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Alterations in grey matter density and functional connectivity in trigeminal neuropathic pain and trigeminal neuralgia: A systematic review and meta-analysis

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ABSTRACT

Background: Various studies reported changes in grey matter volumes and modifications in functional connectivity of cortical and subcortical structures in patients suffering from trigeminal neuralgia (TN) and trigeminal neuropathic pain (TNP). This study meta-analyzed the concordant structural and functional changes in foci and provide further understanding of the anatomy and biology of TN/TNP.

Methods: Relevant articles on magnetic resonance imaging (MRI) and functional MRI in TN/TNP, published before August 2018, were searched for on PubMed and Embase. Following exclusion of unsuitable studies, a meta-analysis was performed using activation likelihood estimation (ALE).

Results: In total, 322 paper were identified, 11 of which could be included based on the predefined inclusion and exclusion criteria. Eight papers, totaling 279 subjects, discussing structural changes and four papers, totaling 102 subjects, discussing functional changes were included (i.e., one paper investigated both structural and functional alterations). ALE analysis showed that in TN/TNP, grey matter decreases are found in the thalamus, (anterior) cingulate gyrus, bilateral striatum, the superior-, middle- and transverse temporal gyrus, subcallosal gyrus, the bilateral insular cortex, the pre- and postcental gyrus, the middle frontal gyrus bilaterally and the anterior cerebellar lobe. Grey matter increases were seen in the periaqueductal grey (PAG). Increased resting state functional organization was found within the bilateral middle- and superior frontal gyri, the (posterior) cingulate cortex and the thalamus/pulvinar.

Conclusions: Structural and functional changes meta-analyzed in this paper may contribute to elucidating the central pathophysiological mechanisms involved in TN/TNP. These results may be used as biomarkers to predict the response to medication and, ideally, in the future to offer personalized treatments.

1. Introduction

Painful lesions of the trigeminal nerve or pain attributed to a lesion or disease of the trigeminal nerve forms one group of facial pain disorders in the International Classification of Headache Disorders III-beta (ICHD3-beta) (Olesen, 2018). This group is made up predominantly by 1) trigeminal neuralgia (TN) and 2) trigeminal neuropathic pain (TNP). TN is defined as recurrent, electric, shock-like (neuropathic) pain in one or more divisions of the trigeminal nerve. Generally, a subdivision into primary or classical TN and secondary or symptomatic TN can be made. In classical TN, pain can be paroxysmal or concomitant persistent. Symptomatic TN concerns TN-like pain associated to pathology of the central nervous system (i.e., multiple sclerosis lesions or space-occupying lesions) (Olesen, 2018). TN is frequently misdiagnosed and underdiagnosed, leading to incidence rates ranging from 4.3 to 27 new cases per 100,000 people per year (Katusic et al., 1990; MacDonald et al., 2000; Mueller et al., 2011). In 1934, Dandy already proposed that in at least 30% of the TN patients, a microvascular

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compression of the trigeminal nerve could be found (Dandy, 1934), which is now generally agreed to be the most common cause of classical TN(Maarbjerg et al., 2015). In addition, atrophy of the trigeminal root as measured by magnetic resonance imaging (MRI) has been described as well (Leal et al., 2014, 2011; Wang et al., 2016). Nevertheless, in only half of the TN patients, morphological changes of the trigeminal root can be seen on MR images and in even 12% of the cases, no neurovascular conflict can be identified. Besides, in approximately 30% of the patients, neurosurgical decompression surgery does not provide long-term pain relief, indicating that the hyperexcitable state of the trigeminal nerve was not reversed (Maarbjerg et al., 2017). TNP is defined as facial pain in the distribution(s) of one or more branches of the trigeminal nerve caused by another disorder and indicative of neural damage. The primary pain is usually continuous or near-continuous and is commonly described as burning or squeezing or likened to pins and needles. On top of that, brief pain paroxysms may occur, but these are not the predominant pain type. This combination distinguishes TNP from the subtypes of TN clinically (Olesen, 2018). TNP can arise from different causes (i.e., post-traumatic, post-herpetic, idiopathic) and prevalences and incidences vary due to the heterogeneous aetiologies (Baad-Hansen and Benoliel, 2017; Olesen, 2018). As a group of diagnoses, TNP has an estimated global prevalence of 7% (Antczak-Bouckoms, 1995; Lipton et al., 1993; Macfarlane et al., 2002). Within the diagnostic challenge of this group of disorders, MR imaging plays a less distinct role in clinical care. In research, however, TN and TNP as a group of diagnoses has been found to be accompanied by a broad variety of structural (increases or decreases in voxel-based morphometry (VBM)) and functional changes (as measured by functional MRI (fMRI)) within the central nervous system.

In the past, previous studies have been performed in which similar outcome measures (i.e., VBM and fMRI) were investigated in patients suffering from various neuropathic pain syndromes (Friebel et al., 2011; Peyron et al., 2000). However, in these large meta-analyses, various pain syndromes were merged, including allodynia, hyperalgesia, postherpetic pain, trigeminal pain, complex regional pain syndrome and fibromyalgia (Friebel et al., 2011; Peyron et al., 2000). The limitation of translating these findings to TN/TNP is formed by the heterogeneity of the studied population, which is often the case in pain research (Baad-Hansen and Benoliel, 2017; Evers, 2017). This preludes the drawing of a sound conclusion for specific pain syndromes and was exemplified by Svensson and Mai in migraine treatment efficacy (Svensson and May, 2017), although this model can be translated to improved imaging of pain syndromes, including TN/TNP.

This study therefore performed a combined analysis of the reported structural- and functional changes in TN/TNP patients in order to contribute to the elucidation of central pathophysiological mechanisms involved in TN/TNP.

