Innovations and Controversies in Brain Imaging of Pain: Methods and Interpretations
Review
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Trigeminal nerve and white matter brain abnormalities in chronic orofacial pain disorders

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Abstract

The orofacial region is psychologically important, given that it serves fundamental and important biological purposes. Chronic orofacial pain disorders affect the head and neck region. Although some have clear peripheral etiologies, eg, classic trigeminal neuralgia, others do not have a clear etiology (eg, muscular temporomandibular disorders). However, these disorders provide a unique opportunity in terms of elucidating the neural mechanisms of these chronic pain conditions: both the peripheral and central nervous systems can be simultaneously imaged. Diffusion-weighted imaging and diffusion tensor imaging have provided a method to essentially perform in vivo white matter dissections in humans, and to elucidate abnormal structure related to clinical correlates in disorders, such as chronic orofacial pains. Notably, the trigeminal nerve anatomy and architecture can be captured using diffusion imaging. Here, we review the trigeminal somatosensory pathways, diffusion-weighted imaging methods, and how these have contributed to our understanding of the neural mechanisms of chronic pain disorders affecting the trigeminal system. We also discuss novel findings indicating the potential for trigeminal nerve diffusion imaging to develop diagnostic and precision medicine biomarkers for trigeminal neuralgia. In sum, diffusion imaging serves both an important basic science purpose in identifying pain mechanisms, but is also a clinically powerful tool that can be used to improve treatment outcomes.

Keywords: Pain, Trigeminal, TMD, Neuralgia, Orofacial pain, Diffusion weighted imaging, DTI, Biomarker

To say that the white matter is but a uniform substance like wax in which there is no hidden contrivance would be too low an opinion of nature's finest masterpiece. We are assured that wherever in the body there are fibres, they everywhere adopt a certain arrangement among themselves, created more or less according to the function for which they are intended.

-Steno [translated by Refs. 95,98]

1. Introduction

Some of the most common pain conditions affect the craniofacial region, including acute pain conditions such as toothaches and headaches, to more complex chronic pain conditions such as trigeminal neuralgia (TN) and temporomandibular disorders (TMD). Some of these chronic pain disorders have clear peripheral etiologies (eg, classic TN), whereas others do not have clear peripheral sources of pain (eg, atypical TN[114] and chronic TMD myalgia[47]). In the cases of these idiopathic pain disorders, it is believed that these disorders are centrally mediated, and thus neuroimaging can help shed light on the mechanisms underlying pain. Uniquely, the trigeminal system can be imaged in its entirety—from the trigeminal nerve to the brain—using neuroimaging techniques that can assess white matter structure, ie, diffusion-weighted imaging (DWI).

Here, we review trigeminal neuroanatomy, and DWI acquisition and analysis methods. Next, we review DWI findings in chronic orofacial pain disorders (COFPs), and discuss how these have informed our understanding of the neural mechanisms of these disorders, in particular TN and TMD. Finally, we discuss DWI's potential as a diagnostic and treatment–response biomarker.

2. Trigeminal sensory pathways

The craniofacial region is partially innervated by the trigeminal nerve (CNV). The CNV, the largest cranial nerve, is a mixed nerve: the sensory aspect innervates the skin of the face, oral mucosa, the nasal cavity, paranasal sinuses, cornea, teeth, temporomandibular joint (TMJ), parts of the tongue, facial and masticatory muscles, other smaller muscles, as well as most of the dura mater and the cerebral arteries; and the motor aspect (brachial motor nerves) supply the

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masticatory muscles (the temporalis, the masseter, lateral and medial pterygoids, and the anterior belly of the digastric muscle), as well as the mylohyoid, the *tensor veli palatini,* and the *tensor tympani*. However, the sensory segment is much larger than the motor portion.[92,96,108] The CNV has 3 main branches: the ophthalmic branch (V_1), the maxillary branch (V_2), and the mandibular branch (V_3).

The sensory aspect of the nerve receives input from receptors that encode touch, nociceptive, proprioceptive, and temperature stimuli from the face, facial and masticatory muscles, and the oral cavity.[96] Aδ and C fibres in the orofacial region, especially in the TMJ and muscles of mastication, are very similar to those present in the spinal nociceptive system.[96] There are some notable tissues that are innervated by the CNV, such as the tooth pulp, the cornea, and the dura regions that are only (or predominantly) innervated by nociceptors, but do not have other somatosensory receptors.

The sensory fibres of the 3 branches of the CNV converge at the trigeminal ganglion, where the cell bodies of afferent fibres are located. The trigeminal ganglion is similar to the dorsal root ganglion in the spinal somatosensory system in terms of markers associated with nociception and nociception-related receptors.[1,5,13,60,77] From the ganglion, a single sensory root emerges and enters the central nervous system (CNS) at the level of the pons—the root entry zone (REZ). Primary afferent fibres terminate in the principal sensory nucleus (or main sensory nucleus [MSN]) and the spinal trigeminal nucleus (STN). There is another specialized trigeminal nucleus in the brainstem: the mesencephalic nucleus of the CNV (MeT), but this is outside the scope of this review. Together, the MSN, the STN, and the MeT form the trigeminal brainstem sensory nuclear complex (VBSNC). Unlike the dorsal horn of the spinal cord, the VBSNC is composed of several nuclei with unique cytoarchitectonic and organizational features.[13]

The MSN is similar to the dorsal column (gracile and cuneate) nuclei where large-diameter myelinated primary afferents that encode touch and position information from the body synapse onto second-order fibres. Like these nuclei, the MSN maintains a somatotopic map of the regions from which it receives touch and position information, namely the orofacial region.[48] The second-order fibres from the MSN bifurcate, and a larger branch of these second-order fibres forms the trigeminal lemniscus, which decussates and runs parallel to the medial lemniscus. The medial lemniscus, which carries touch and position from the body, terminates at the ventroposterior lateral nucleus of the thalamus. The trigeminal lemniscus terminates in the ventroposterior medial (VPM) nucleus of the thalamus. The smaller branch ascends ipsilaterally to the ipsilateral VPM.

The STN is a long nucleus that is located between the pons and the upper cervical spinal cord (around C2) and is composed of 3 subnuclei, organized rostrocaudally: oralis, interpolaris, and caudalis (V_o, V_i, and V_c, respectively).[84] V_c is cytoarchitectonically similar to the spinal dorsal horn,[84] and has been termed the medullary dorsal horn.[43] Aβ fibres bifurcate and terminate in the MSN and along the STN, and Aδ and unmyelinated C fibres terminate predominantly in the STN at the level of V_c and to the upper cervical spinal cord dorsal horn. Interestingly, some Aδ primary afferents carrying pain and temperature information synapse onto second-order fibres in V_o and V_i, but this does not occur with C-fibres.[112] There are several somatotopic maps along the VBSNC. Specifically, somatotopy is maintained in the dorsoventral plane of each nucleus: the mandibular region is encoded in the dorsal segment, then the maxillary region, and, ventrally, the ophthalmic region. In V_c, the somatotopic organization has been shifted, and has an "onion-skin" arrangement, where oral regions are represented rostrally, and lateral regions of the face are represented more caudally. There is a second somatotopic representation along the mediolateral axis of V_c where the head is inverted.[56,97] Second-order fibres from the STN form the trigeminothalamic tract (TTT) and the trigeminobulbar tracts, which project to the thalamus and the various brainstem nuclei, while maintaining a somatotopic organization.

