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# Gray matter volume reduction reflects chronic pain in trigeminal neuralgia

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ABSTRACT

Trigeminal neuralgia (TN) is supposedly caused by an ectatic blood vessel affecting the trigeminal nerve at the root entry zone of the brain stem. Recent evidence suggests an additional central component within trigeminal pain-processing in the pathophysiology of TN. Therefore, we aimed to identify specific brain regions possibly associated with the development or maintenance of TN using magnetic resonance imaging (MRI) voxel-based morphometry (VBM).

Sixty patients with classical TN were compared to 49 healthy controls. Eighteen patients had TN with concomitant constant facial pain, a condition previously described as a predictor of worse treatment outcome.

We found gray matter (GM) volume reduction in TN patients compared to healthy controls in the primary somatosensory and orbitofrontal cortices, as well as the in the secondary somatosensory cortex, thalamus, insula, anterior cingulate cortex (ACC), cerebellum, and dorsolateral prefrontal cortex. GM volume decrease within the ACC, parahippocampus, and temporal lobe correlated with increasing disease duration in TN. There were no differences comparing patients with and without concomitant constant facial pain. No GM increase was found comparing patient subgroups with each other and with healthy controls.

The observed changes probably reflect the impact of multiple, daily attacks of trigeminal pain in these patients similar to what was previously described in other chronic pain conditions and may be interpreted as adaptation mechanism to chronic pain in regard to neuronal plasticity. The ACC, parahippocampus and temporal lobe volume reduction in parallel with disease duration may point to a pivotal role of these structures in chronic pain.



## Introduction

According to current opinion classical trigeminal neuralgia (TN) is caused by a proximal compression of the trigeminal nerve root close to the brainstem (root entry zone) by a tortuous or ectatic blood vessel (artery or vein) leading to mechanical compression of nerve fibers and secondary demyelination, probably mediated by microvascular ischemic damages (Marinkovic et al., 2007). While Jannetta (1967) initially described 88% of his investigated patients to have a nerve vessel conflict (usually the superior cerebellar artery) (Jannetta, 1967), more recent investigations demonstrated that not all patients have a nerve vessel conflict and that between 25 to 49% of people without any clinical signs of TN show a nerve vessel contact on magnetic-resonance imaging (Adamczyk et al., 2007; Kakizawa et al., 2008). However, the quick pain relief following microvascular decompression surgery in almost 90% of patients is a strong indicator for the relevance of this mechanism, but lacks explanation why certain patients (i.e., 30%) experience recurrence of their complaints in the long run (Gronseth et al., 2008; Zakrzewska and Akram, 2011). It was suggested that hyperexcitability of the compressed nerve is necessary but alone insufficient to cause the disease. In turn a nerve-vessel conflict may represent a risk factor for the development of TN but alone does not elicit the disease (Hamlyn and King, 1992). Abnormal expression of voltage-gated sodium channels was detected in patients with TN and a channelopathy was discussed as its pathophysiological correlate (Siqueira et al., 2009). Nav1.7, Nav1.3, and Nav1.8 were affected and are responsible for rapid activation and inactivation as well as maintenance of the action potential. They are co-expressed in nociceptive neurons of the dorsal root ganglions (Siqueira et al., 2009). Possible involvement of central factors comes more and more into focus of current research, but with indistinct role for the pathophysiology of TN. A recent voxel-based morphometry (VBM) study showed gray matter (GM) changes in the thalamus, putamen, anterior and posterior insula, primary somatosensory cortex in a mixed patient group with TN (N = 8) and trigeminal neuropathy (N = 13) (Gustin et al., 2011). Central facilitation and resulting central

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hyperexcitability of the trigeminal system initiated or sustained by peripheral mechanisms (e.g., nerve-vessel conflict, channelopathy) were discussed (Borsook et al., 2007; Obermann et al., 2007). Whether central mechanisms are part of the underlying cause of TN or merely a consequence of the disease remains in discussion. Recent investigations focused on TN with persistent concomitant dull background pain between the typical paroxysmal neuralgic attacks as strong indicator of the possible role of central mechanisms in TN (Obermann et al., 2007). This condition must not be confused with trigeminal neuropathy that describes similar pain characteristics but is due to a lesion or trauma to the nerve often associated with sensory neurological deficit (Nurmikko and Eldridge, 2001). Central allodynic mechanisms that may engage the nociceptive neurons at the trigeminal nucleus, thalamic and cortical levels were suspected to be the correlate of this persistent pain (Borsook et al., 2007; Obermann et al., 2007). The clinical relevance was highlighted in different studies clearly demonstrating that concomitant background pain is associated with poor medical and surgical outcome (Aggarwal et al., 2010; Obermann et al., 2008; Sandell and Eide, 2008; Szapiro et al., 1985).

Our objective was (i) to detect regional GM volume changes in patients with TN compared to healthy controls in order to identify specific brain areas that may be associated with the development and persistence of this debilitating facial pain condition, and (ii) to detect differences between TN patients with and without concomitant persistent facial pain as morphological correlate for the central component in the pathophysiology of TN as suspected previously.