2. Materials and methods

2.1. Search strategy

Literature was searched for until August 2018. PRISMA and MOOSE guidelines were followed during the conduction of this systematic review (Liberati et al., 2009; Stroup et al., 2000). Pubmed, MEDLINE, Embase, The Cochrane Library and Google Scholar were systematically searched in order to find eligible articles regarding structural and functional changes in TN patients as measured by MR-based VBM and fMRI. The search strategy used the following key words : “Chronic orofacial pain”; “Orofacial pain”; “Neuropathic orofacial pain”; “Trigeminal neuralgia”; “Trigeminal neuropathic pain”; “Magnetic resonance imaging”; “MRI”; “Resting state functional magnetic resonance imaging”; “functional magnetic resonance imaging”; “fMRI”; “Structural magnetic resonance imaging” “sMRI”; “Voxel-based morphometry” and “VBM”. When available, Medical Subject Headings (MeSH-) terms of the aforementioned keywords were implemented.

This meta-analysis included only papers 1) that evaluated the association of grey matter changes and TN on a case-control- or cohort-control design; 2)that contained information on the sample sizes and disease conditions; 3) that reported whole brain results of changes in stereotactic coordinates; and 4) that used thresholds for significance corrected for multiple comparisons or uncorrected with special extent thresholds. Exclusion criteria comprised 1) non-original papers; 2) studies in which the comparison between patients with TN and healthy controls did not include changes in grey matter; 3) studies in which the field of view was confined to a restricted region of the cortex or to specified subcortical structures which was not based on previously published evidence; 4) studies in which patients suffered from neurological or psychiatric co-morbidities or another chronic pain condition; 5) articles which presented non-significant results; 6) studies in which no healthy control group was present; 7) papers in which task-based/stimulus-based fMRI was applied; 8) papers in which the grey matter functional changes were investigated with methods other than by using oxygen level dependent imaging or functional connectivity analysis; and 10) studies with less than five TN patients.

Studies in which task-based/stimulus-based fMRI was applied were excluded as these designs are strongly influenced by compliance of the subject, the task performance of subjects (Di Martino et al., 2008; Tahmasian et al., 2017) and, especially for TN/TNP, the degree of allodynia and/or the (hyper)sensitivity of patients’ painful region. Instead, this systematic review only included resting-state fMRI, which is based on fluctuations of the BOLD signal, associated with the intrinsic neuronal activity of the brain while subjects are in the awake state without performing any specific task (Biswal, 2012; Snyder and Raichle, 2012). In contrast to task-based/stimulus-based fMRI, resting-state fMRI substantially reduces potential disturbing interindividual influences (Di Martino et al., 2008; Tahmasian et al., 2017). Within this paper, we used the term functional connectivity when reporting findings from the included fMRI studies, which included both global measures and local measures of functional organization. Global measures of functional connectivity refer to the similarity of the BOLD signal across distant brain areas (such as using a seed-based approach). Local measures of functional connectivity comprised regional homogeneity (ReHo) which is a local measure reflecting the similarity of the BOLD signal in a voxel to its surrounding voxels.

Based on these criteria, each article was reviewed for full-text analysis by two researchers independently (J.D., R.K., M.S., and/or A.W.). Incongruent findings were reviewed by a third researcher (D.H.), upon which the article was included or excluded. The selection-process is showed in Fig. 1 as a flow-diagram.

2.2. Data extraction

Three authors (J.D., R.K., M.S., D.H. and/or A.W.) independently extracted data from each study using a predefined data extraction form. Any lack of clarity or disagreement was resolved through discussion. The investigators abstracted data from each study to obtain information on authors, data of publication, sample size, characteristics of the studied population (i.e., sex and age), information concerning the severity of TN/TNP, technical information (i.e., MRI scanning system, field-strength, timing and methodology) and the main findings from each study. Furthermore, statistical thresholds used for voxel-wise inference were noted as discussion in the literature has been reported concerning the most optimal cut-off value and the possible reporting of false-positive neuroimaging findings (Eklund et al., 2016). Coordinates of regions of interest of each study were independently extracted according to the ALE method.

2.3. Statistical analysis

Ginger ALE version 2.3.6 (http://brainmap.org/ale/) was used to evaluate the presence of common patterns of grey matter alterations. To

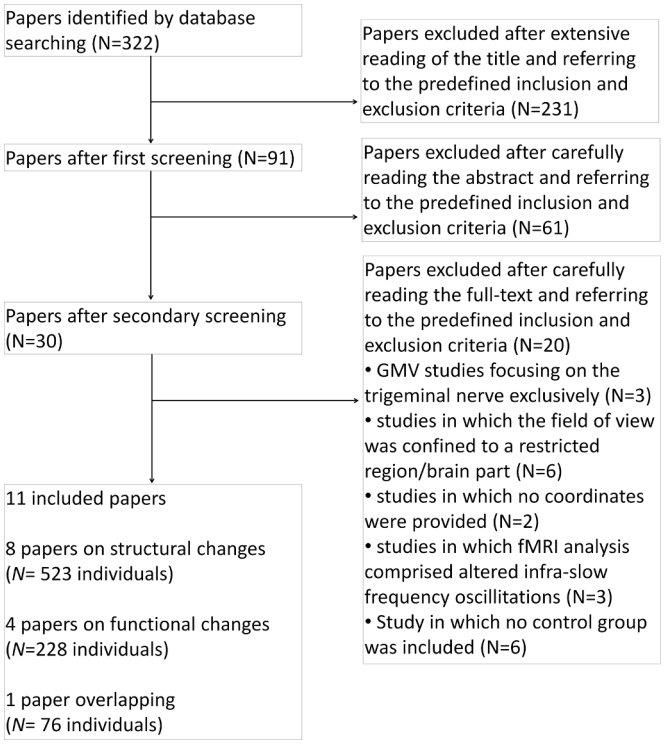

Fig. 1. Flow-chart describing the study selection methods.
fMRI = Functional magnetic resonance imaging; *N* = Number of papers; *N* = Number of individuals.

