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Predicting pain relief: Use of pre-surgical trigeminal nerve diffusion metrics in trigeminal neuralgia

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ABSTRACT

Trigeminal neuralgia (TN) is a chronic neuropathic facial pain disorder that commonly responds to surgery. A proportion of patients, however, do not benefit and suffer ongoing pain. There are currently no imaging tools that permit the prediction of treatment response. To address this paucity, we used diffusion tensor imaging (DTI) to determine whether pre-surgical trigeminal nerve microstructural diffusivities can prognosticate response to TN treatment.

In 31 TN patients and 16 healthy controls, multi-tensor tractography was used to extract DTI-derived metrics—axial (AD), radial (RD), mean diffusivity (MD), and fractional anisotropy (FA)—from the cisternal segment, root entry zone and pontine segment of trigeminal nerves for false discovery rate-corrected Student's *t*-tests. Ipsilateral diffusivities were bootstrap resampled to visualize group-level diffusivity thresholds of long-term response. To obtain an individual-level statistical classifier of surgical response, we conducted discriminant function analysis (DFA) with the type of surgery chosen alongside ipsilateral measurements and ipsilateral/contralateral ratios of AD and RD from all regions of interest as prediction variables.

Abnormal diffusivity in the trigeminal pontine fibers, demonstrated by increased AD, highlighted non-responders (n = 14) compared to controls. Bootstrap resampling revealed three ipsilateral diffusivity thresholds of response—pontine AD, MD, cisternal FA—separating 85% of non-responders from responders. DFA produced an 83.9% (71.0% using leave-one-out-cross-validation) accurate prognosticator of response that successfully identified 12/14 non-responders.

Our study demonstrates that pre-surgical DTI metrics can serve as a highly predictive, individualized tool to prognosticate surgical response. We further highlight abnormal pontine segment diffusivities as key features of treatment non-response and confirm the axiom that central pain does not commonly benefit from peripheral treatments.

1. Introduction

An important contemporary challenge in the surgical treatment of pain is the selection of the optimal surgical procedure that will maximize pain relief. Prediction of response will permit tailoring of treatment and facilitate individualized, patient-centered care. Classical trigeminal neuralgia (TN) is a severe chronic neuropathic facial pain disorder characterized by intermittent unilateral electric-like pain (Eller et al., 2005). TN is one of the most frequently occurring type of facial neuropathic pain (Koopman et al., 2009). While surgical treatment for TN often results in complete resolution of pain, a subgroup of patients, nonetheless, achieve minimal surgical benefit and thus require multiple, repeat interventions. TN is thought to result from neurovascular compression of the trigeminal nerve at its root entry zone (Jannetta, 1967; Love and Coakham, 2001; Nurmikko and Eldridge, 2001)—a site targeted by microvascular decompression (MVD) surgery. Less invasive procedures such as Gamma Knife radiosurgery (GKRS) instead target the cisternal segment of the trigeminal nerve by delivering of a single dose of radiation (Kondziolka et al., 1996). It is thought that TN's successful surgical outcome is partly due to its peripheral

Abbreviations: (AD), axial diffusivity; (DTI), diffusion tensor imaging; (FA), fractional anisotropy; (FSPGR), fast spoiled gradient-echo; (GKRS), Gamma Knife radiosurgery; (MD), mean diffusivity; (MR), magnetic resonance; (MVD), microvascular decompression; (RD), radial diffusivity; (ROI), region of interest; (TN), trigeminal neuralgia; (XST), eXtended Streamline Tractography

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pathophysiology. In contrast, other forms of neuropathic pain tend to not respond as well to treatment. For those patients, neuromodulation strategies such as deep brain stimulation can be relied upon (Boccard et al., 2013; Hodaie and Coello, 2013). While many TN patients achieve pain relief after their first surgical procedure for TN, nearly 20% of patients either do not respond or have very early recurrence of TN pain within a year and thus require additional surgeries for TN (Dhople et al., 2009; Hodaie and Coello, 2013; Oesman et al., 2011). It is currently unclear what distinguishes these two populations apart from each other. Pre-surgical differentiation of these groups, in particular, the prediction of non-response may allow clinicians to optimize surgical treatment of TN patients—minimizing unnecessary procedures.

Diffusion tensor imaging (DTI) is a non-invasive magnetic resonance (MR) imaging technique that allows *in vivo* visualization of white matter tracts (Alexander et al., 2007). Specific diffusion metrics—axial (AD), radial (RD) and mean diffusivities (MD), as well as a composite metric, fractional anisotropy (FA)—can provide scalar measures of white matter microstructural properties. Biologically, AD, RD, MD have been linked with axonal integrity (Brennan et al., 2013; Song et al., 2003), degree of myelination (Brennan et al., 2013; Song et al., 2005, 2003), and underlying neuro-edema (Beaulieu, 2002), respectively. Similarly, FA provides insight into white matter integrity and has been shown to be altered in various human diseases associated with chronic pain such as temporomandibular disorder (Moayedi et al., 2012) and multiple sclerosis (Chen et al., 2015). Current DTI analyses are limited to the periphery due to crossing nerve fibers in the brainstem and demonstrate that patients with TN have lower FA and higher AD, RD, and MD within the TN-affected, ipsilateral trigeminal nerve root entry zone (DeSouza et al., 2014; Herweh et al., 2007; Leal et al., 2011). With eXtended Streamline Tractography (XST) (Qazi et al., 2009)—a multi-tensor deterministic DTI tractography algorithm—our group recently overcame this technical limitation and successfully visualized brainstem trigeminal fibers (Chen et al., 2015). Thus, using XST DTI, here we aim to investigate both peripheral and brainstem portions of the trigeminal nerve and to identify pre-surgical diffusivity patterns that distinguishes long-term responders from non-responders. We hypothesize that there are pre-surgical trigeminal nerve microstructural differences between long-term responders and non-responders–possibly due to a more severe and central TN pathology affecting non-responders.