Nociceptive input from the craniofacial region is transported to the CNS through the CNV. The primary afferents project on the VBSNC. Second-order neurons mostly decussate (ie, cross the midline) and form 2 pathways: the trigeminal lemniscus (also called the ventral TTT) and the dorsal TTT. The contralateral dorsal TTT comprises subnuclear projections, primarily from V_c. Notably, and unique to the trigeminal system, only about 80% of tracts cross the midline, and 20% do not decussate, and ascend ipsilaterally.[51,81] As a result, there is bilateral cortical representation of the orofacial region.[96] The ascending TTT projects to several thalamic nuclei, including the ventroposterior medial (VPM), mediodorsal ventral caudal (MDvc), intralaminar (ILN), and ventroposterior inferior and ventromedial posterior (VMpo) thalamus.[81] Third-order neurons from the various thalamic nuclei project to cortical regions, forming the thalamocortical tracts. For instance, tracts from VPM project to primary and secondary somatosensory cortices (S1 and S2, respectively).[81] These tracts ascend to these cortical targets through the corona radiata, through the posterior limb of the internal capsule.[23] The mediodorsal ventral caudal thalamus projects to the cingulate cortex and the insular cortex through the anterior corona radiata, which course through the anterior limb of the internal capsule (aIC).[23] Furthermore, animal studies have demonstrated that the trigeminobulbar tracts project to supraspinal regions through the hypothalamus.[28] Therefore, it is likely that these fibres provide input to limbic circuits of the brain, which include the hippocampus, the amygdala, the hypothalamus, the parahippocampal and entorhinal cortices, the mammillary bodies, the anterior thalamic nucleus, the cingulate gyrus, and the insula, among other cortical and subcortical regions.[68]

There are key white matter fibre bundles that connect these brain regions, and that are implicated in emotional processing: the fornix, the mammillothalamic tract, anterior thalamic projections, the cingulum bundle, and the uncinate fasciculus, among others (**Fig. 1**; for a comprehensive review, see Ref. 17). The fornix connects the hippocampus with the mammillary bodies, the hypothalamus, the anterior thalamic nuclei, and has interhemispheric connections through the hippocampal commissure.[81] The mammillothalamic tract (also known as the bundle of Vicq d'Azyr) comprises 2 short bundles, one that projects to anterior thalamic nuclei, and another—the mammillotegmental tract—that projects ventrally to tegmental nuclei, including the hypothalamus and midbrain nuclei. The anterior thalamic projections form part of the anterior internal capsule and project to the anterior cingulate gyrus and the orbitofrontal cortex. The cingulum bundle comprises several tracts connecting the cingulate cortex to the rest of the brain. The longest tracts project from the medial temporal lobe (the hippocampus, parahippocampal gyrus, and amygdala) to the subgenual cingulate cortex. Other tracts connect the cingulate cortex to adjacent cortices. Finally, the uncinate fasciculus connects the frontal polar, orbitofrontal, cingulate, and insular cortices to temporal lobar regions, including the hippocampus, parahippocampal gyrus, and amygdala.[16] Together, these tracts provide the structural basis for the functional limbic network.[90]

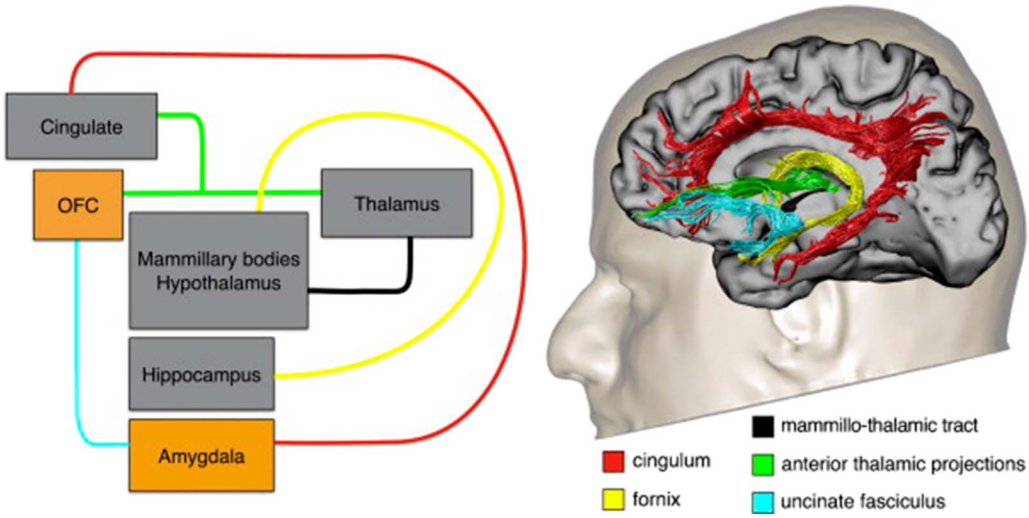

Figure 1. Diagrammatic representation of the limbic system and tractography reconstruction of its main pathways. The colours in both figures correspond to the tracts in the legend. Reproduced with permission from Ref. 17.

3. White matter analysis

The study of white matter neural pathways is called brain *hodology*, and comes from the Greek *hodos*, which means path. Brain hodology in humans has mainly been on postmortem studies of white matter, which date back to antiquity.

The advents of DWI and diffusion tensor imaging (DTI) have provided a method to essentially perform in vivo dissections of the white matter in humans,[7] and to elucidate abnormal white matter structure related to clinical correlates in disorders, such as chronic pain. Furthermore, these methods can also be used to examine peripheral and cranial nerves,[54] such as the CNVs.[65]

4. What is diffusion tensor imaging?

Diffusion-weighted imaging is an MR modality that is sensitive to the diffusion of water molecules.[9] Diffusion-weighted imaging's ability to discern microstructural features of a tissue is based on the notion that water molecules sample the microscopic environment at a very high resolution (much higher than the average magnetic resonance imaging [MRI] resolution at the same field strength), roughly 10 μm per 50 ms.[64] This sampling includes collisions, interactions, and crossing of water molecules with cell membranes, fibres, and other macrostructural features, such as macromolecules. A DW image provides a summary of the bulk motion of a diffusion molecule within a voxel (a 3D pixel), which can reveal structural and geometric organization of a tissue.[7,63]

The molecule of choice in human DWI is the water molecule because 90% of the protons in the human body are located in water molecules. Diffusion occurs in all 3 dimensions of space and, when unhindered, will diffuse equally in all directions (the expected vector sum of displacement is zero), a process known as isotropic diffusion. When diffusion is hindered, eg, by a tissue, we observe anisotropic diffusion. Anisotropic diffusion of water has been observed in muscles, the spinal cord, and the cerebral white matter[64]—tissues that are known to have compartments.