## Methods

### *Subjects*

Sixty patients (36 women) with classical TN were recruited prospectively from a tertiary headache center (West German Headache Center) between February 2007 and March 2010. The diagnosis of TN was reconfirmed in a face-to-face interview by headache experienced neurologists (MO, DM, MY, ZK) according to the International Classification of Headache Disorders (ICDH-II) (Benoliel et al., 2008; International Headache Society, 2004). All patients had active TN painful attacks at time of study inclusion. Additional neurological examination was unremarkable in all patients. No patient had prior micro-vascular decompression (MVD) surgery or other invasive treatments for TN (i.e., gasserian ganglion procedures). Patients were compared to 49 healthy controls of the same age- and gender (28 women). Exclusion criteria were symptomatic TN (e.g., due to MS), post-herpetic neuralgia and other causes of facial pain, any other primary headache disorder (e.g., migraine or tension type headache), other severe somatic or psychiatric illnesses, past surgical treatment of TN or refractory to medical treatment. Patients with neurological deficits such as hyper- or hypoesthesia, as well as allodynia were not included in the study. For demographics and patient characteristics see Table 1.

**Table 1**
Demographics and patient characteristics.

| | TN [total] | TN | cTN | Healthy controls |
|---|---|---|---|---|
| Number of patients | 60 | 42 | 18 | 49 |
| Gender [women/men] | 36/24 | 24/18 | 12/6 | 28/21 |
| Age [years] | 62 ± 13.2 (range: 31–86) | 61.5 ± 13 (range: 31–86) | 63.3 ± 14.1 (range: 35–85) | 61.8 ± 9 (range: 43–76) |
| Duration of illness [years] | 8.3 ± 6.7 (range: 1–29) | 8.5 ± 5.8 (range: 1–22) | 8.2 ± 7.5 (range: 1–29) | n.a. |
| Attack frequency [per day] | 8.5 ± 10.1 (range: 1–80) | 9.1 ± 10.2 (range: 1–80) | 8.1 ± 7.6 (range: 1–40) | n.a. |
| Pain location V1/V2/V3 [%] | 26/86/60 | 23/81/66 | 28/86/49 | n.a. |
| Pain intensity [VRS] | 7.7 ± 1.8 | 7.8 ± 2.1 | 6.9 ± 1.2 | n.a. |
| Nerve-vessel contact detected on MRI | 49 | 38 | 11 | n.a. |
| Medication [%] | | | | |
| Carbamazepine | 53 | 51 | 49 | n.a. |
| Gabapentin | 27 | 28 | 38 | n.a. |
| Pregabalin | 14 | 15 | 13 | n.a. |
| None | 6 | 6 | 0 | n.a. |

TN = trigeminal neuralgia; TN = classical trigeminal neuralgia; cTN = trigeminal neuralgia with concomitant chronic facial pain; VRS = verbal rating scale (0 = no pain; 10 = worst possible pain); n.a. = not applicable.

### *Standard protocol approvals, registrations, and patient consents*

All participants gave their written informed consent according to the Declaration of Helsinki prior to study inclusion. The local ethics committee of the University of Duisburg-Essen approved the study protocol.

### *Voxel based morphometry (VBM)-data acquisition*

Imaging was performed on a Siemens Sonata scanner operating at 1.5 T using a standard 8-channel birdcage head coil. T1-weighted magnetic resonance imaging 3D datasets were obtained using magnetization prepared rapid acquisition gradient echo (MP-Rage) sequence (TR/TE/TI = 2400 ms/4.38 ms/1200 ms, flip angle = 8°, field of view = 256 mm, 160 slices, voxel size $1 \times 1 \times 1$ mm$^3$). The same scanner and the same scanning protocol were used for all patients and healthy controls. All images were evaluated by an experienced neuro-radiologist (NT) and screened for symptomatic causes of TN.

### *Processing of structural data*

VBM is a whole-brain technique capable of revealing subtle, specific changes in GM by applying voxelwise statistics within the context of Gaussian random fields (Ashburner and Friston, 2000). It has been cross validated with region-of-interest measurements and functional data in several studies (Maguire et al., 2000; May et al., 1999; Richardson et al., 2004). Data processing and analysis was performed with SPM8 (http://www.fil.ion.ucl.ac.uk/) including the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/) and DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra) using Matlab (Matlab 7, The MathWorks, Natick, MA, USA). Preprocessing involved spatial normalization into the Montreal Neurological Institute (MNI) template space, gray matter segmentation, spatial smoothing, and modulation in order to adjust for volume changes during spatial normalization (Ashburner and Friston, 1997; Friston, 1995; Wright et al., 1995). The spatially normalized and modulated GM partitions were smoothed with an isotropic Gaussian kernel of 8 mm full-width at half maximum (FWHM). Additionally, 25 images were flipped to the symptomatic side after preprocessing, as previously recommended (Good et al., 2001a). We calculated the laterality index for the flipped subjects and also used a symmetric template. All images have to be regarded as pain located on the right side of the face. Unflipped images were also analyzed to avoid bias from brain asymmetry, but provided the same results with lesser effect strength.

### *Statistical analysis*

Statistical analysis tested GM volume differences between TN patients and healthy controls. The full factorial model included three groups: 1.) healthy controls, 2.) classical trigeminal neuralgia patients (TN), and 3.) trigeminal neuralgia patients with concomitant persistent facial pain (cTN). To control for age related GM changes, age was implemented in our statistical model as covariate. To avoid any unintentional bias by a priori hypotheses in the primary analysis a whole brain analysis was performed. To correct for multiple comparisons, a region of interest (ROI) analysis was performed based on anatomic structures previously