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Hippocampus diffusivity abnormalities in classical trigeminal neuralgia

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Abstract

Introduction: Patients with chronic pain frequently report cognitive symptoms that affect memory and attention, which are functions attributed to the hippocampus. Trigeminal neuralgia (TN) is a chronic neuropathic pain disorder characterized by paroxysmal attacks of unilateral orofacial pain. Given the stereotypical nature of TN pain and lack of negative symptoms including sensory loss, TN provides a unique model to investigate the hippocampal implications of chronic pain. Recent evidence demonstrated that TN is associated with macrostructural hippocampal abnormalities indicated by reduced subfield volumes; however, there is a paucity in our understanding of hippocampal microstructural abnormalities associated with TN.

Objectives: To explore diffusivity metrics within the hippocampus, along with its functional and structural subfields, in patients with TN.

Methods: To examine hippocampal microstructure, we utilized diffusion tensor imaging in 31 patients with TN and 21 controls. T1-weighted magnetic resonance images were segmented into hippocampal subfields and registered into diffusion-weighted imaging space. Fractional anisotropy (FA) and mean diffusivity were extracted for hippocampal subfields and longitudinal axis segmentations.

Results: Patients with TN demonstrated reduced FA in bilateral whole hippocampi and hippocampal body and contralateral subregions CA2/3 and CA4, indicating microstructural hippocampal abnormalities. Notably, patients with TN showed significant correlation between age and hippocampal FA, while controls did not exhibit this correlation. These effects were driven chiefly by female patients with TN.

Conclusion: This study demonstrates that TN is associated with microstructural hippocampal abnormalities, which may precede and potentially be temporally linked to volumetric hippocampal alterations demonstrated previously. These findings provide further evidence for the role of the hippocampus in chronic pain and suggest the potential for targeted interventions to mitigate cognitive symptoms in patients with chronic pain.

Keywords: Trigeminal neuralgia, Hippocampus, Diffusion tensor imaging, Neuropathic pain, Sex differences

1. Introduction

Chronic pain is a prevalent, debilitating, and complex disorder with widespread health implications.[19] Patients with chronic pain frequently report a decline in cognition and memory, functions attributed to the hippocampus.[14,27,66,90] There is mounting evidence that chronic neuropathic pain adversely impacts the hippocampus and its histologically distinct subfields *Cornu Ammonis* (CA1-CA4), subiculum, and dentate gyrus (DG) and functionally distinct subregions head, body, and tail.[8,39,50,51,88,92]

Structural magnetic resonance imaging (MRI) provides macroscopic assessments of hippocampal structures. Hippocampal subfield volumes are reduced in different chronic pain

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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conditions.[3–5,73,92] Similarly, hippocampal neurogenesis is blunted in chronic pain,[5,28,41] which may contribute to abnormal hippocampal structure and function seen in chronic pain.[28,71,80] However, there is a paucity in our understanding of the relationship between abnormal molecular environment and macrostructural change.

Diffusion tensor imaging (DTI) is an MRI technique that utilizes localized water molecule diffusion to assess tissue microstructure.[35] Although DTI has been frequently utilized to assess white matter structures, an emerging application of DTI involves assessment of gray matter microstructure.[61,77,97] Diffusion tensor imaging–derived diffusivity metrics have important physiological correlates. For instance, mean diffusivity (MD) quantifies overall water molecule diffusion and is related to local water content, neuroinflammation, and tissue cytoarchitecture.[10,17,24,58,59] Comparatively, fractional anisotropy (FA) quantifies direction-dependent diffusion and may be reduced in the hippocampus due to multiple fibers with differing directionality.[17,24,59,94] Abnormal hippocampal diffusion has been studied in a variety of conditions, including epilepsy,[52,101] multiple sclerosis,[16] and Alzheimer disease.[31,65] In addition, hippocampal diffusivity metrics are sensitive to physiologic aging and may provide a more sensitive assessment of mild cognitive impairment (MCI) than volumetric analyses.[2,24,70,76,87] These studies highlight the capability of DTI to detect microstructural hippocampal changes that precede significant volume loss. However, no prior study has reported the impact of chronic pain on hippocampal microstructure.