Anisotropic diffusion in neural tissues has generated much interest in understanding the connectional anatomy of the brain. Specifically, water molecules within or between white matter tracts have anisotropic diffusion because the bulk diffusion is parallel to the main axis of the fibre tract. This anisotropy comes from the geometrical structure of the axon—it is tubular in shape, and many axons form a fibre tract. Specifically, the diffusion of water is restricted by cellular barriers, such as myelin, cell membranes, and macromolecules (such as microtubules and neurofilaments), and the molecules tend to diffuse along the primary axis of the tract, whereas diffusion perpendicular to this axis is impeded. Changes in the cerebral vasculature and glia may also contribute to diffusivity changes. Magnetic resonance imaging acquisition parameters can be adjusted to acquire images that provide information about the diffusion of water, and thus, the connectivity, integrity, and orientation of white matter in the brain.

Diffusion tensor imaging fits a tensor model to DWI data (for a comprehensive review of the tensor model, see Refs. 7,8). Briefly, this model assumes that white matter tracts can be fit with an ellipsoid model, (**Fig. 2**), where the 3 main axes of diffusion are modeled. These measures can be used to derive 4 useful metrics that can be used to evaluate tissue in the nervous system: mean diffusivity (MD), fractional anisotropy (FA), radial diffusivity (RD), and axial diffusivity (AD) (**Fig. 2**). In DTI analysis, FA is the most commonly used measure because it is scaled between 0 and 1, where 0 represents complete isotropic diffusion and 1 represents complete anisotropic diffusion. Assuming that these measures represent white matter integrity along a tract,[115], then white matter integrity within a population or between populations can be evaluated. Furthermore, by combining FA and AD, we can determine the orientation of white matter tracts at each voxel, allowing for 3-dimensional reconstruction of the fibre tracts, ie, tractography.

4.1. Tractography: mapping brain white matter tracts

Another method to evaluate white matter in the brain with DTI is tractography. In general, this method allows us to perform in vivo "dissections" of white matter tracts (ie, visualize the tract), and delineate the anatomical connectivity of cranial nerves and the brain. Notably, the CNV was first mapped out using tractography by Upadhyay et al.,[107] where the authors could delineate the 3 branches of the CNV, the ganglion, and the nerve trunk projecting to the brainstem. They next segmented the brainstem trigeminal somatosensory pathways using tractography. This study was a proof of principle in the power of tractography in delineating trigeminal anatomy and architectural features at higher resolution than ever before.

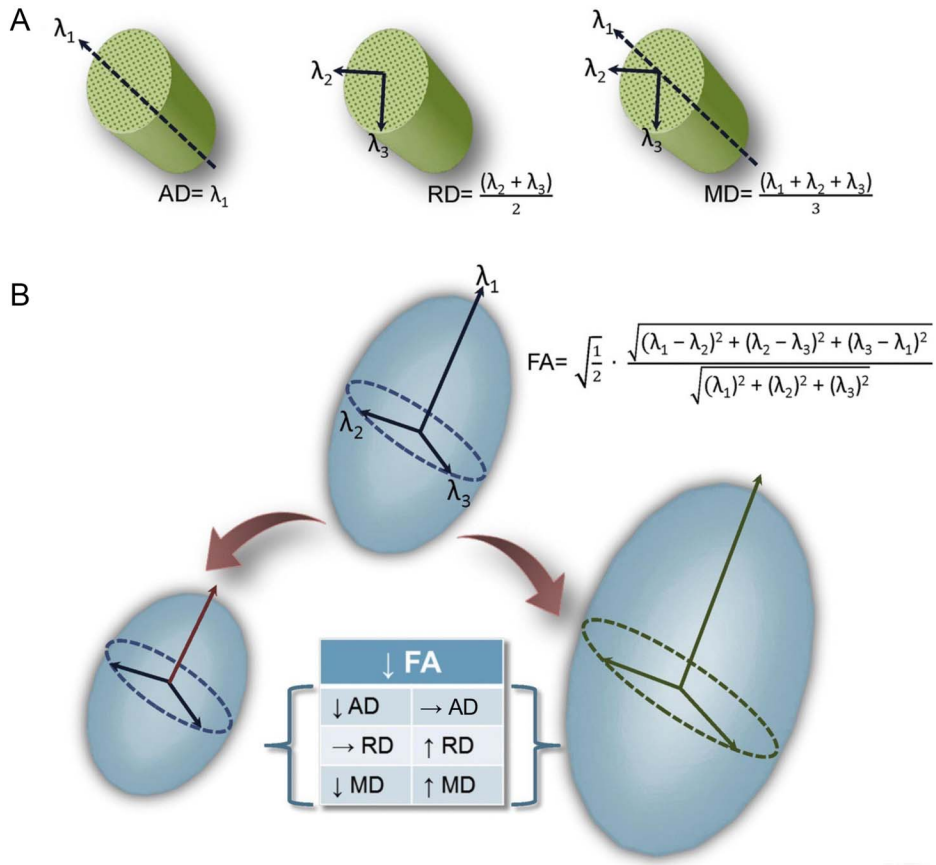

Figure 2. Schematic representation of diffusion tensor imaging (DTI)-derived metrics and tensor changes that can occur with lower FA. Four DTI-derived metrics derived from the eigenvalues of the tensor model were examined. Schematic representations of how these metrics were calculated and their formulas are shown in panel (A), with AD being diffusion along the length of the axon ([lambda]1) (left), RD being diffusion perpendicular to the length of the axon (average of [lambda]2 and [lambda]3) (center), and MD being the magnitude of diffusion regardless of direction (average of [lambda]1, [lambda]2, and [lambda]3) (right). (B) The tensor model and the formula for FA (top). Also illustrated are 2 scenarios where FA has decreased, but the shape of the tensors are different due to differences in the other 3 DTI-derived metrics (shown in chart). The first scenario is when AD and MD decrease, but RD remains stable (bottom left); and the second is when RD and MD increase, but AD remains stable (bottom right). AD, axial diffusivity; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity. Reproduced with permission from Ref. 25.

The concept of tractography is based on the signal information collected in a DWI scan and the tensor model used in DTI. Briefly, when we apply the tensor model to a DWI data set, we obtain eigenvalues and eigenvectors for each voxel in the image, which represent the orientation and magnitude of water diffusion within the voxel. When diffusion is restricted, by a biological tissue for instance, then the diffusion is anisotropic. We can use the orientation information within each voxel to reconstruct white matter pathways in the brain, called tractography. The fundamental assumption of white matter tractography is that the primary eigenvector (v_1) is parallel to the primary axis of the white matter tract. It is, however, noteworthy that this assumption is often violated in regions of complex white matter (eg, crossing fibres and fibre dispersions). More complex algorithms have been developed to address these issues and to increase the sensitivity and reliability of DTI. Two of the most commonly used methods, deterministic and probabilistic tractography, are described in further detail below. Although there are other, more complex methods being developed, these are outside the scope of this review.