perform an activation likelihood estimation (ALE) meta-analysis, all coordinates were used on coordinates in the Talraich space. ALE is one of the most widely used algorithms for foci based meta-analysis and treats foci form neuroimging studies as spatial probability distributions centered at given coordinates rather that as single foci points. For each voxel, Ginger ALE estimates the cumulative probabilities that at least one of the included papers discussed activation for that focus. ALE-maps are subsequently obtained by computing the union of activation probabilities for each voxel. Differentiation between true convergence of foci and random clustering is controlled for by use a permutation procedure (Eickhoff et al., 2009; Laird et al., 2005; Turkeltaub et al., 2012). By using random effects within the ALE methods variable uncertainty based on the sample size was incorporated into the algorithm (Eickhoff et al., 2012). Such a random effects model assumes a higher than chance likelihood of consensus between different experiments, but not in relation to activation variance within each study. During an ALE analysis, each activation focus is modeled as the center of a Gaussian probability distribution, and is used to generate a modeled activation (MA) map for each study. Foci coordinates that were not expressed in Talraich coordinates were transformed into Talairach space by use of the icbm2tal function (Lancaster et al., 2007). A recommended, conservative threshold of $p < 0.001$ was chosen with a minimum cluster size of 100mm^3 in order to control for publication bias with regard to reported foci (Jia and Yu, 2017b). All numerical statistical data was analyzed using IBM SPSS Statistics version 25 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

3. Results

In total, 322 paper were identified by searching the aforementioned databases. Based on title and abstract, 261 papers were excluded from the database. Based on full-text reading, papers were excluded when 1) they focused on the trigeminal nerve exclusively ($N = 3$); 2) the field of view was confined to a restricted region/brain part ($N = 6$); 3) no

Table 1
Demographic and clinical characteristics of the subjects and healthy controls of the included papers investigating grey matter volume in patients suffering from TN/TNP
CBZ: Carbamazepine; GBP: Gabapentine; HC: Healthy controls; NSAID: Non-steroidal anti-inflammatory drugs; PGB: Pregabalin; TCA: Tricyclic antidepressants; VPA: Valproic acid.

Author (year)	Ref	Studied disorder	*N* individuals with TN Age ± SD/range (years) (*N* males)	*N* individuals HCAge ± SD/range (years) (*N* males)	Mean duration of illness ± SD/range (years)	Affected side	Use of medication at the moment of brain scanning?
Gustin et al. (2011)	Gustin et al. (2011)	TN+TNP	21 (4) 54.7 ± 2.1	30 (6) 53.6 ± 3.2	8.5 ± 2.1	Mixed	Yes; CBZ, GBP; TCA; NSAID and/or PGB
DeSouza et al. (2013)	DeSouza et al. (2013)	TN	24 (9) 48.5 ± 12.7	24 (9) 47.6 ± 12.3	6.3 ± 3.0	Right	Yes: CBZ; GBP; TCA; VPA and/or PGB Some patients received no medication
Obermann et al. (2013)	Obermann et al. (2013)	TN	60 (24) 62.0 ± 13.2	49 (21) 61.8 ± 9.0	8.3 ± 6.7	Right	Yes: CBZ; GBP; and/or PGB Some patients received no medication
Wilcox et al. (2015)	Wilcox et al. (2015)	TN+TNP	21 (4) 48.7 ± 1.7	42 (8) 48.6 ± 2.0	5.5 / 2–16	Mixed	Yes; CBZ; GBP; TCA; NSAID and/or PGB
DeSouza et al. (2015)	DeSouza et al. (2015)	TN	25 (10) 57.6 ± 11.5	14 (5) 51.7 ± 10.9	8.0 ± 6.4	Right	Yes: CBZ; GBP; TCA; VPA and/or PGB Some patients received no medication
Wang et al. (2017)	Wang et al. (2017)	TN	38 (16) 55.9 ± 8.4	38 (16) 55.9 ± 8.1	7.1 ± 5.3	Mixed	Unknown
Li et al. (2017)	Li et al. (2017)	TN	28 (15) 45.9 ± 11.2	28 (15) 44.8 ± 9.2	8.4 ± 3.7	Mixed	Yes: CBZ Some patients received no medication
Tsai et al. (2018)	Tsai et al. (2018)	TN right side TN left side	36 (16) 58.0 ± 7.7 26 (8) 59.0 ± 6.6	19 (4) 55.6 ± 8.2	5.8 ± 6.3 5.3 ± 4.9	Right Left	No

Table 2
Technique details of studies investigating the structural changes in patients suffering from TN/TNP
CTA: Cortical thickness analysis; T: Tesla; TN: Trigeminal neuralgia; VBM: Voxel-based morphometry; * Study does not specify laterality.

Author (year)	Ref	MRI scanner	Region studied	Methods	Statistical threshold	Main findings
Gustin et al. (2011)	Gustin et al. (2011)	3.0T	Whole brain	VBM	$P < 0.01$	Grey matter volume of TNP patients was reduced in the primary somatosensory cortex, anterior insula, putamen, nucleus accumbens, and the thalamus, whereas gray matter volume was increased in the posterior insula. The thalamic volume decrease was only seen in the TNP patients classified as having trigeminal neuropathy but not those with trigeminal neuralgia.
DeSouza et al. (2013)	DeSouza et al. (2013)	3.0T	Whole brain (medial and lateral cortical areas, basal ganglia, thalami and brainstem)	VBM/CTA	$P < 0.05$	Increased grey matter volumes were observed in the sensory subnuclei of the thalamus, the amygdala, periaqueductal gray, putamen, caudate nucleus and nucleus accumbens. Greater cortical thickness was found in the contralateral primary somatosensory cortex and frontal pole. Reduced cortical thickness was found in the pregenual anterior cingulate cortex, the insula and the orbitofrontal cortex. No relationship was observed between structural abnormalities and duration of trigeminal pain.
Obermann et al. (2013)	Obermann et al. (2013)	1.5T	Whole brain	VBM	$P < 0.001$	Grey matter volume reduction was observed in the primary- and secondary somatosensory- and orbitofrontal cortices, the thalamus, insula, anterior cingulate cortex, cerebellum and dorsolateral prefrontal cortex. Also, grey matter volume decreased within the ACC, parahippocampus, and temporal lobe correlated with increasing disease duration of trigeminal pain.
Wilcox et al. (2015)	Wilcox et al. (2015)	3.0T	Whole brainstem	VBM	$P < 0.05$	Grey matter volume decreased in the ipsilateral principal sensory nucleus, the oral subnucleus of the trigeminal spinal nucleus, contralateral middle cerebellar peduncle and ipsilateral trigeminal lemniscus.
DeSouza et al. (2015)	DeSouza et al. (2015)	3.0T	Whole brain (medial and lateral cortical areas, basal ganglia, thalami and brainstem)	VBM/CTA	$P < 0.05$	Reduced cortical thickness in the right ventral anterior insula, posterior insula bilaterally, left oribtofrontal cortex, and right posterior cingulate cortex. Increased cortical thickness was observed in the left primary motor cortex, the left primary somatosensory cortex and the frontal pole bilaterally. Grey matter volume increases were seen in the putamen bilaterally, periaqueductal grey and thalami.
Wang et al. (2017)	Wang et al. (2017)	3.0T	Whole brain	VBM	$P < 0.001$	Grey matter volume reductions were seen in the anterior cingulate cortex and mid-cingulate cortex, insula, secondary somatosensory cortex, primary motor cortex, premotor area and several unspecified regions in the temporal lobe. Additionally, grey matter volume of left inferior temporal gyrus was negatively correlated with current pain intensity and disease duration in patients.
Li et al. (2017)	Li et al. (2017)	1.5T	Whole brain	VBM	$P < 0.05$	Decreased grey matter volume in the bilateral superior temporal gyrus, bilateral middle temporal gyrus, bilateral parahippocampal area, left anterior cingulate cortex, caudate nucleus, right fusiform gyrus, and right cerebellum. In addition, it was found that the grey matter volume in the bilateral superior- and middle temporal gyri was negatively correlated with the duration of trigeminal pain.
Tsai et al. (2018)	Tsai et al. (2018)	3.0T	Whole brain	VBM	$P < 0.05$	Patients with right sided trigeminal pain showed grey matter volume reduction in components of the prefrontal cortex, precentral gyrus, cerebellar tonsil, thalamus, hypothalamus, and nucleus accumbens.
			Whole brain			Patients with left sided trigeminal pain showed grey matter volume reduction in components of the inferior frontal gyrus, precentral gyrus, cerebellum, thalamus, ventral striatum, and putamen