This study utilizes trigeminal neuralgia (TN) to investigate hippocampal microstructure in chronic pain. Trigeminal neuralgia is one of the most prevalent chronic orofacial neuropathic pain conditions.[42,54,102] Uniquely, TN pain is characterized by stereotypical features, unilateral presentation, and a lack of negative symptoms including sensory loss. We recently reported that patients with TN have a subfield specific reduction in hippocampal volume,[92] mostly driven by female patients.[92] In this study, we utilize TN as a model to assess in vivo hippocampal diffusion to delineate chronic pain-mediated hippocampal microstructural abnormalities.

Specifically, we aim to (1) investigate diffusivity metrics in the hippocampus and its functional and structural subfields in patients with TN, (2) examine the impact of sex on diffusivity metrics in the hippocampi of patients with TN, (3) evaluate the impact of pain duration and severity on patients with TN diffusivity metrics, and (4) assess the association between the age of patients with TN and hippocampal diffusivity metrics. We hypothesize that FA will be reduced in hippocampal subfields of patients with TN, particularly the subfields responsible for neurogenesis. Similarly, we hypothesize that there will be sex-specific abnormalities in hippocampal diffusion consistent with our previous work on TN hippocampal volume. Prolonged pain duration and severity is hypothesized to be associated with abnormal diffusion in patients with TN. Finally, the age of patients with TN is hypothesized to be associated with reduced FA.

2. Methods

2.1. Ethics

This retrospective study was approved by the University Health Network (UHN) Research Ethics Board. No active participation was required for this retrospective study. Therefore, individual consent to be incorporated within this study was not required. The recruitment of healthy controls and image acquisition protocol was approved by the UHN Research Ethics Board. Individual informed consent was obtained from healthy participants. All MRI scans were completely anonymized before any image and statistical analysis.

2.2. Research subjects

Patients with right-sided TN (R-TN) seen at the Toronto Western Hospital were included in this study, each meeting the following criteria: (1) diagnosis of classical TN according to International Classification of Headache Disorders, third edition criteria,[74] and (2) no surgical interventions before MRI. Patients with neurodegenerative disorders, TN secondary to multiple sclerosis, stroke, other chronic pain disorders, cranial tumors, other neurologic diseases, and history of known psychiatric disorders were excluded from this study. Healthy controls were recruited at Toronto Western Hospital.

2.3. Image acquisition

For all subjects, presurgical high-resolution, T1-weighted fast spoiled gradient-echo (FSPGR) anatomical and diffusion-weighted spin-echo echo planar imaging whole-head MRIs were acquired in the axial plane on a 3 Tesla GE Signa HDx scanner with an 8-channel head coil. The FSPGR MRI acquisition parameters were acquisition voxel size = 0.94 mm × 0.94 mm × 1 mm, 256 × 256 matrix (controls) and 234 × 234 matrix (patients), echo time (TE) = 5.2 milliseconds, repetition time (TR) = 12.2 milliseconds, flip angle = 20°, and field of view (FOV) = 240 × 240 mm^2 (controls) and 220 × 220 mm^2 (patients). The diffusion-weighted MRI acquisition parameters were 60 diffusion-encoding directions with b = 1000 s/mm^2, 1 volume of b = 0 s/mm^2 (b_0) 1 excitation, ASSET, acquisition voxel size = 0.94 mm × 0.94 mm × 3 mm, 128 × 128 matrix, TR/TE = 17,000/88.8 milliseconds (controls) and 12,000/88.2 milliseconds (patients), flip angle = 90°, and FOV = 240 × 240 mm^2. Voxel sixes are designed to have high levels of discrimination of the lateral/medial borders in the axial plane.