4.2. Streamline (deterministic) tractography

Deterministic tractography algorithms use the orientation information within voxels to track the path of white matter tracts.[2] The resultant image is a tractogram, which is based on the primary (or major) eigenvector within each voxel. The tractogram is initiated from a seed location (a single voxel or a group of voxels of interest). Because the algorithms use a threshold for FA to distinguish between gray matter and white matter, the seed is usually located within the white matter.[2] If the seed was in the gray matter, or in a voxel with FA below the threshold, then tracts could not be generated. Several restraints can be placed on the algorithm to remove spurious connections and to ensure that the tracts are consistent with the predicted pattern of connectivity.[2]

There are several deterministic tractography algorithms that can produce tractograms. Most of these methods use a streamline approach. This approach calculates the stepwise progression of the tract (or the path), beginning from a seed. The progression of the path is based on the direction of the primary eigenvector. The termination of a tract is based on an arbitrarily selected parameter.[59] For instance, an FA value is selected where the primary eigenvalue is well defined, eg, FA $\geq$ 0.15. Another parameter used to terminate a tract is the curvature angle, which is also arbitrarily chosen. The specific aspects of deterministic algorithms are outside the scope of this review, but for a detailed review of these methods, see Ref. 2.

There are both advantages and disadvantages to deterministic tractography. The most significant advantage is that fewer

diffusion-encoding directions are required to produce tractograms, compared with other algorithms, such as probabilistic tractography, or diffusion spectrum imaging (see below). Furthermore, the analysis is not as computationally intensive as some of the other methods (including probabilistic tractography). However, deterministic tractography can only be used as a qualitative means of visualizing tracts in the brain, although the images can serve as masks to perform quantitative analysis, eg, evaluate measures of white matter microstructure, such as FA. The images produced with deterministic tractography are visually appealing, but this can instill a false sense that the visualized tracts are more precisely accurate than they actually are, highlighting the importance of anatomical familiarity. There are many potential sources of errors in deterministic tractography: DTI is very sensitive to motion and other sources of noise. Even small perturbations in the image can lead to tracking spurious connections. The largest source of error in tractography is tract dispersion, or the variance of trajectories, which increases from the seed because there is an increasing number of potential paths.[2] Another source of error comes from tract deviation, or errors in tract position. These are related to the step size, especially in regions where the curvature of the tract is high. In general, a larger step size will increase the chance of error.[62] Another source of error in deterministic tractography is that of crossing fibres, as discussed above. Crossing fibres can lead to false-negatives in the tractograms.[15] For instance, most deterministic algorithms are not able to resolve tracts within the CST emerging from the lateral motor cortex and projecting to the pyramids in the brainstem.[2] This is the result of the crossing fibres in the centrum semiovale, which contains association fibres, callosal fibres, and short U-shaped fibres, which project in different directions. As a result of the multiple fibre directions in voxels within this region, the primary eigenvalue is diminished, and the tractography algorithms fail to track the rest of the tract. Therefore, experiments that seek to resolve tracts using deterministic algorithms should have strong hypotheses and predictions based on known anatomical pathways, from animal studies and human postmortem studies.

4.3. Probabilistic tractography

Probabilistic (or stochastic) tractography is a method that attempts to address some of the limitations of deterministic tractography. Specifically, probabilistic tractography acknowledges that there are inherent errors that occur in tract-tracing algorithms, and accounts for this variability. Therefore, the inherent variability in the data is included in probability estimates of a tract.[86] To do so, algorithms use probability density functions (PDF), which consider the expected distribution of the possible fibre orientations, at the level of the voxel.[89] The PDF are used instead of discrete measures of fibre orientation. An advantage of probabilistic tractography, compared with deterministic tractography, is that the PDF allow tractography to continue in a region where deterministic tractography would normally stop. Another advantage of probabilistic tractography is that we can quantitatively compare the connectivity of tracts based on the probability of connections.

The PDF is composed of 3 orientation density functions (ODFs): the diffusion ODF (dODF), the fibre ODF (fODF), and the uncertainty ODF (uODF).[10] The dODF and the fODF are biophysical properties of the tissue that is being measured. The fODF describes the proportion of the fibres in each direction. For instance, as in the example above, if we have 2 orthogonal fibres in a voxel, the resultant fODF will appear as a cross, in the direction of the fibres.[102] The fODF is useful in that it contains a proportion, which can be used to estimate the connectivity of a tract connecting A to B, providing a quantitative method that is both useful and biophysically meaningful.[10] However, DWI measures the diffusion of water within each voxel in the brain, and not the proportion of fibres, and so the measure we obtain is dODF, a measure of the orientation of diffusion within a voxel.[105] If water molecules diffused exactly along the axis of a tract, then the dODF would be exactly equal to the fODF. However, in reality, water molecules diffuse primarily along the axis of the tract, but there is also diffusion in other directions. Therefore, the dODF is necessarily broader than the fODF. Although the dODF and fODF are properties of the tissue which can be measured, the uODF is a measure of the error that can be predicted, or as Behrens puts it: "it (uODF) is a function that describes our *belief*".[10] Specifically, the uODF represents the uncertainty that is included in the data because of the noise inherent to it.

These variables have very important implications in tractography. It can no longer be assumed that the primary eigenvector is the path of the tract because there is an infinite number of paths within each voxel, each associated to a probability of being the correct orientation. To calculate the probability of connection of 2 regions, every possible path and its probability must be considered, and then the probabilities associated with each path connecting the 2 regions is summed.[12] Rather than attempt to solve this equation, more reasonable approaches have been developed that allow us to sample the probability distributions.[12,45,59,87–89] Briefly, these algorithms sample many paths from a seed at subvoxel to subvoxel steps (or for lower resolution, or larger step size, at voxel to voxel steps). Each step considers the distribution of possibilities, resulting in many possible paths, each with a probability. These results are summarized within the voxel as a proportion of the number of samples that pass through the voxel.[59] Although deterministic algorithms rely on arbitrary FA values or curvature angles to stop tractography, probabilistic algorithms do not rely on these parameters for termination. In contrast to deterministic tractography, this allows the algorithm to propagate even when a seed is in the gray matter. The criterion for termination of a tract is usually the angular deviation between successive steps (*c.f.* FA values in deterministic tractography), which prevents a tract from looping back onto itself, or if a streamline enters the same voxel more than once.[12,59] The specific differences between probabilistic tractography algorithms are outside the scope of this review. For a comprehensive review, see Refs. 10,89.

The results of probabilistic tractography should be interpreted with care. These results have a very specific meaning: a calculated probability is the probability that a connection from a given seed to a target through the diffusion data exists within the context of the model for the diffusion signal and the model of connections. These tracts do not provide anatomical evidence for the existence of a path within the brain. However, if a hypothesis is based on known anatomical pathways from postmortem studies in humans (and homologues from tracing studies in monkeys), then we can infer that the tract we have identified is "real." Otherwise, we must interpret the presence or absence of a tract with caution.

Crossing fibres are still a consideration in probabilistic tractography; in fact, it is a shortcoming of the tensor model. Some groups have developed alternate, nonparametric models to replace the tensor model, which can better resolve crossing fibres, such as diffusion spectrum imaging,[104,109] q-ball imaging,[103,105] spherical deconvolution,[102] persistent angular structure MRI,[58] and diffusion orientation transform.[85] However, these are outside the scope of this review (see Ref. 3 for

a comprehensive review). Some groups have tried to resolve crossing fibres within the tensor model. The most common approach is to model more than one tensor per voxel: the multitensor model.[11] The number of "fibres" that can be modeled per voxel depends on the signal-to-noise ratio and the number of diffusion-encoding directions.