Table 3
Demographic and clinical characteristics of the subjects and healthy controls of the included papers investigating functional changes in patients suffering from TN/TNP
CBZ: Carbamazepine; GBP: Gabapentine; HC: Healthy controls; NSAID: Non-steroidal anti-inflammatory drugs; PGB: Pregabalin; TCA: Tricyclic antidepressants; VPA: Valproic acid.

Author (year)	Ref	Studied disorder	*N* individuals with TN (*N* males)	Age ± SD/range (years)	*N* individuals HC (*N* males)	Age ± SD/range (years)	Mean duration of illness ± SD/range (years)	Affected side	Use of medication at the moment of brain scanning?
Wang et al. (2015)	(Wang et al., 2015)	TN	17 (7)	63.4 ± 7.3	19 (9)	62.5 ± 7.4	7.0 ± 5.6	Mixed	Unknown
Wang et al. (2017)	Wang et al. (2017)	TN	38 (16)	55.9 ± 8.4	38 (16)	55.9 ± 8.1	7.1 ± 5.3	Mixed	Unknown
Mills et al. (2018)	Mills et al. (2017)	TNP	24 (8)	46.3 ± 3.0	46 (17)	42.0 ± 2.0	6.9 ± 1.0	Mixed	Yes; CBZ; GBP; TCA; NSAID and/or PGB
Yuan et al. (2018)	Yuan et al. (2018)	TN	23 (14)	59.6 ± 12.5	23 (12)	63.1 ± 9.8	5.7 ± 3.3	Mixed	Unknown

coordinates were provided ($N = 2$); 4) fMRI analysis comprised altered infra-slow frequency oscillations ($N = 3$) and; 5) no control group was included in the analysis ($N = 6$). An overview of the study selection process is depicted in Fig. 1. In total, 11 papers were included; 8 papers focused on structural changes of grey matter structures in patients suffering from TN/TNP and 4 papers investigated functional changes of grey matter structures in patients suffering from TN/TNP. One paper investigated both structural and functional changes (Wang et al., 2017). The functional changes were divided into two groups: studies investigating functional organization (functional organization refers to the similarity of the BOLD signal across distant brain areas) and studies investigating ReHO. The included papers focusing on structural changes contained 279 pain patients (106 males and 173 females; mean age of 54.6 ± standard deviation 1.7 years) and 244 healthy controls (84 males and 160 females; mean age of 52.6 ± standard deviation 1.8 years). The clinical characteristics and technical details of the included studies are presented in Tables 1–4. No statistical significant differences were observed in the mean age ($p = 0.142$), the number of males ($p = 0.157$) or the number of females ($p = 0.157$) between the group containing pain patients and group containing healthy controls. The ALE results showed that, compared with healthy controls, trigeminal neuralgia and trigeminal neuropathic pain are associated with a common core set of grey matter decreases in the thalamus, cingulated gyrus, head of the caudate nucleus bilaterally, the bilateral putamen, the superior-, middle- and transverse temporal gyrus, subcallosal gyrus, the anterior cingulated cortex, the bilateral insula, the precental gyrus, the postcentral gyrus, the middle frontal gyrus bilaterally, and the anterior cerebellar lobe. Grey matter increases were seen in the periaqueductal grey (PAG) (see Fig. 2 and Table 5). The included papers focusing on functional changes contained 102 pain patients (45 males and 57 females; mean age of 56.1 ± standard deviation 4.4 years) and 126 healthy controls (54 males and 72 females; mean age of 55.8 ± standard deviation 6.2 years). No statistical significant differences were observed in the mean age ($p = 0.497$), the number of males ($p = 0.157$) or the number of females ($p = 0.157$) between the group containing pain patients and group containing healthy controls. Alterations in functional organization were found in the thalamus/pulvinar (see Fig. 3 and Table 6). Increased ReHo was observed at the bilateral middle- and superior frontal gyri and the (posterior) cingulate cortex (see Fig. 3 and Table 6). Regions within the brain showing an overlap of both structural and functional alterations were 1) the middle frontal gyri; 2) the cingulate cortex; and 3) the thalamus.