2.4. Magnetic resonance imaging processing

Diffusion-weighted MRIs underwent eddy current and motion artifact correction using affine transformation with individual subjects' gradient images to b_0 image utilizing FMRIB Software Library (FSL) v6.0 program.[99] Volumetric segmentation of cortical and subcortical structures including the hippocampus was performed by FreeSurfer v7.1.0.[32] In addition, Hippocampal Subfield Segmentation protocol was utilized to delineate both structural and functional hippocampal subfields and extract hippocampal volume.[44] Hippocampal segmentations along its longitudinal axis into head, body, and tail are used to address functional segmentation of the hippocampus. The b_0 images were upsampled to T1 resolution, through FSL and subsequently registered to T1 anatomical images using FreeSurfer's bbregister function. Whole-brain FA and MD maps were obtained using FSL DTIFIT and upsampled to T1 anatomic resolution.[99] Hippocampal segmentations were transformed into diffusion-weighted imaging space, and hippocampal subfields FA and MD values were obtained. The ipsilateral and contralateral sides were determined based on the side of pain experienced by the patients. As only patients with right-sided TN were included in the study, the right side for both R-TN patients and healthy controls was considered ipsilateral, while the left side was considered contralateral. **Figure 1** shows a schematic diagram of image processing pipeline, and **Figure 2** shows hippocampal subfield segmentation in diffusion MRIs.

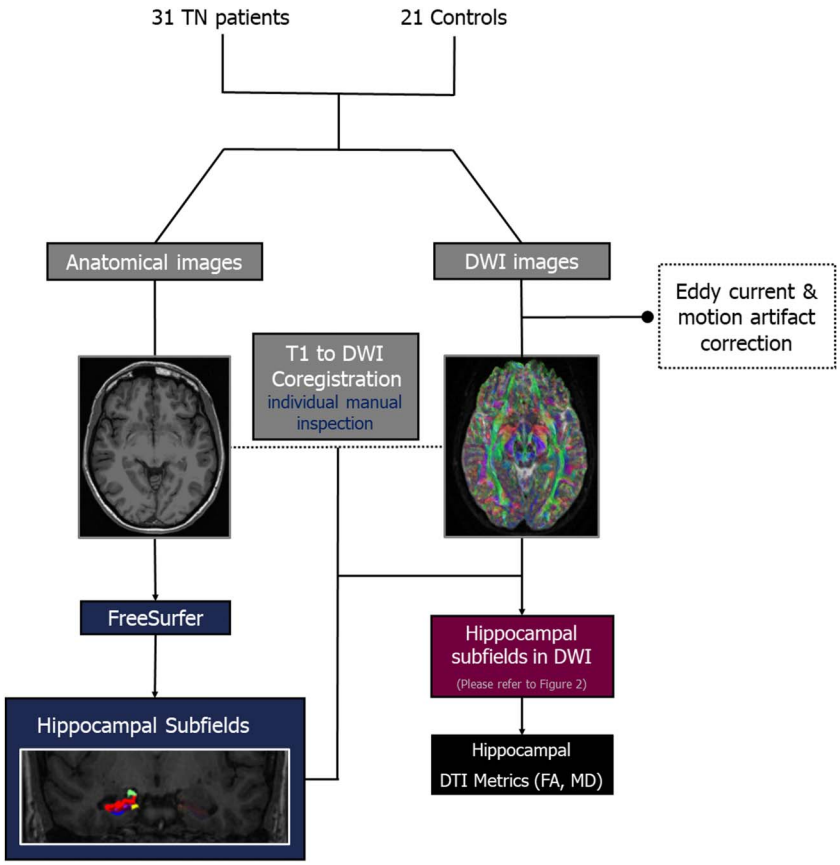

Figure 1. Image processing pipeline for 31 patients with TN and 21 healthy controls with T1 anatomical images and eddy current and motion corrected DWI scans. T1-weighted and diffusion-weighted images were coregistered. T1-weighted images underwent hippocampal segmentation via FreeSurfer v7.1.0. Hippocampal segmentations were transformed into DWI space. FA and MD were extracted for hippocampal subfields CA 1 to 4 and longitudinal axis segmentations head, body, and tail. CA, cornu ammonis; DWI, diffusion-weighted imaging; FA, fractional anisotropy; MD, mean diffusivity