In sum, there are several advantages and limitations to tractography. Nonetheless, when care is taken to acquire, check, and denoise the data, and seeds are selected carefully, based on known landmarks, and results correspond to known tracts within the brain, then tractography can be a very useful and informative tool. In addition, tractography can be qualitative (visualizing tracts) and quantitative (calculating the probability of a connection). The latter allows for group comparisons of connectional anatomy.

5. White matter abnormalities in chronic pain

There has been an increasing number of studies investigating CNV and brain white matter abnormalities in COFPs disorders. Of these, 2 have used VBM to evaluate white matter volume from T1-weighted images, and 4 have used DTI to delineate abnormalities in white matter microstructure, or gray matter microstructure. The 2 studies that have used DTI to investigate the gray matter[39,72] and the white matter VBM studies[42,71] are omitted from this review because of flaws in the experimental designs and methodologies. The other 3 that did identify abnormalities are described below.

The first study to test for abnormalities in white matter microstructure associated with chronic pain, by DaSilva et al.,[21] reported decreased FA along tracts between the brainstem and the thalamus and the thalamus and S1 cortex of patients with migraine. The authors concluded that there are abnormalities along the ascending nociceptive pathways in patients with migraine.

In addition to the aforementioned studies that have investigated white matter abnormalities in the brains of patients with chronic pain, 2 DTI studies have investigated abnormalities along the CNV in patients with TN. One study by Fujiwara et al.[40] did not find any significant abnormalities in the FA, the MD, or the cross-sectional area of the patients' CNV. This study reported no significant group differences in the ratio of FA of the affected to the unaffected nerve. However, the study reported significantly more variance in the FA values of patients' CNV, compared with controls, and this value was positively correlated with the affected:unaffected ratio of the cross-sectional area of the CNV. The other study, by Leal et al.,[65] reported that the affected CNV had significantly increased MD, and decreased FA, nerve volume, and cross-sectional area. Furthermore, the decrease in FA was positively correlated with the decrease in volume and cross-sectional area of the CNV. Decreased FA and increased MD indicate that there is increased diffusion, or less organization. Therefore, it is possible that the CNV has a larger diameter, is inflamed, or damaged. However, the interpretation is limited because other measures of white matter integrity (RD and λ_1) were not provided. These studies indicate that there are structural abnormalities along the CNV in patients with TN, and suggest that DTI can be used to investigate the CNV for abnormalities in TMD.

6. White matter abnormalities in craniofacial pain disorders

6.1. Trigeminal neuralgia

The unique entity of TN has been of longstanding interest to clinicians and scientists. There have been limited advances to the study of TN beyond clinical measures alone. Evaluation of TN using conventional MR imaging takes place routinely in clinical practice. The most likely anatomical correlate with TN pain is the identification of contact, compression, or distortion of the nerve REZ or proximal segments of the cisternal CNV by an arterial vessel loop, giving rise to the so called concept of neurovascular compression (NVC). Based on this concept, surgical treatment of TN frequently consists of microvascular decompression, a procedure pioneered by Jannetta, and currently one of the mainstays of surgical treatment of TN.[57] Despite being the key to surgical intervention, NVC has been of limited use in fully explaining the pain in TN[35] because approximately 40% of patients without significant NVC present with very classic TN symptoms and, likewise, NVC can be identified in about 17% of patients without pain, who have imaging for other reasons.[78] At the same time, there is MR evidence of greater bilateral NVC in patients with TN, compared to patients without TN. The significance of bilateral NVC in the setting of overwhelmingly unilateral pain is as yet not clear.

Despite the limitations in our clinical understanding of NVC in TN, advances in imaging and specifically DTI have helped shed some light on these important questions. The premise of the use of DTI is the use of an imaging technique to derive information from changes in the nerve as a consequence of NVC. Although vascular compression is the finding most directly related to TN, pain must be a result of the effect of nerve compression.

The earliest studies on the assessment of CNV microstructure focused on the question of possible diffusivity changes in the REZ, the segment of the nerve most closely associated with TN and the anatomical region of microvascular decompression. The REZ in patients with TN demonstrating NVC does indeed show decreased FA,[19,52,65,73,74,116] suggesting a greater level of focal disorganization of the white matter. This important finding is impactful in several ways. First, DTI is able to detect changes in very small regions of the white matter and provides metrics from microstructural changes. In addition, the changes in DTI metrics point to the REZ, the site most closely linked clinically to TN. Accordingly, studies have identified a link between CNV abnormalities in TN and pain severity,[70] whereas other studies have not identified such a link.[74] We studied DTI changes in the REZ in the context of assessment of changes in the brain white matter in TN.[25] In addition to the consistent decrease in FA, DTI distinguished bilateral changes in the nerves, with both ipsilateral and contralateral nerves differing from values obtained from healthy controls (**Fig. 3**). The significance of bilateral changes is not understood. Although both conventional MR studies[78] and now multiple DTI studies suggest that there are bilateral CNV changes in TN, the expression of the pain is almost uniformly unilateral. Whether the brain "chooses" a side for the clinical expression of pain, or whether there is a threshold beyond which pain is manifested is not yet clear.

6.1.1. Brain white and gray matter alterations associated with trigeminal neuralgia pain

Diffusion tensor imaging studies of the peripheral white matter can be extended to the study of the brain white matter, to understand the potential impact of chronic pain. Because it is uncommon for patients with TN to have sensory abnormalities, the study of brain white matter allows for a more direct correlation of changes with pain. Previous studies have demonstrated changes in brain WM in the context of direct peripheral nerve injury[99]; however, this makes it difficult to contextualize the changes, whether they are due to the associated sensory abnormalities, and therefore represent an impact on the integrative sensory networks, or whether it is primarily the effect of the resultant neuropathic pain.