4. Discussion

Key areas with structural and/or functional changes in TN/TNP patients, as identified by this ALE meta-analysis, concern the thalamus, the striatum, the PAG, the cingulate cortex, the middle frontal gyri, the insular cortex and the somatosensory cortex.

4.1. Discrepancies between structural and functional alterations

Areas of TN/TNP which were found to be changed structurally and functionally in TN/TNP patients were the middle frontal gyri, the cingulate cortex and the thalamus. Nevertheless, structural changes were found in more brain regions, including the PAG, the striatum, the somatosensory cortex and the insular cortex. Such discrepancies can be explained by the fact that less fMRI studies are available and could therefore be included. Furthermore, in most studies, only the areas showing significant changes in grey matter density were included as seeding masks for fMRI analyses. Furthermore, the present paper excluded several studies were excluded as these papers did not use functional connectivity derived from seed-to-brain masks (e.g., papers using altered spontaneous brain activity as an outcome (Alshelh et al., 2016, 2018)).

Table 4
Technique details of studies investigating the functional changes in patients suffering from TN/TNP
KCC: Kendall coefficient of concordance; T: Tesla.

Author (year)	Ref	MRI scanner	Region studied	Methods	Statistical threshold	Details	Main findings
Wang et al. (2015)	Wang et al. (2015)	1.5T	Whole brain	Voxel-based ReHo	$P < 0.01$	ReHo was computed as a KCC value of the ranked time series of a given voxel to its nearest neighbors in a voxel-wise way.	Decreased ReHo in the left amygdala, right parahippocampal gyrus, and left cerebellum and increased ReHo in the right inferior temporal gyrus, right thalamus, right inferior parietal lobule, and left postcentral gyrus. Furthermore, the increase in ReHo in the left precentral gyrus was positively correlated with visual analog scale.
Wang et al. (2017)	Wang et al. (2017)	3.0T	Whole brain (cortical areas of both the medial and lateral pain system)	Functional connectivity	$P < 0.001$	Functional connectivity was performed using the seed-voxel correlation approach, in which the time-course signal in a seed region is correlated with all voxels in the brain. Seeds were defined as 6-mm-radius spheres centered on the peak voxels for the GMV clusters showing significant differences between TN/TNP patients and healthy controls.	Enhanced functional connectivity between the right insula/secondary somatosensory cortex and the anterior cingulate cortex, medial prefrontal cortex, posterior cingulate cortex and bilateral dorsolateral prefrontal cortex in patients suffering from trigeminal pain. Furthermore, connectivity of the right insula/secondary somatosensory cortex and anterior cingulate cortex was negatively correlated with pain intensity, depression, and anxiety ratings.
Mills et al. (2018)	Mills et al. (2017)	3.0T	Whole brainstem	Functional connectivity	$P < 0.001$	Functional connectivity was performed using the seed-voxel correlation approach, in wich the rostral ventromedial medulla was used as a seed region.	Increased functional connectivity between the rostral ventromedial medulla and the ventrolateral periaqueductal gray and locus ceruleus were observed. Furthermore, an increased functional connectivity of the rostral ventromedial medulla with the spinal trigeminal nucleus was reported. In addition, the ventrolateral periaqueductal gray and locus ceruleus displayed increased functional connectivity strengths with higher brain regions, including the hippocampus, nucleus accumbens, and anterior cingulate cortex.
Yuan et al. (2018)	Yuan et al. (2018)	3.0T	Whole brain	Voxel-based ReHo	$P < 0.05$	Individual ReHo maps were generated by calculating the KCC for purification of the activated brain clusters.of the time series of a given voxel with those of its neighbors (26 voxels) in a voxel-wise way. As such, ReHo reflects the local coherence of spontaneous neuronal activity. Then a whole-brain mask was adopted to remove the nonbrain tissues.	Increased ReHo was observed in the cerebellum, cingulate cortex, temporal lobe, putamen, occipital lobe, limbic lobe, precuneus, insula, medial, and superior frontal gyrus. A correlation was found between the ReHo values within the aforementioned brain regions and the visual analogue scales.