2.5. Intracranial and hippocampal volumes

The intracranial and bilateral hippocampi volumes were extracted from the FreeSurfer segmentations. To account for variations in head size among our participants, we implemented the residual approach, as explained by Buckner et al.[15] As previously described,[15,73,83,94] we adjusted whole hippocampal volume using the residual method with the following formula:

$$VOI_{adj} = VOI - b(ICV - ICV_{mean})$$

Where VOI_{adj} is the adjusted volume of interest, VOI is the output volume from the FreeSurfer pipeline, b is the slope of the linear regression between VOI and on intracranial volume (ICV), and the ICV_{mean} is the sample mean of the ICV. The *t* test analysis was utilized to compare the intracranial and whole hippocampal volume between healthy control and patients with TN.

2.6. Quality assurance

To validate the quality assurance within the imaging pipeline, we have incorporated several essential steps. First, to confirm that comparison of differently acquired image parameters is feasible, we compared the signal-to-noise ratio (SNR) in diffusion-weighted imaging (DWI) data for our 2 cohorts. We utilized the MRTrix imaging framework to calculate the noise and SNR for b0 and b1000 volumes of DWI, to ensure that the differences in the imaging protocols did not introduce bias to the data.

Finally, the segmentation and T1 to DWI registration results underwent manual inspection by 3 authors (S.H., A.N., and M.H.) to identify alignment and registration errors. The inspections were conducted independently, with the authors being blinded to each other's assessment.

2.7. Statistical analyses

All statistical analyses were done in Graphpad Prism v9.3.0 (Graphpad, 2020) and R 3.5.1.[78] Age was compared at the group level using the Welch *t* test, to investigate their differences, as well as Bayesian Estimate Supersedes the *t* test (BEST),[55] to investigate their similarities. These comparisons were performed between all TN subjects and healthy controls, female patients with TN age and female healthy controls, and male patients with TN age and male healthy controls. The Shapiro–Wilk test revealed that diffusivity metrics are not normally distributed (*P*-values >0.05). Therefore, the Mann–Whitney *U* test was utilized to assess non-normally distributed diffusivity metrics. The statistical analyses include (1) comparison of diffusivity metrics of TN subjects compared with healthy controls using the Mann–Whitney *U* test; (2) assessment of sex differences in diffusivity using the Mann–Whitney *U* test; and (3) assessment of pain duration, severity, and age using Spearman correlation; and (4) the χ^2 test to determine a relationship between sex (male and female) and treatment group (TN and control). All statistical analyses underwent correction for multiple comparisons through Bonferroni correction with statistical significance set for *P*-value <0.05.