2. Material and methods

2.1. Research subjects

With University Health Network Research Ethics Board approval, a total of 31 patients with classic, type 1 TN characterized by recurrent episodes of severe, lancinating, electric shock-like pain (Eller et al., 2005) were identified through retrospective chart reviews spanning from 2011 to 2015. Only patients without prior surgical treatment for TN were included in this study. Patients with TN secondary to multiple sclerosis, cranial tumors, or vertebrobasilar dolichoectasia resulting in brainstem compression were excluded from this study. Based on an all-or-none presence of TN pain at least one year after their first surgical treatment for TN (GKRS or MVD), we subdivided these patients into 17 long-term responders and 14 non-responders to neurosurgical therapy of TN (Table 1). At this time point, patients with any TN pain were deemed non-responders while those without pain were responders. 16 healthy control subjects were also recruited. Ipsilateral and contralateral nerves in these controls were based on the laterality of TN in matched patients. That is, controls matched to left TN patients will have ipsilateral nerve on the left, and vice versa. Research ethics approval was obtained for both retrospective chart review and MR imaging—including DTI—of patients with TN. Similarly, recruitment and MR imaging of healthy controls was conducted with institutional research ethics board approval. The images of six TN patients were reported as part of a prior study (DeSouza et al., 2014).

Table 1
Trigeminal neuralgia patient demographics.

ID	Group	Sex	Age	TN side	Affected branches	Surgical treatment	Pain med(s)
P01	Responder	F	70	L	V2/3	GKRS	PGB
P02	Responder	F	65	L	V3	GKRS	GPN
P03	Responder	F	71	L	V2/3	GKRS	None
P04	Responder	M	36	L	V2	MVD	CBZ
P05	Responder	M	44	R	V2/3	MVD	CBZ
P06	Responder	M	53	R	V1	MVD	CBZ
P07	Responder	F	79	R	V3	GKRS	CBZ
P08	Responder	F	65	R	V2	GKRS	CBZ, GPN
P09	Responder	M	59	R	V1/2	GKRS	CBZ
P10	Responder	F	76	R	V2/3	GKRS	CBZ
P11	Responder	F	77	R	V2/3	GKRS	GPN
P12	Responder	F	56	L	V1/2	MVD	GPN
P13	Responder	F	75	R	V2/3	GKRS	GPN
P14	Responder	F	59	R	V1/2/3	GKRS	PGB, CBZ
P15	Responder	F	47	R	V1/2/3	GKRS	GBP, CBZ
P16	Responder	M	38	R	V2	GKRS	CBZ, PGB
P17	Responder	F	52	R	V1	MVD	CBZ
P18	Non-responder	F	54	L	V1/2/3	MVD	CBZ
P19	Non-responder	F	43	L	V1/2/3	MVD	GBP
P20	Non-responder	F	78	R	V2/3	GKRS	OCZ
P21	Non-responder	F	50	L	V2	GKRS	CBZ
P22	Non-responder	F	63	L	V1/2	MVD	CBZ
P23	Non-responder	F	38	R	V1/2	GKRS	GPN
P24	Non-responder	M	66	R	V2/3	MVD	CBZ, PGB
P25	Non-responder	F	47	R	V1/2/3	GKRS	CBZ, PGB
P26	Non-responder	M	64	R	V3	GKRS	None
P27	Non-responder	F	46	R	V3	GKRS	PGB
P28	Non-responder	F	70	R	V2	GKRS	CBZ
P29	Non-responder	M	25	R	V3	MVD	CBZ
P30	Non-responder	M	62	R	V1/2/3	GKRS	PGB
P31	Non-responder	F	73	R	V2/3	GKRS	GPN

Abbreviations: PGB = pregabalin, GPN = gabapentin, CBZ = carbamazepine, OCZ = oxcarbazepine.

2.2. Magnetic resonance image acquisition

For all subjects, pre-surgical high resolution, T1 fast spoiled gradient-echo (FSPGR) anatomical and diffusion-weighted whole-head MR images were acquired on a 3 Tesla GE Signa HDx scanner with an 8 channel head coil. The FSPGR MR image acquisition parameters were: voxel size = 0.94 mm × 0.94 mm × 1 mm, 256 × 256 matrix, *TE* = 5.1 ms, *TR* = 12.0 ms, flip angle = 20°, field of view = 24 cm (controls) and 22 cm (patients). The diffusion-weighted MR image acquisition parameters were: 60 directions, 1 B_0, b = 1000 s/mm^2, spin echo EPI sequence, 1 excitation, ASSET, voxel size = 0.94 mm × 0.94 mm × 3 mm, 128 × 128 matrix, *TE* = 86.4 ms, *TR* = 17 s (controls) and 12 s (patients), flip angle = 90°, field of view = 24 cm.

2.3. Magnetic resonance image processing

Eddy current and motion artifacts within diffusion-weighted MR images were corrected with affine transformations of each subject's gradient images to B_0 image in FSL v 5.0 (Smith et al., 2004). In order to estimate subject-specific diffusion tensor images and scalar diffusion metric images (i.e. FA, AD, RD, and MD), diffusion-weighted MR images were further processed in 3D Slicer v 4.3.1 (Fedorov et al., 2012). Trigeminal nerves for each subject were then virtually reconstructed bilaterally from diffusion-weighted MR images using XST (Westin planar cut-off = 0.2, tensor fraction cut-off = 0.2, minimum