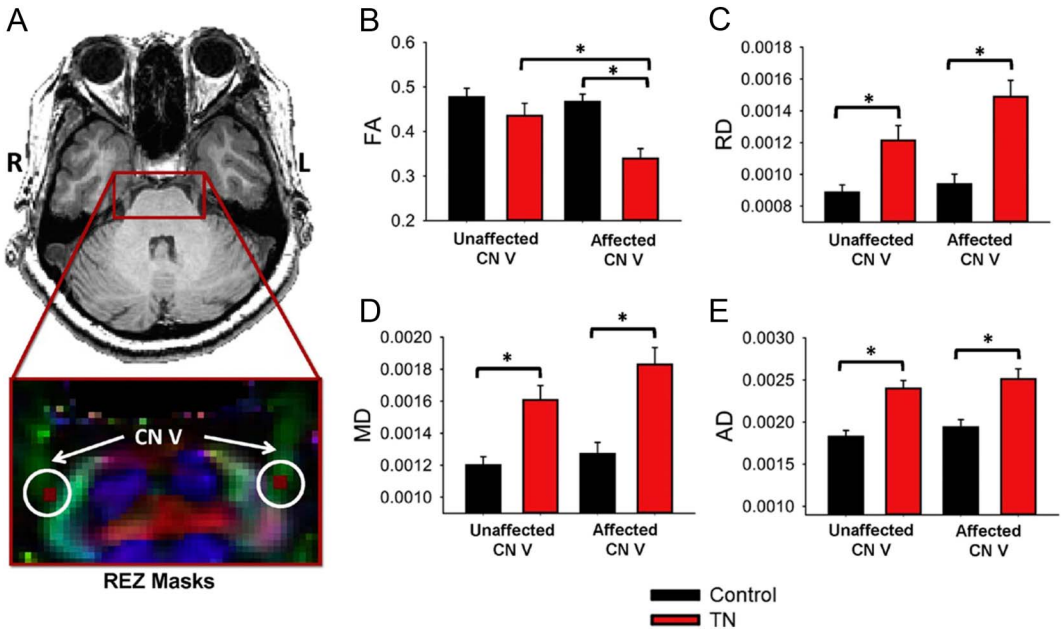

Figure 3. Trigeminal neuralgia is associated with bilateral changes in the root entry zone (REZ), compared with a cohort of healthy controls. Each trigeminal REZ mask is placed at the root of the trigeminal nerve on axial images (panel A), and placement is confirmed on both conventional (top) and colour-by-orientation maps (bottom) views. Panels B–D demonstrate differences between affected and unaffected diffusivities, with * denoting significant differences ($P < 0.05$). (reproduced from Ref. 27 under Creative Commons Attribution License).

Brain white matter changes extend beyond the nerve alone, and important differences between patients with TN and controls have been identified in several regions, including the corpus callosum, cingulum bundle, coronal radiata, and superior longitudinal fasciculus.[26,49,69,113] These abnormalities provide evidence for TN pain signatures in the white matter that connects brain areas responsible for pain integration, cognitive–affective, and motor functions, and highlight also possible compensatory mechanisms for this pain.[25] Some studies have found that these white matter abnormalities are related to various clinical factors, such as pain intensity and/or pain duration.[69] In some cases, these white matter abnormalities are correlated with changes in brain function and gray matter structure.[19,100]

Recent evidence from our group has shown that white matter imaging can serve both as a diagnostic and treatment- response biomarker. First, we have shown a multivariate pattern algorithm trained to differentiate TN and healthy controls based on whole brain white matter connectivity could successfully classify patients and controls with 88% accuracy.[117] Furthermore, in patients who underwent gamma-knife surgery to treat TN, postsurgical microstructural metrics, such as FA, were shown to predict the level of pain relief 6 months after surgery.[101] More specifically, responders had lower FA and achieved at least 75% reduction in pain. Nonresponders did not show the expected decrease in diffusion metrics. More remarkably, we further showed that presurgical CNV diffusion metrics could predict which TN patients would respond to gamma-knife surgery, and those who would be treatment-resistant with an ~84% accuracy.[55] These data indicate that DW imaging of the CNV is a powerful and clinically useful tool to stratify patients into appropriate treatment streams.

6.1.2. Trigeminal neuralgia–related gray matter changes in the brain are dynamic and can be altered as a result of treatment

Although diffusivity studies are important in pointing changes in white matter fibers, gray matter analysis can point to abnormalities related to cortical gray matter (cortical thickness analysis) or subcortical gray (voxel-based morphometry) to determine their correlation with TN pain. Using these techniques, we demonstrated key abnormalities in brain gray matter, in areas such as key anatomical regions that are involved in modulation of pain, both from the sensory–discriminatory pathways as well as cognitive–affective areas.[27] Changes in thickness in at least some of the identified neuroanatomical sites, such as the thalamus, primary motor and S1 cortices as well as orbitofrontal, cingulate gyrus, and insula, have been previously linked to chronic pain conditions (**Fig. 4**).[6,22]

The pattern of changes seen in TN, a unique neuropathic pain condition, seem to differ from more chronic forms of conditions such as back pain.[4,41] The fact that a peripheral event, relating to a segment of a cranial nerve immediately outside the CNS, can result in profound gray and white matter changes points possibly to the role of the CNS in at least contributing to the maintenance of this pain. In the setting of patients who have undergone surgical treatment of TN, a reversal of the thinning of the insula is seen, demonstrating that the gray matter changes are dynamic and associated with pain relief as insula changes are strictly observed in the group with successful pain relief after surgery.[24]

6.1.3. Implications of imaging of trigeminal neuralgia

Of the many types of trigeminal pain, TN is the only one associated with high surgical success.[53] Measures towards a more accurate diagnosis are therefore crucial. Current methods of diagnosis consist in primarily clinical symptoms, accompanied typically by evidence of NVC—however, in the setting of patients with some atypical symptoms, or unclear degree of compression, the decision of whether surgery should be offered becomes difficult. It is hoped that these microstructural imaging characteristics will in fact result in greater ability to assess clinical scenarios, both as a guide for surgical decision-making and potentially as a means to assess nonresponder status.