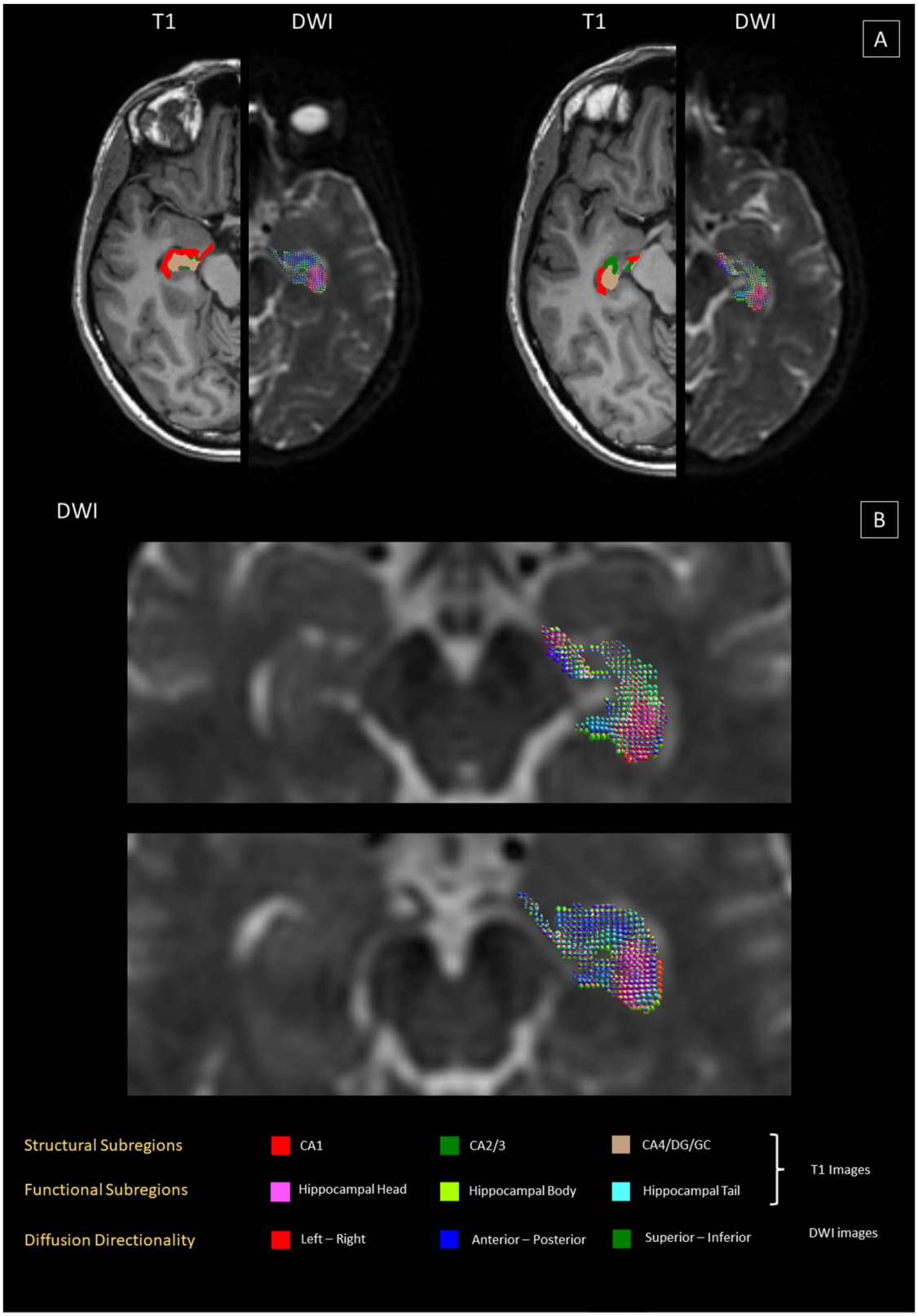

Figure 2. Automated hippocampal subfield segmentation and diffusion directionality in the hippocampus. Panel A shows axial views, with the left side images depicting T1 Structural MR and right images illustrating the closest axial section of the corresponding diffusion-weighted MRIs. Panel B shows zoom-in axial views of DWI images. The hippocampus is outlined on the diffusion images and is color-coded based on diffusion directionality. Panels C and D show a zoom-in axial and sagittal view of the bilateral hippocampi in T1, respectively. The hippocampus and its subfields are color-coded on T1 images according to FreeSurfer 7.0 segmentations. Notably, our investigation focuses on the histological subregions including CA 1, CA2/3, and CA4/DG, as well as functional subregions, including head, body, and tail of the hippocampus. CA, cornu ammonis; DG, dentate gyrus; DWI, diffusion-weighted imaging; HP, hippocampal proper.

