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Altered regional brain T2 relaxation times in individuals with chronic orofacial neuropathic pain

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ABSTRACT

The neural mechanisms underlying the development and maintenance of chronic pain following nerve injury remain unclear. There is growing evidence that chronic neuropathic pain is associated with altered thalamic firing patterns, thalamocortical dysrhythmia and altered infra-slow oscillations in ascending pain pathways. Preclinical and post-mortem human studies have revealed that neuropathic pain is associated with prolonged astrocyte activation in the dorsal horn and we have suggested that this may result in altered gliotransmission, which results in altered resting neural rhythm in the ascending pain pathway. Evidence of astrocyte activation above the level of the dorsal horn in living humans is lacking and direct measurement of astrocyte activation in living humans is not possible, however, there is evidence that regional alterations in T2 relaxation times are indicative of astrogliosis. The aim of this study was to use T2 relaxometry to explore regional brain anatomy of the ascending pain pathway in individuals with chronic orofacial neuropathic pain. We found that in individuals with trigeminal neuropathic pain, decreases in T2 relaxation times occurred in the region of the spinal trigeminal nucleus and primary somatosensory cortex, as well as in higher order processing regions such as the dorsolateral prefrontal, cingulate and hippocampal/parahippocampal cortices. We speculate that these regional changes in T2 relaxation times reflect prolonged astrocyte activation, which results in altered brain rhythm and ultimately the constant perception of pain. Blocking prolonged astrocyte activation may be effective in preventing and even reversing the development of chronic pain following neural injury.

1. Introduction

Chronic neuropathic pain is a complex disease resulting from actual or presumed damage to the somatosensory nervous system. The constant perception of pain that characterizes neuropathic pain is associated with increased thalamic bursting activity (Gerke et al., 2003; Iwata et al., 2011; Lenz et al., 1989), reduced thalamic blood flow (Hsieh et al., 1995; Iadarola et al., 1995; Moisset and Bouhassira, 2007; Youssef et al., 2014) and increased cortical power, often termed thalamocortical dysrhythmia (Di Pietro et al., 2018; Sarnthein et al., 2006; Walton and Llinás, 2010). The increase in cortical power is associated with an altered relationship with thalamic GABAergic content (Di Pietro et al., 2018) and we have proposed that the thalamocortical dysrhythmia that occurs in chronic neuropathic pain results from altered interactions between the ventrocaudal thalamus, thalamic reticular nucleus and the cerebral cortex (Henderson and Di Pietro, 2016).

In addition to cortical resting activity changes, as read with electroencephalography (> 2 Hz) we have previously shown that chronic neuropathic pain is associated with increased infra-slow frequency (< 0.1 Hz) oscillatory activity throughout the ascending pain pathway, including the region of the primary afferent synapse, ventrocaudal thalamus, thalamic reticular nucleus and primary somatosensory cortex (Alshelh et al., 2016). Interestingly, these infra-slow oscillation increases occurred at approximately the same frequency range as reported calcium waves in astrocytes, i.e. 0.03–0.06 Hz (Crunelli et al., 2002). Astrocytes are known to modulate synaptic activity by the release of gliotransmitters and it is well-documented in preclinical animal models that neuropathic pain is associated with prolonged astrocyte activation in the dorsal horn/spinal trigeminal nucleus (Garrison et al., 1991; Okada-Ogawa et al., 2009). Given these data, we have speculated that following nerve injury, prolonged astrocyte activation results in increased infra-slow oscillations in the ascending pain pathway which in turn is associated with thalamocortical dysrhythmia and the constant perception of pain (Henderson and Di Pietro, 2016).

Abbreviations: NP, neuropathic pain; PET, Positron Emission Tomography; PCS, Pain Catastrophizing Scale; BDI, Beck Depression Inventory

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Whilst it is clear from preclinical animal models that neuropathic pain is associated with astrocyte activation in the dorsal horn and brainstem (Hsieh et al., 1995; Okada-Ogawa et al., 2009), robust evidence is lacking in humans. There is, however, evidence from a post-mortem study which revealed prolonged astrocyte activation, but no microglial activation, in the dorsal horn of individuals with neuropathic pain associated with HIV (Shi et al., 2012). Indirect measurements of glial activation using Positron Emission Tomography (PET) have also revealed chronic glial activation in humans with neuropathic pain. Banati and colleagues (Banati et al., 2001) reported increases in binding of [^{11}C](R)-PK11195 (a sensitive in vivo marker of glial cell activation) in the contralateral (to injury) thalamus of patients with phantom limb pain. Similarly, Loggia and colleagues recently used the same technique to show increased glial activation in the thalamus and primary somatosensory cortex, contralateral to pain, of individuals with chronic low back pain (Loggia et al., 2015). Whilst these brain imaging studies are important and suggest chronic glial activation in the thalamus and above, technical limitations mean that they cannot explore changes at the level of the brainstem or, more importantly, the primary afferent synapse.

One non-invasive technique that has been used to measure glial activation is T2 relaxometry (Jackson et al., 1994; Wagner et al., 2012), a magnetic resonance imaging technique that can characterise changes in the brainstem and above. There is immunohistochemical evidence that decreased T2 relaxation times are associated with increased glial activation (Schwarz et al., 1996) and in this investigation we hypothesize that chronic orofacial neuropathic pain is associated with significantly reduced T2 relaxation time in the ascending pain pathway, including the region of the spinal trigeminal nucleus, ventrocaudal (Vc) thalamus, thalamic reticular nucleus and the orofacial region of the primary somatosensory cortex.