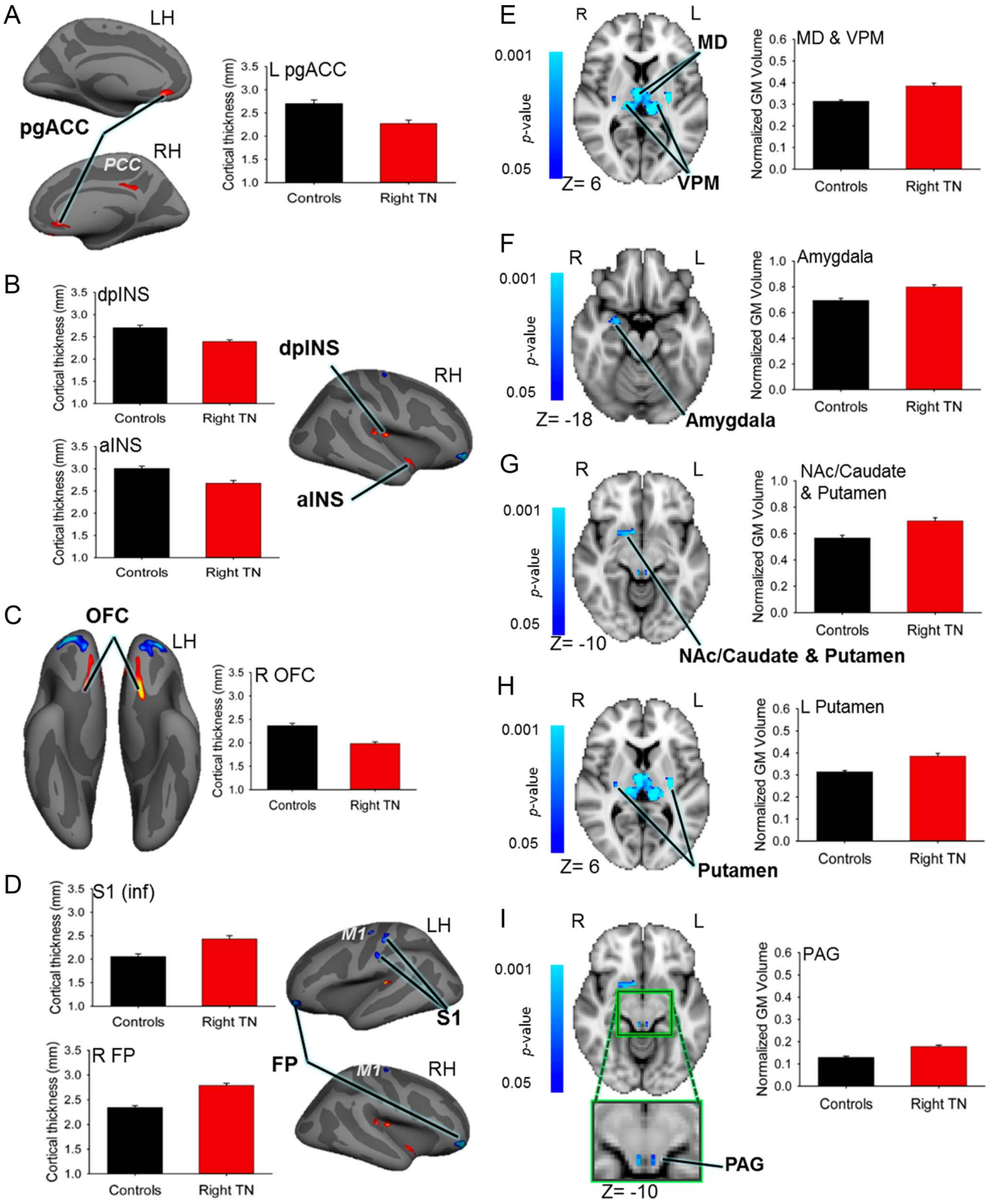

Figure 4. Cortical (A–D) and subcortical (E–I) gray matter changes in trigeminal neuralgia (reproduced with permission from Ref. 17).

6.2. Temporomandibular disorders

Temporomandibular disorders comprise clinical problems involving the structures of and around the TMJ, the masticatory musculature, or both.[50,82] Temporomandibular disorders represent the most common orofacial chronic pain disorder,[32] and are primarily characterized by spontaneous pain, or pain associated with jaw function, which can affect mandibular range of motion and produce TMJ sounds during jaw function. Pain

from TMD can arise from the muscles of mastication, the TMJ, or both, and, in general, when combined (ie, muscular and TMJ pain), the chief complaint tends to be muscular in nature.[46] Temporomandibular disorders are estimated to affect between 10% and 20% of the population.[29,66,67,75] Temporomandibular disorders is 1.5 to 9 times more prevalent in women,[14,20,31,32,37,91] and a nationwide epidemiological study in the United States reported that 84% of persons with TMD were women.[31]

In some cases, there is no clear aetiological evidence for TMD pain, and the pain is considered idiopathic.[30,33,34,83] In this group of patients, it has been suggested that abnormal function in the CNS may initiate or maintain TMD pain.[94] One line of evidence for abnormal CNS function is that TMD symptomatology, including persistent pain, allodynia, and hyperalgesia, occurs not only in the orofacial region, but also in other body sites.[36,38,44,76,93,106] These centrally mediated processes provide further evidence for CNS dysfunction in TMD and provide evidence for the involvement of ascending nociceptive pathways and/or descending pain-modulatory pathways.[61]

In line with this hypothesis, we found structural brain abnormalities along the entire CNV nociceptive pathways. First, we found that TMD patients had lower white matter integrity at the REZ of the CNVs (**Fig. 5**), and this abnormality was related to the duration of TMD symptomatology, indicating that the abnormalities were TMD pain-driven.[80] Similarly, a finding by Wilcox et al.[111] found that the trigeminal nerve, and brainstem white matter tracts—believed to be the spinal trigeminal tract, and the TTT—had lower FA than healthy controls. We further found widespread reduced white matter integrity in the brain, including in the brainstem, and thalamocortical tracts projecting to somatomotor cortices.[80] Combined with our gray matter findings,[79] where we found a correlation between thalamic gray matter and pain duration, and thicker S1 cortex in TMD, these data suggest that there is increased nociceptive drive to the CNS. This would suggest that there must be a peripheral source for idiopathic muscular TMD pain. Future studies should investigate potential sources for this nociceptive barrage, including the muscles of mastication.

In addition to identifying a potential mechanism for nociceptive input in idiopathic TMD, DTI found a novel set of connectional abnormalities in TMD (**Fig. 6**). Specifically, we found reduced white matter connectivity in the corpus callosum, and performed tractography to better characterize the finding. We found that patients with TMD had reduced connectivity to the dorsolateral prefrontal cortex (dlPFC)—a key brain region in top–down pain

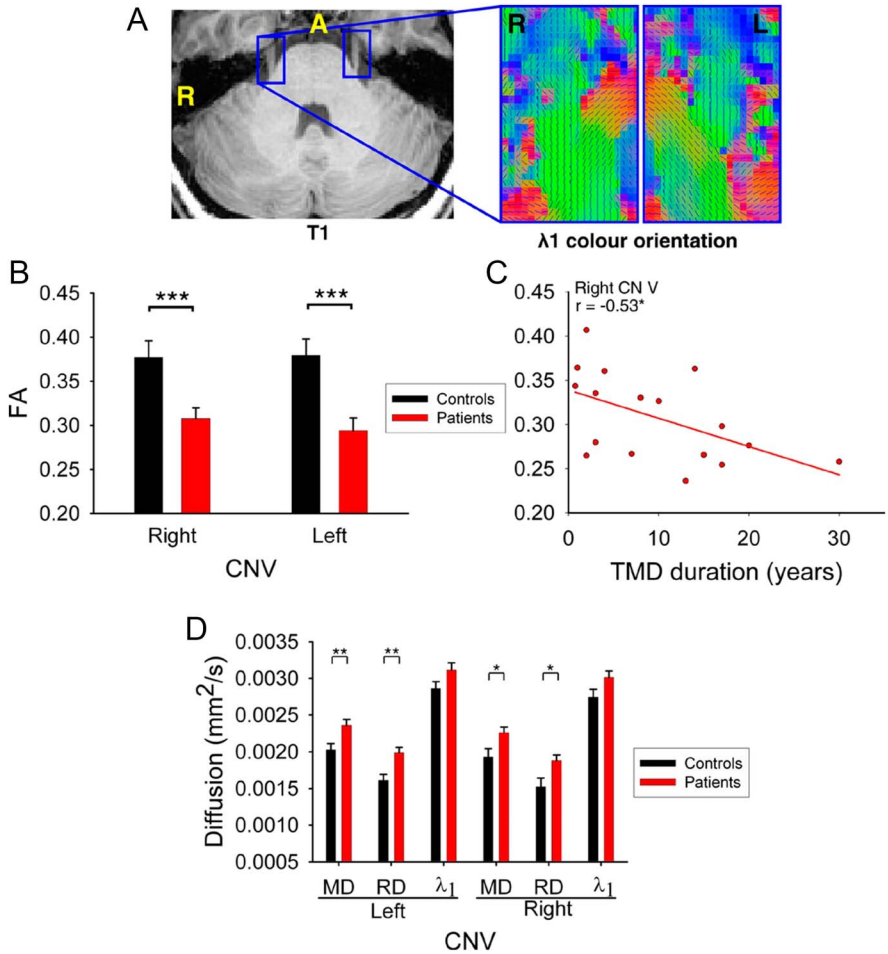

Figure 5. Trigeminal nerve fractional anisotropy abnormalities in TMD. (A) The trigeminal nerve roots (within the blue boxes) at the pontine level are shown on an axial slice from a high-resolution T1-weighted MRI scan. The magnified view of the right nerve is from a diffusion-weighted scan. The direction of the primary vector of the tensor model (λ1) within each voxel is color-coded (green—anterior–posterior, red—left–right, blue—in the inferior–superior plane) and the primary vector shown within each voxel. (B) Patients with TMD have lower fractional anisotropy in bilateral trigeminal nerves, compared to controls. (C) Fractional anisotropy is negatively correlated with TMD duration. (D) Group differences in trigeminal nerve mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (λ1). *$P < 0.05$; **$P < 0.01$; ***$P < 0.005$. CNV, trigeminal nerve; TMD, temporomandibular disorders. Reproduced from Ref. 80 with permission.