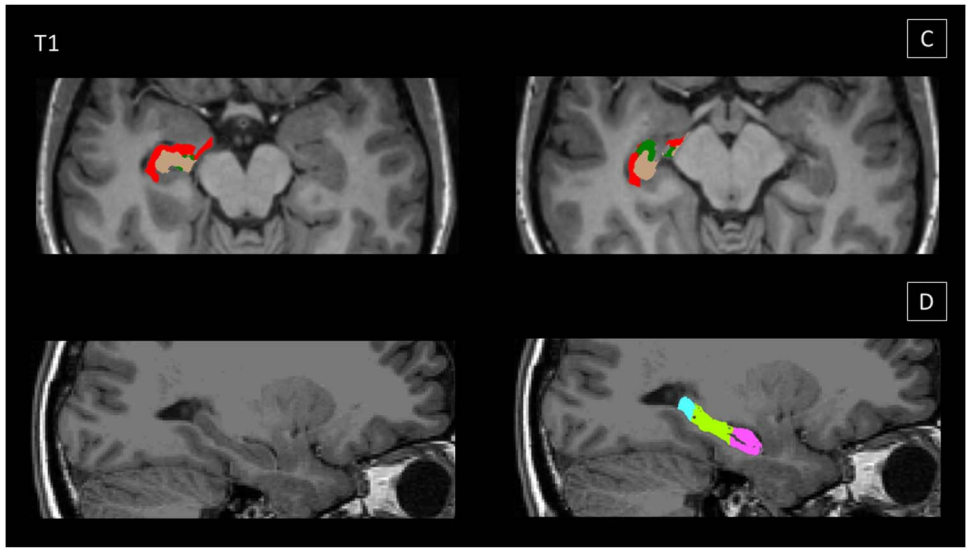

Figure 2.

Continued

3. Results

3.1. Subject demographics and healthy control validation

Thirty-three patients with R-TN were included in this study (20 F, 11 M). The average age of patients with TN at the time of image acquisition was 50.9 ± 10.8 years (mean ± SD; F: 54.1 ± 9.0; M: 45.2 ± 11.9). Twenty-one healthy controls were included in this study (13 F, 8 M). The average age of healthy controls at the time of image acquisition was 45.8 ± 10.1 (F: 49.7 ± 8.8; M: 39.4 ± 9.2). Unequal sample sizes were utilized to maximize subject inclusion within the study. Age was not statistically different between all TN patients and healthy controls ($P = 0.09$), female TN patients and female healthy controls ($P = 0.18$), and male TN patients compared to male healthy controls ($P = 0.25$). Patient demographics are presented in **Table 1**.

Age comparisons did not reveal any statistically significant differences between the patients with TN and healthy controls. All corrected *P*-values for the Welch *t* test comparing age between patients with TN and health controls were above 0.05. In addition, BEST tests comparing age between patients with TN and healthy controls, female patients with TN and female healthy controls, male patients with TN and male healthy controls revealed 95% Highest Density Interval of true differences which included zero. As such, age is not only statistically different between groups but also statistically similar. The age comparison results are summarized in **Table 2**. In addition, the χ^2 test to investigate a relationship between sex (male and female) and treatment group (TN and control) did not reveal a statistically significant difference ($P = 0.85$).

3.2. Imaging pipeline and quality assurance

The *t* test analysis comparing the noise and SNR between healthy controls and patients with TN did not show a statistically significant difference (results reported in **Table 3**). We further confirm that the DWI images for healthy controls and patients with TN share the same b-value, resolution, gradients, TE, and FOV and are acquired on the same type of scanner (GE Signa). Considering the absence of any SNR disparities, we are confident that the different protocols did not introduce any bias into the data.

3.3. Trigeminal neuralgia is associated with specific hippocampal diffusivity abnormalities and volumes

Patients with TN had significantly reduced FA in bilateral whole hippocampi ($P_{contra} = 0.01$, $P_{ipsi} = 0.02$) (**Fig. 3**). Mean diffusivity values were not significantly different between patients with TN and healthy controls (**Table 4**).

Analyses of hippocampal subfields revealed subfield-specific diffusivity differences between R-TN and healthy controls. Patients with TN had significantly reduced FA in contralateral hippocampal subfields CA2/3 ($P_{contra} = 0.006$) and CA4 ($P_{contra} = 0.001$). With respect to functional hippocampal subdivisions, our evaluation depicted a bilateral decrease in TN hippocampal body FA ($P_{contra} < 0.001$, $P_{ipsi} = 0.04$) (**Fig. 4**). Subfield MD values were not statistically significant between patients with TN and healthy controls (all *P*-values >0.05).