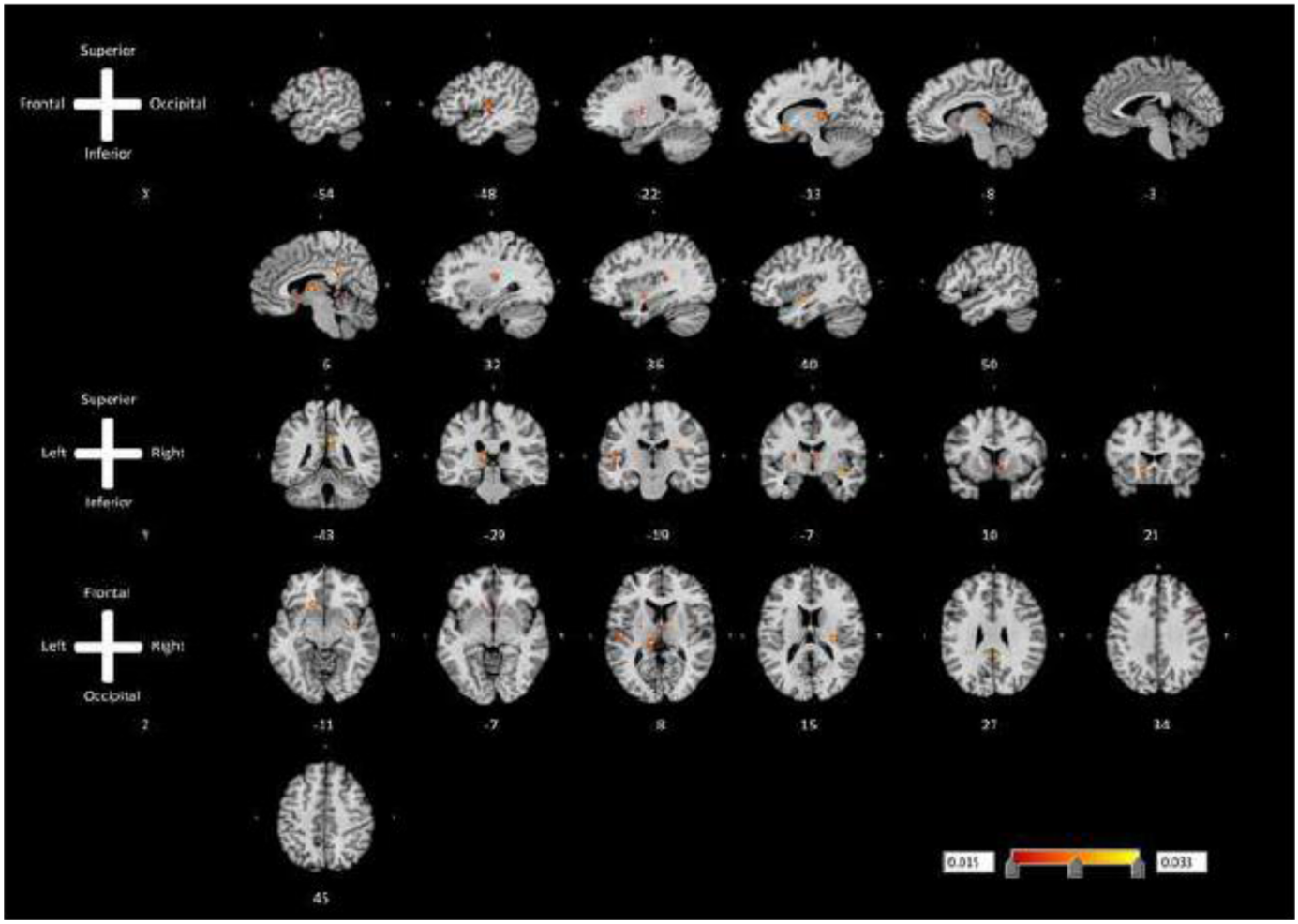

Fig. 2. ALE map investigating differences in grey matter volume between patients suffering from TN/TNP and healthy controls
This image summarizes the results of all the papers involved in this meta-analysis on grey matter volume changes. Red color shows grey matter decreases (ALE maps were computed at a threshold of $p < 0.001$).

4.2. Regions with modified grey matter density

Key areas with modified grey matter density changes in TN/TNP which are identified by this ALE meta-analysis concern the thalamus, the striatum, the PAG, the anterior cingulate cortex, the insular cortex and the somatosensory cortex. Previous research on other pain syndromes reported similar findings. A quantitative VBM based meta-analysis showed that in neuropathic pain patients, grey matter volume (GMV) decreased in bilateral anterior insula and thalamus, right superior frontal gyrus and left postcentral gyrus. Increased GMV were reported in right medial frontal gyrus and right posterior insula (Pan et al., 2015). In fibromyalgia pain syndrome patients, ALE meta-analysis reported structural and functional changes in the insula, amygdala, anterior/mid cingulate cortex, superior temporal gyrus, the primary and secondary somatosensory cortex, and lingual gyrus (Dehghan et al., 2016). In addition, another ALE-study reported that migraineurs had concordant decreases in the GMV in the bilateral inferior frontal gyri, the right precentral gyrus, the left middle frontal gyrus and the left cingulate gyrus. GMV decreases in right claustrum, left cingulated gyrus, right anterior cingulate, amygdala and left parahippocampal gyrus were reported to be related to estimated frequency of migraine attacks (Jia and Yu, 2017a). The reported key areas in the brain on pain show to overlap present findings. This has led to the concept of chronic pain as a brain disorder with structural and functional changes rather than a temporal continuum of acute pain (Apkarian et al., 2009; Kuner and Flor, 2016). The sensorimotor cortex, supplementary motor cortex, cingulate cortex, prefrontal cortex, insular cortex, thalamus, striatum, amygdala, hippocampus and PAG have been reported as brain areas which undergo reorganization when the subject is exposed to chronic pain (Kuner and Flor, 2016).

However, alterations in GMV can be the reflection of different histological processes, including 1) decreased GABAα-receptor density in combination with increased amount of neuronal matter; 2) compromised neuronal integrity with concomitant extreme upregulation of the GABAα-receptor; 3) chronic state of dehydration in chronic pain patients; or 4) a reduced CBF to, from and within cortical regions (Pomares et al., 2017). The histological correlate of GMV changes in chronic neuropathic pain still remains an unanswered question in science, although more and more evidence points in the direction of alterations in the GABAα system (Lorenzo et al., 2013). Improved understanding of the candidate cellular mechanisms might provide new insights which could lead to improved diagnostic tools and eventually improved treatment options.

4.3. Networks in the brain

The different key regions found in this systematic review represent key nodes within the salience- (anterior cingulate cortex, anterior insula, temporoparietal junction, thalamus, nucleus accumbens, amygdala), default- (medial prefrontal cortex, posterior cingulate cortex, hippocampus and amygdala) and sensorimotor network (thalamus; M1; S1) (Raichle et al., 2001; Seeley et al., 2007). This indicates that all

