultaneous with the experience of pain, activation of the mOFC increases.²⁹ The orbitofrontal cortex is involved in value-guided decision-making and reducing attention to aspects of the non-selected behavior³⁰ and therefore may help coordinate inhibition of pain behaviors (e.g. activity avoidance) in order to engage in rewarding activity. While we only evaluated activity at rest, those with SCI-NP similarly showed increased activity in the mOFC. Arguably, most resting state studies, including the present study, are not truly measuring a “resting” state. There are various cognitive processes, motivations or other “states” that may be captured. The participants with SCI-NP were in pain yet physically participated in the study (traveling to, transferring and lying in the scanner) for a perceived rewarding outcome (e.g. helping further scientific understanding, receiving financial compensation). The increased activity of the mOFC may be the result of task selecting and active inhibition of the cognitive-evaluative aspects of pain that the persons with SCI-NP experienced in order to proceed

Figure 1 Contrast of activation between healthy control participants and persons with SCI-NP in cerebellar Crus I/II and cortical insular regions. Higher resting CASL among healthy, pain-free participants is shown in yellow; higher resting CASL among those with SCI-NP is shown in red.

with a goal-driven activity. On the contrary, prior studies have shown that those with chronic low back pain (without SCI) have reduced blood flow in the PFC and increased blood flow in the cerebellum.³¹ This is opposite of what we found and may reflect differences in the types of pain (e.g. musculoskeletal vs. neuropathic) or conditions to which the pain is associated (low back pain vs. spinal cord injury).

Results of this study serve as pilot data from which to guide future imaging studies of persons with SCI-NP, and inherent in pilot work are a number of limitations. Nuanced correlations between resting cortical activity and self-reported pain levels were not considered here. Likewise, the small size of this pilot did not allow us to examine differences attributable to SCI itself versus the secondary complication of pain. Including individuals with SCI but without pain may isolate activation differences attributable to pain above and beyond supraspinal changes that SCI alone may induce. Differences have been observed between individuals with SCI with and without SCI-NP in terms of thalamic activity and

neurochemistry via fMRI and magnetic resonance spectroscopy.³² However, other brain regions, such as the cerebellum and prefrontal cortices, were not examined.

Further, examining potential differences in activation patterns between those with tetraplegia versus those with paraplegia would be important, as the former appears to experience a greater prevalence of neuropathic pain³³ and in particular, below-level SCI-NP.³⁴ This suggests that the subtype of SCI-NP is of equal or possibly greater importance when assessing differences. For example, neuronal hyperexcitability at the supraspinal level may potentially underlie centrally mediated (e.g. below-level) SCI-NP.³⁵ Differences in subtype of SCI-NP may also relate to duration of injury. At-level SCI-NP tends to occur in the earlier phases post-SCI, while individuals can experience the onset of below-level SCI-NP years following their injury.³⁴ Lastly, measures that have been developed specific to SCI-related pain, such as the Spinal Cord Injury Pain Instrument³⁶ would likely offer improved construct validity of neuropathic pain in this population. Future neuroimaging

Figure 2 Contrast of activation between participants with SCI-NP and healthy participants in medial prefrontal/orbitofrontal regions and rostral ventromedial medulla. Higher resting CASL among healthy, pain-free participants is shown in yellow; higher resting CASL among those with SCI-NP is shown in red.

studies that include larger samples will allow for stratification on the above factors, therefore possibly a clearer picture with respect to functional neurological correlates implicated in SCI-NP.

Conclusions

Results demonstrate decreased resting activity in cerebellar regions associated with higher order cognitive functions and increased activity in the mOFC among those with SCI-NP. This may reflect unique activity patterns pertaining to affective-motivational and cognitive-evaluative states of pain among those with SCI-NP. Larger ASL studies are needed to determine if findings generalize to others with SCI-NP. Functional connectivity studies may also reveal activation patterns among these regions and differences from acute pain or other forms of chronic pain.

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Conflicts of interest Authors have no conflict of interests to declare.

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