2. Methods

2.1. Subjects

Thirty-seven subjects with chronic orofacial neuropathic pain (NP; 28 females, mean age 46.1 ± 2.5 years [± SEM]) and 40 healthy controls without ongoing pain (24 females, mean age 40.6 ± 2.7 [± SEM]) were recruited for this study. All NP subjects were diagnosed using the Liverpool criteria as having post-traumatic painful trigeminal neuropathy (Nurmikko and Eldridge, 2001). Written informed consent was obtained for all procedures and the study was approved by Institutional Human Research Ethics Committees, University of Sydney.

For each NP subject, the intensity of their on-going pain was recorded on a 10 cm horizontal visual analogue scale (VAS) with 0 indicating "*no pain*" and 10 indicating "*worst imaginable pain*", three times a day for the seven days prior to a magnetic resonance imaging (MRI) session (Carlsson, 1983). These pain intensity scores were averaged over the 7-day period to create a mean pain intensity score. On the day of the MRI, all subjects were experiencing pain and were asked to draw the distribution of their ongoing pain. Subjects were also asked to complete a McGill Pain Questionnaire (Melzack, 1975), the Beck Depression Inventory (BDI) (Beck et al., 1961) and the Pain Catastrophizing Questionnaire (PCS) (Sullivan et al., 1995). A subset of the control and NP subjects was used in a previous investigation (Alshelh et al., 2016).

2.2. MRI acquisition

All subjects lay supine on the bed of a 3 Tesla MRI scanner (Philips Achieva) with their head immobilized in a tight-fitting 32-channel SENSE head coil. With each subject relaxed and at rest, a high resolution T1-weighted anatomical image set covering the entire brain was collected (turbo field echo; field of view 250 × 250 mm; matrix size 288 × 288; slice thickness 0.87 mm; repetition time 5600 ms; echo time 2.5 ms; flip angle 8°; raw voxel size 0.87 × 0.87 × 0.87 mm). Following this, T2-weighted image sets covering the entire brain were collected (field of view 250 × 250 mm; matrix size 556 × 556; slice thickness 5 mm; repetition time 3000 ms; echo times 20, 40, 60, 80, 100 ms; raw voxel size 0.4 × 0.4 × 5 mm thick). Multiple echo times were used to create multiple image sets for subsequent calculation of T2-relaxation time maps.

2.3. MRI analysis

Using SPM12 (Friston et al., 1995) and custom software, the following equation was used to calculate T2 relaxation time brain maps: $T_2 = (TE_2 - TE_1)/\ln(SI_1/SI_2)$ where TE_1 and TE_2 are the echo times for proton density and T2-weighted images, and SI_1 and SI_2 represent proton density and T2-weighted image signal intensities, respectively. A ceiling threshold of 500 ms was applied to eliminate cerebrospinal fluid. In each subject, T2 relaxation maps were co-registered to each individual's T1-weighted anatomical image set. The T1-weighted anatomical image was then spatially normalized to a template in Montreal Neurological Institute (MNI) space and the parameters applied to the T2 relaxation time maps. Finally, the T2 brain maps were spatially smoothed using an 8 mm full-width-at-half-maximum Gaussian filter. In those NP subjects with pain restricted to the left side of the face (n = 17), T2-weighted images were reflected across the midline so that T2 differences could be assessed ipsilateral and contralateral to the side of highest ongoing pain.

In addition to a wholebrain T2 relaxation analysis, we performed a brainstem-specific analysis. The T2 relaxation maps were cropped to include only the brainstem and cerebellum, and a mask of these regions was created using the Spatial Unbiased Infratentorial Template (SUIT) toolbox (Diedrichsen, 2006). These brainstem/cerebellum masks were then manually adjusted to accurately encompass the brainstem and cerebellum only. Using this mask, T2 relaxation brainstem images were spatially normalized to the SUIT template in MNI space and spatially smoothed using a 3 mm full-width-at-half-maximum Gaussian filter.

Significant differences in T2 relaxation time between controls and NP subjects were determined using a voxel-by-voxel analysis of the wholebrain and the brainstem only ($p < 0.05$, random effects, false discovery rate corrected for multiple comparisons, minimum cluster 10 voxels, age and gender as nuisance variables). A brain mask that excluded CSF as well as the brainstem was applied to the wholebrain analysis. For both the wholebrain and brainstem only analyses, mean (± SEM) T2 relaxation times of significantly different clusters were extracted and plotted. Significant correlations between T2 relaxation times and pain intensity, BDI and PCS scores were also determined ($p < 0.05$). In addition, to determine if medication use had a significant effect on T2 relaxation times, for each cluster, T2 relaxation times were compared between those NP subjects taking acute analgesic medication alone (n = 5) or those taking prophylactic analgesic medication (n = 11) with those not taking medication (n = 21) ($p < 0.05$, two-tailed, two-sample *t*-tests).

3. Results

3.1. Psychophysics

Individual NP subject characteristics are shown in Table 1, and overall pain distributions and pain descriptors in Fig. 1. In 34 of the NP patients, their on-going pain was unilateral (17 right, 17 left), and the remaining 3 NP subjects reported bilateral pain. In all NP subjects, pain was located in the 2nd and 3rd trigeminal nerve divisions, with 7 subjects also reporting pain in the 1st division. The mean (± SEM) pain intensity over the 7 days prior to the MRI scanning session was 3.8 ± 0.4 out of 10 and the mean duration of pain was 4.1 ± 0.9 years. Using the McGill Pain Questionnaire, NP subjects most frequently described their pain as "throbbing", "tender" and