modulation, and the increased connectivity to the frontal polar cortex (FPC), which is involved in executive control and multitasking. The abnormalities in the dlPFC provide neuroanatomical support for the hypothesis that dysfunctional central pain modulatory circuits contribute to TMD pain. The FPC finding converges with structural gray matter abnormalities[79] and functional MRI findings[110] in the same TMD cohort, where there was increased FPC gray matter and FPC function during a cognitive task, respectively. These data suggest that pain may pose a cognitive load, in line with the cognitive branching model.[18]

In sum, white matter imaging, in conjunction with functional MRI and structural gray matter imaging, has provided support for various idiopathic muscular TMD pain. These data have laid the groundwork for future studies to investigate the contribution of masticatory muscles to TMD, and the cognitive load of pain.

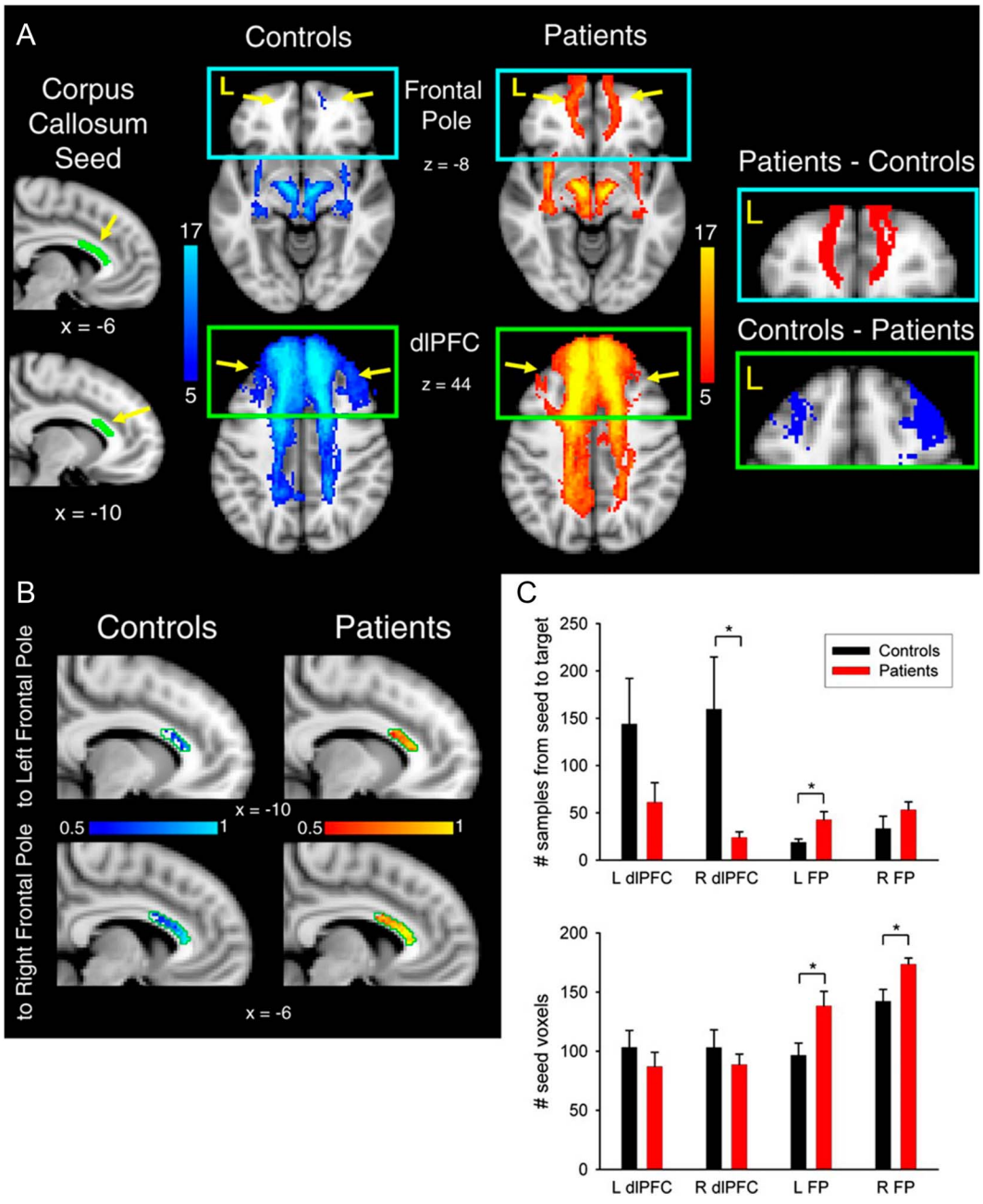

Figure 6. Abnormal white matter connectivity in TMD. Qualitative analysis of probabilistic tractography of the cluster-mass corrected ($t > 2.3$, $P < 0.05$) cluster in the left corpus callosum revealed that (A) this abnormal white matter region has different connections (yellow arrowhead) in TMD and controls. The right panel shows a subtraction map that reveals that patients have denser connections between the corpus callosum seed and the frontal pole (blue box), and sparser connections to the dorsolateral prefrontal cortex (dlPFC; green box). The colour bar indicates the number of subjects (between 5 and 17) contributing to the cluster at each voxel (controls are in blue–light blue, and patients are in red–yellow). Quantitative tractography (B and C) revealed that more voxels from the seed region (in green) in the corpus callosum project to the frontal pole in the patients, compared to controls. The colour bar in (B) represents the proportion of subjects with projections to the frontal pole in each voxel (controls are in blue–light blue, and patients are in red–yellow). (C) Also, controls have a higher connection probability between the corpus callosum and the right dlPFC, whereas patients have a higher probability of connection between the corpus callosum and the left frontal pole. Graphs show mean number of samples (±SE) that reach the target in each group (top panel), and the mean number of voxels (±SE) in the seed mask that have samples that project to the target masks. *$P < 0.05$. Reproduced from Ref. 80 with permission. TMD, temporomandibular disorders.

7. Conclusion

Chronic pain disorders affecting the craniofacial region are unique in that both the peripheral nerves, ie, CNV, and the CNS can be imaged simultaneously. This provides an opportunity to elucidate the neural mechanisms of COFPs. Indeed, diffusion imaging of white matter structure has provided novel mechanistic insight for TN and TMD, and has led to novel therapeutic targets. In addition, CNV diffusion metrics could serve as diagnostic and patient stratification biomarkers in TN.

Disclosures

The authors have no conflict of interest to declare.

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