The corrected hippocampal volumes based on the intracranial volume were bilaterally smaller in patients with TN compared with healthy controls (*P*-values: ipsilateral <0.001, contralateral <0.001). These results are in line with and replicate the previously reported finding of smaller hippocampal volumes in patients with TN compared with healthy controls.[73] In addition, the intracranial volume was not statistically different between patients with TN and healthy controls (*P*-value = 0.08).

3.4. Hippocampal diffusivity abnormalities are driven by female patients with trigeminal neuralgia

Abnormal diffusion was restricted to female patients with R-TN. Female patients with TN displayed a significantly reduced FA in the whole ipsilateral and contralateral hippocampus compared with healthy controls ($P_{contra} = 0.01$, $P_{ipsi} = 0.02$). Analyses of female hippocampal subfields demonstrated a subfield-specific reduction in contralateral subfields CA2/3 ($P_{contra} = 0.003$) and CA4 ($P_{contra} = 0.009$). Analysis of female hippocampal longitudinal axis segmentations demonstrated a reduction in FA for the contralateral hippocampal body ($P_{contra} = 0.02$). No significant differences were found for female ipsilateral subfields and longitudinal sections (all *P*-values >0.05). No significant differences were found for male TN patients whole hippocampi, subfields, and longitudinal axis segmentations (all

Table 1

Demographic summary of patients with trigeminal neuralgia.

ID	Age (y)	Sex	Distribution	Pain severity (NRS)	Medications	Pain duration (y)
TN01	38	F	V3	10	Carbamazepine	6
TN02	39	F	V2, V3	2	Carbamazepine, lamotrigine	6
TN03	40	F	V1, V3	6	Gabapentin, baclofen, clonazepam, paracetamol–oxycodone	8
TN04	44	F	V2, V3	10	Carbamazepine	1
TN05	47	F	V1	9	Paracetamol–oxycodone	2
TN06	49	F	V2	10	Carbamazepine, baclofen, pregabalin	8
TN07	51	F	V2, V3	10	Topiramate and duloxetine	1
TN08	52	F	V1	*	Carbamazepine	3
TN09	54	F	V2, V3	10	Carbamazepine, gabapentin	3
TN10	55	F	V3	3	Carbamazepine	*
TN11	55	F	V1, V2, V3	9	Carbamazepine	9
TN12	59	F	V2	8	Carbamazepine, pregabalin	4
TN13	59	F	V1, V2, V3	10	Pregabalin, carbamazepine acetaminophen–codeine	3
TN14	59	F	V2, V3	5	Gabapentin	2
TN15	60	F	V2	9	Carbamazepine	6
TN16	61	F	V1, V2, V3	9	Carbamazepine, gabapentin	4
TN17	61	F	V3	10	Carbamazepine, pregabalin	9
TN18	65	F	V2	10	Carbamazepine, gabapentin	30
TN19	67	F	V3	8	Pregabalin, baclofen, duloxetine	2
TN20	67	F	V3	10	Gabapentin	1
TN21	23	M	V2	5	Carbamazepine	3
TN22	29	M	V3	4	Carbamazepine	2
TN23	38	M	V2	10	Carbamazepine, pregabalin	1
TN24	40	M	V1, V2	4	Carbamazepine, pregabalin	3
TN25	44	M	V3	10	Carbamazepine, venlafaxine, pregabalin	1
TN26	46	M	V2, V3	10	Pregabalin, gabapentin, carbamazepine	8
TN27	51	M	V3	10	Pregabalin, baclofen	2
TN28	53	M	V1	5	Lamotrigine, carbamazepine, hydromorphone	6
TN29	55	M	V2	7	Gabapentin, carbamazepine	11
TN30	59	M	V2, V3	9	Carbamazepine	2.5
TN31	59	M	V1, V2	3	Carbamazepine, medical marijuana	12

Pain distribution indicates the branch of trigeminal nerve affected (V1: ophthalmic branch, V2: maxillary branch, V3: mandibular branch, *: lost in follow-up).
NRS, numerical rating scale; TN, trigeminal neuralgia.

