Trigeminal Nerve Anatomy in Neuropathic and Non-neuropathic Orofacial Pain Patients

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Abstract: Trigeminal neuralgia, painful trigeminal neuropathy, and painful temporomandibular disorders (TMDs) are chronic orofacial pain conditions that are thought to have fundamentally different etiologies. Trigeminal neuralgia and neuropathy are thought to arise from damage to or pressure on the trigeminal nerve, whereas TMD results primarily from peripheral nociceptor activation. This study sought to assess the volume and microstructure of the trigeminal nerve in these 3 conditions. In 9 neuralgia, 18 neuropathy, 20 TMD, and 26 healthy controls, the trigeminal root entry zone was selected on high-resolution T1-weighted magnetic resonance images and the volume (mm^3) calculated. Additionally, using diffusion-tensor images (DTIs), the mean diffusivity and fractional anisotropy values of the trigeminal nerve root were calculated. Trigeminal neuralgia patients displayed a significant (47%) decrease in nerve volume but no change in DTI values. Conversely, trigeminal neuropathy subjects displayed a significant (40%) increase in nerve volume but again no change in DTI values. In contrast, TMD subjects displayed no change in volume or DTI values. The data suggest that the changes occurring within the trigeminal nerve are not uniform in all orofacial pain conditions. These structural and volume changes may have implications in diagnosis and management of different forms of chronic orofacial pain.

Perspective: *This study reveals that neuropathic orofacial pain conditions are associated with changes in trigeminal nerve volume, whereas non-neuropathic orofacial pain is not associated with any change in nerve volume.*

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The orofacial region represents one of the most common sites of pain in the body.[23] In general, chronic orofacial pain arises either from trigeminal and/or central nervous system damage (neuropathic pain) or from nociceptor activation (nociceptive pain).

These different orofacial pain conditions also present differently. For example, trigeminal neuralgia (an example of a neuropathic pain condition) is characterized by sharp, shooting paroxysms of pain that last seconds to minutes, whereas trigeminal neuropathy (neuropathic) is characterized by a lower intensity and a more prolonged or continuous burning pain. Evidence suggests that the most common cause of trigeminal neuralgia is mechanical compression of the trigeminal nerve at its root entry zone, commonly by a blood vessel.[22] In contrast, although a small percentage (~20%) of trigeminal neuropathy patients also display neurovascular compression,[16] it is suggested that the majority of cases result from direct trauma to or inflammation of the trigeminal nerve.[14]

Whereas trigeminal nerve root neurosurgery is a highly effective treatment for patients with trigeminal neuralgia, it is less successful and can even be detrimental

when attempted in patients with trigeminal neuropathy. Because trigeminal nerve resection is often performed in patients with trigeminal neuralgia, a number of studies have investigated the anatomy of the trigeminal nerve in these patients. For the main part, it has been revealed that trigeminal neuralgia is associated with smaller trigeminal nerves and decreased nerve fiber numbers,[5] a situation that is thought to result in short episodes of sharp, shooting pain. In contrast, the anatomy of the trigeminal nerve in patients with trigeminal neuropathy or temporomandibular disorder (TMD) has not been explored. It is possible that changes also occur in the trigeminal nerve in these patients and that targeting the trigeminal nerve may provide a potential treatment option. The aim of this case-controlled study is to use structural magnetic resonance imaging (MRI) to determine the volume and diffusion tensor imaging (DTI) to assess the microstructure of the trigeminal nerve in patients with trigeminal neuralgia, trigeminal neuropathy, and nociceptive TMD and compare these results to healthy pain-free controls. We hypothesized that the trigeminal nerve volumes would be reduced in both neuropathic pain conditions and remain unchanged in non-neuropathic orofacial pain.