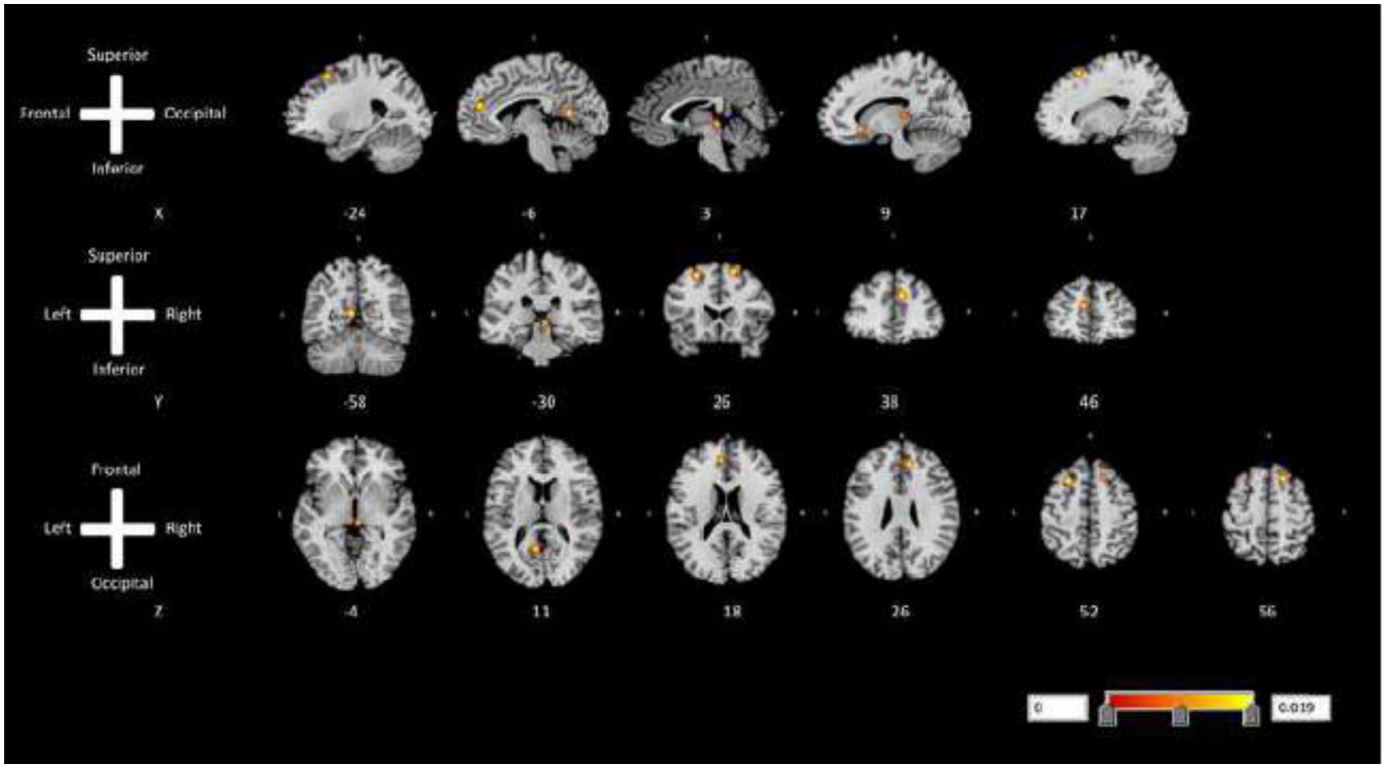

Fig. 3. ALE map investigating differences in functional MRI functional connectivity patterns between patients suffering from TN/TNP and healthy controls
This image summarizes the results of all the papers involved in this meta-analysis on grey matter volume changes. Red color shows increased resting state functional organization (ALE maps were computed at a threshold of $p < 0.001$).

Table 5
Regional differences of grey matter volume between patients suffering from TN/TNP and healthy controls
L: Left; R: Right.

Cluster #	Volume (mm^3)	Weighted Center (x,y,z)			Extrema Value	Label	L/R	Brodmann area
1	880	−11.1	−27.2	7.1	0.029	Pulvinar	L	N/A
2	736	−49.8	−17.8	4.7	0.030	Superior Temporal Gyrus	L	Brodmann area 22
3	592	−13.7	22.2	−10	0.033	Subcallosal Gyrus	L	Brodmann area 47
4	552	29.3	−21.9	16.2	0.033	Insula	R	Brodmann area 13
5	520	5.2	−8.7	5.4	0.029	Thalamus	R	N/A
6	520	4.9	−42.7	28.3	0.032	Cingulate Gyrus.	R	Brodmann area 31
7	496	39	−6.8	−12.8	0.031	Middle Temporal Gyrus	R	Brodmann area 21
8	360	7.6	8.2	−5.1	0.025	Caudate Head	R	N/A
9	296	−23.3	−7.8	7.7	0.019	Putamen	L	N/A
10	216	35.8	−32.3	11	0.021	Transverse Temporal Gyrus	R	Brodmann area 41
11	136	−8.5	7.8	1.9	0.020	Caudate Head	L	N/A
12	136	−55.9	.7	27.5	0.018	Precentral Gyrus	L	Brodmann area 6
13	128	−1.7	33.7	8	0.019	Anterior Cingulate Cortex	L	Brodmann area 24
14	120	−20.6	7.7	3.7	0.020	Putamen	L	N/A
15	112	−3.6	−43.9	−7.3	0.020	Anterior Cerebellar Lobe	L	N/A
16	112	17.8	60.6	2.1	0.020	Medial Frontal Gyrus	R	Brodmann area 10
17	112	48.7	12	33.3	0.019	Middle Frontal Gyrus	R	Brodmann area 9
18	112	−53.5	−18.7	45.8	0.019	Postcentral Gyrus	L	Brodmann area 1
19	104	34.3	12.7	−8.3	0.019	Insula	R	Brodmann area 13
20	104	6.3	−48	−5.4	0.019	Culmen	R	N/A
21	104	9.7	−62.3	27.2	0.019	Precuneus	R	Brodmann area 31
22	104	10	27.4	32.3	0.019	Medial Frontal Gyrus	R	Brodmann area 9

these systems are involved in processing TN/TNP. This neural signature of the pain network has been investigated before by various others, describing that each network has its own functionality. The salience network has been reported to show greater activation when a subject is focusing on a noxious stimulus and to show suppression when a subject is paying less attention to the stimulus itself (mind wandering). The default network is thought to form the opposite of the salience network and is suggested to be activated during mind wandering and to show less activation when focused on pain. With regard to the sensorimotor system, the somatosensory cortex and the thalamus are well-known centers in the brain that process and modulate pain (Brooks and Tracey, 2005; Bushnell et al., 1999; Greenspan and Winfield, 1992; Kanda et al., 2000; Nieuwenhuys et al., 2008). The involvement of M1 in the processing of pain, on the other hand, remains an interesting topic of research. Anatomically, it is known that every thalamic nucleus receives feedback from various layers of the primary motor cortex, suggesting that modulation of the primary motor cortex could be involved with the pathophysiology of chronic pain (Sherman, 2016).

Table 6
Contrast analysis results for functional connectivity for patients suffering from TN/TNP and healthy controls
fMRI:: functional magnetic resonance imaging; L: Left; R: Right; ReHo: Regional homogeneity.

Cluster #	Volume (mm^3)	Weighted Center (x,y,z)			Extrema Value	Label	L/R	Brodmann area	fMRI technique
1	472	10.1	38.7	27.5	0.019	Medial Frontal Gyrus	R	Brodmann area 9	ReHo
2	408	−6.9	−58.8	9.5	0.018	Poster Cingulate Cortex	L	Brodmann area 30	ReHo
3	400	−23.8	19	51.6	0.018	Superior Frontal Gyrus	L	Brodmann area 6	ReHo
4	392	16.9	21.4	55.3	0.018	Superior Frontal Gyrus	R	Brodmann area 6	ReHo
5	248	3.9	−28.9	−4.5	0.014	Thalamus/Pulvinar	R	N/A	Resting state functional organization

Furthermore, functional changes in motor cortex function have also been described extensively before (for a review, see (Parker et al., 2016)).

4.4. Clinical relevance

Diagnostic opportunities can arise from neuroimaging studies in TN/TNP. It is well accepted that MR imaging already plays a role in clinical care for patients suffering from TN/TNP. However, GMV measurements are not commonly used in regular clinical care, which is mostly due to the fact that such group analyses cannot be performed on a single subject to measure grey matter density per person. Regarding resting-state fMRI, this method has been regarded as a useful method to measure intrinsic large-scale functional brain organization in general, and, more specific, to measure the altered pain network in the brain. Resting-state fMRI involves the acquisition of fMRI data in the absence of a stimulus or task. With this data, functional brain connectivity which relates to a combination of spontaneous thought processes and ongoing neural and physiological maintenance processes can be investigated. In chronic pain, these processes include those involved in ongoing pain (Kucyi and Davis, 2015). Moreover, variability in brain activity can provide insight into brain health, pain characteristics and brain plasticity, which can differ between patients and healthy individuals and can therefore be used in a clinical setting (Davis et al., 2017). A challenge in resting-state fMRI is that the nature of any particular change in the pattern of resting-state connectivity associated with pain has not yet been determined. Furthermore, new insights can arise from imaging studies. Different studies reported on bilateral activation patterns on fMRI of the somatosensory system was found in both acute, experimental in healthy subjects (de Leeuw et al., 2006; Nash et al., 2010; Weigelt et al., 2010) and in TN/TNP patients (Albuquerque et al., 2006; DaSilva et al., 2008; Henderson et al., 2013; Mills et al., 2017). These findings indicate that still part of the anatomical relay system involved in pain processing in TN/TNP remains elusive, although histological studies aim to contribute to an improved understanding (Henssen et al., 2018). Furthermore, new treatment options can arise from the findings of MR imaging studies. For example, involvement of the motor cortex in TN/TNP, as shown by imaging studies, can lead to a new neuromodulation target. Clinically, it is known that stimulation of M1, either invasive (i.e. epidural motor cortex stimulation (Tsubokawa et al., 1991a, b)) or non-invasive (i.e. transcranial magnetic stimulation (Cruccu et al., 2007; Klein et al., 2015)), can be used as a target for modulating TN/TNP (Monsalve, 2012) and pain in general (Fontaine et al., 2009).

Based on the signature of pain in the brain as investigated by use of multiple neuroimaging techniques, researchers have prompted to extract these neuroimaging findings in order to obtain an objective biomarkers of pain. However, most of the brain responses observed when pain is present have also be observed when pain is absent, for example, by non-painful auditory, tactile and visual stimuli (Mouraux and Iannetti, 2018). However, the use of neuroimaging to predict response to trigeminal neuropathic pain treatment has already been described and shows to be promising (Hung et al., 2017).

4.5. Strengths and limitations

Strengths of this review concern the combination of both structural and functional MR imaging to elucidate TN/TNP. However, the use of imaging techniques in pain, such diffusion weighted MRI, PET-CT (positron emission tomography–computed tomography) (Davis et al., 2017; Haanpaa et al., 2011), MEG (magnetoencephalography) (Lang et al., 2005) and EEG (electroencephalography) (Babiloni et al., 2001; Pigg et al., 2010) were not included in this review, which forms a limitation. In an attempt to attenuate the random effect of small cohorts and thereby strengthening the results, studies with a sample size smaller than 5 patients were excluded. Another limitation of the present study can be found in the well-known limitations of voxel-wise neuroimaging studies, including a high risk of false positive results and publication bias leading to underreporting of studies reporting non-significant results. Furthermore, significant alterations in brain structure and function were included in this review, which provides stronger evidence for the listed regions. However, this could also induce an underestimation or overestimation of the alterations of brain structure and function in TN/TNP patients. Another strength of this study was the exclusion of studies without matched healthy controls as this gives a more accurate representation of the modifications that occur due to TN/TNP. Furthermore, using a matched healthy control group, which is prone to outliers, is still believed to prevent overestimation of the findings at the highest possible level. Another limitation concerns the inclusion of fMRI studies using functional organization and fMRI studies using ReHo as outcome measures. As these analyses measure different processes, this can confound our findings. Nevertheless, by presenting the results separately, the authors aimed to include a broad variety of functional changes in the brain of TN/TNP patients without merging incomparable findings. Finally, a new MRI technique which can be used to study pain in vivo can be added to the armamentarium of neuroimaging: positron emission tomography/magnetic resonance imaging (PET/MRI). PET/MRI shows to be capable of visualizing nerve injury in a neuropathic pain model (Shen et al., 2017). PET/MRI can furthermore be used to unravel the brain on pain (Torrado-Carvajal et al., 2018), although no PET/MRI studies which investigated TN/TNP were found.

5. Conclusion

Neuroimaging studies have led to advances in the understanding of mechanisms involved in TN/TNP and could lead to a better identification of causes and types of TN/TNP. Key regions which undergo structural- and functional changes that came forth from the ALE analyses were the thalamus, the cingulate cortex, and the middle frontal gyrus. Clinical imaging studies should focus on these regions in their pursuit to improve diagnostic imaging in TN/TNP. Future studies also should elucidate whether the structural- and functional changes can be reversed after effective treatment of TN/TNP. Although the results are promising, we must recognize the difficulty and non-specificity of neuroimaging techniques in neuropathic pain patients, especially on a single-subject level.

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