Methods

Subjects

Nine patients with painful trigeminal neuralgia (2 males, mean [±SEM] age: 64.9 ± 2.6), 18 patients with painful trigeminal neuropathy (3 males, mean [±SEM] age: 48.0 ± 1.7), 20 patients with painful TMD (4 males, mean [±SEM] age: 45.7 ± 2.9), and 26 healthy controls without facial pain (mean [±SEM] age: 52.3 ± 2.95, 5 males [ages: 55, 56, 60, 78, 87], 21 females [ages: 32, 32, 36, 37, 41, 41, 41, 42, 44, 48, 50, 53, 53, 56, 57, 58, 59, 64, 64, 68, 73]) were recruited at the Faculty of Dentistry, University of Sydney, during a period from August 2006 to November 2012. Individual pain patient demographics are shown in Supplementary Table 1. Trigeminal neuropathy and trigeminal neuralgia patients were diagnosed according to the Liverpool criteria.[22] TMD patients were diagnosed using the research diagnostic criteria for TMD.[6] No chronic pain subject was diagnosed as having more than 1 of these 3 pain conditions. Furthermore, healthy controls were excluded only if they gave self-report of chronic pain (pain lasting for more than 3 months, including migraine and headache), were currently taking any form of analgesic medication, or had any neurologic disorder. Informed written consent was obtained for all procedures, and the study was approved by the Institutional Human Research Ethics Committees.

Pain Measures

To assess the intensity of facial pain, each pain subject indicated, with a vertical pencil stroke on a 10-cm horizontal line, the intensity of their pain (0 cm = "no pain" to 10 cm = "maximum imaginable pain") in the morning, noon, and at night. These 21 individual pain rating values

were averaged to provide an indication of each subject's chronic pain rating ("diary pain"). Each subject also drew a distribution map of their ongoing pain onto a standard drawing of the face and completed a McGill Pain Questionnaire[20] in order to assess the nature of their pain. The McGill questionnaire includes a series of graded adjectives in categories related to the sensory component of pain.

MRI Acquisition

Subjects lay supine on the bed of a 3-T MRI scanner (Achieva; Philips Medical Systems, Amsterdam, The Netherlands) with their head immobilized in a tight-fitting head coil. In each subject, 3 high-resolution 3-dimensional T1-weighted anatomic image sets covering the entire brain were collected (turbo field echo; echo time = 2.5 ms, repetition time = 5,600 ms, flip angle = 8°, voxel size = .8 × .8 × .8 mm). Three acquisitions were acquired to improve signal-to-noise ratios. In addition, using a single-shot multisection spin-echo echo-planar pulse sequence (repetition time = 8,788 ms; flip angle = 90°, matrix size = 112 × 112, field of view = 224 × 224 mm, slice thickness = 2.5 mm, 55 axial slices), 4 high-resolution DTI image sets covering the entire brain were collected. For each slice, diffusion gradients were applied along 32 independent orientations with b = 1,000 s/mm^2 after the acquisition of b = 0 s/mm^2 (b_0) images. Four acquisitions were acquired to improve signal-to-noise ratios.

MRI Analysis

Trigeminal Nerve Volume Analysis. Using SPM8,[9] the 3 T1-weighted images from each subject were coregistered, averaged, and resampled at .3 × .3 × .3 mm. Using the resampled images, the left and right trigeminal nerves within the root entry zone were isolated in all subjects (Fig 1). All resampled images were coded with a numerical identifier and the assessor (S.L.W.) was blind to patient group. The root entry zone encompasses the trigeminal nerve within the pontine cistern, that is, from the point at which the nerve emerges from the pons to the point at which it exits the pontine cistern anteriorly. All 3 orthogonal planes were used in defining the nerve, with the axial plane being the first plane used, followed by coronal and sagittal views. The volume (mm^3) within the isolated nerve was then calculated. In addition, the cross-sectional volume of the nerve in each coronal slice was selected and from this the maximal coronal cross-section value (mm^2) was calculated. Additionally, a second blinded assessor (G.F.) also isolated the nerve in a subsample (n = 9) of control subjects in order to asses interrater reliability; the total nerve volume of the 2 assessors was positively correlated (r = .66, P = .003).

Trigeminal Nerve Diffusion Analysis. Using SPM8 and custom software, the 4 diffusion tensor image sets were realigned and averaged. Using diffusion-weighted images collected from 32 directions and b_0 images, the diffusion tensor was calculated from the averaged images using a linear model. Once the elements of diffusion tensor were calculated, fractional anisotropy (FA) and mean diffusivity (MD) maps were derived. The