P-values >0.05). No statistically significant differences were identified when analyzing female and male MD values (all *P*-values >0.05). A subset of hippocampal subfield analysis by sex is presented in **Figure 5**.

3.5. Trigeminal neuralgia hippocampal diffusivity abnormalities are correlated with age

Spearman correlations were performed to assess the relationship between patients with TN age and diffusivity. Trigeminal neuralgia

Table 2

Age comparison summary between healthy controls and patients with trigeminal neuralgia.

Age	Mean ± SD (y)	*t* test comparison	BEST comparison
Healthy controls vs patients with TN	Controls: 45.8 ± 10.1 TN: 50.9 ± 10.8	*P* value = 0.09	95% HDI includes zero
Female healthy controls vs female patients with TN	Controls: 49.7 ± 8.8 TN: 54.1 ± 9.0	*P* value = 0.18	95% HDI includes zero
Male healthy controls vs male patients with TN	Controls: 39.4 ± 9.2 TN: 45.2 ± 11.9	*P* value = 0.25	95% HDI includes zero

BEST, Bayesian Estimate Supersedes the *t* test; HDI, highest-density interval of true differences; TN, trigeminal neuralgia.

Table 3

Noise and signal-to-noise ratio comparison in diffusion-weighted images.

	Mean ± SD	*t* test comparing healthy controls and patients with TN
Noise	Controls: 5.07 ± 0.44 s/mm^2 TN: 4.95 ± 0.77 s/mm^2	*P* value: 0.52 (NSD)
b0 SNR	Controls: 356.39 ± 33.1 TN: 376.22 ± 63.30	*P* value: 0.20 (NSD)
b1000 SNR	Controls: 104.79 ± 10.24 TN: 108.63 ± 16.36	*P* value: 0.35 (NSD)

NSD, not statistically significant different; SNR, signal-to-noise ratio; TN, trigeminal neuralgia.

age was negatively correlated with ipsilateral whole hippocampal FA ($\rho = -0.54$, $P_{ipsi} = 0.002$). There was no significant correlation between TN age and contralateral whole hippocampal FA ($P_{contra} > 0.05$). There was no significant correlation between TN age and hippocampal subfield FA (all *P*-values >0.05). Analyses of hippocampal longitudinal axis segmentations revealed significantly reduced FA in the ipsilateral hippocampal tail ($\rho = -0.58$, $P_{ipsi} = 0.005$). No significant correlations were identified between healthy control age and hippocampal diffusivity metrics (all *P*-values >0.05).

To further investigate the effect of age on female hippocampal diffusivity due to sex-dependent diffusivity reported above, Spearman correlations were performed between female patients with TN age and FA values. Female TN age was significantly negatively correlated with contralateral ($\rho = -0.49$, $P_{contra} = 0.03$) and ipsilateral whole hippocampi FA ($\rho = -0.60$, $P_{ipsi} = 0.005$). There was no significant correlation between hippocampal subfields and male TN age. Analyses of hippocampal longitudinal axis segmentation revealed a significant negative correlation between female TN age and hippocampal tail FA on the contralateral ($\rho = -0.71$, $P_{contra} = 0.004$) and ipsilateral side ($\rho = -0.72$, $P_{ipsi} = 0.002$). No significant correlations were found between female healthy control age and hippocampal diffusivity. A subset of correlation analyses between TN age and hippocampal FA is presented in **Figure 6**.

3.6. Correlation between pain demographics and diffusivity

Spearman correlations were performed to assess relationships between pain duration, severity, and hippocampal diffusivity. Two patients with incomplete demographic information were not included in these analyses. Patients with TN had a mean pain duration of 5.3 ± 5.6 years. No statistically significant correlations between pain duration and FA or MD values for R-TN patients were identified following correction for multiple comparisons (all *P*-values >0.05). Patients with trigeminal neuralgia had a mean pain severity of 7.8 ± 2.7 on the numerical rating scale (NRS). The NRS is an 11-point scale with the anchors 0 referring to no pain and 10 referring to the worst pain imaginable. No significant correlations between pain severity and FA or MD values were identified (all *P* values >0.05).

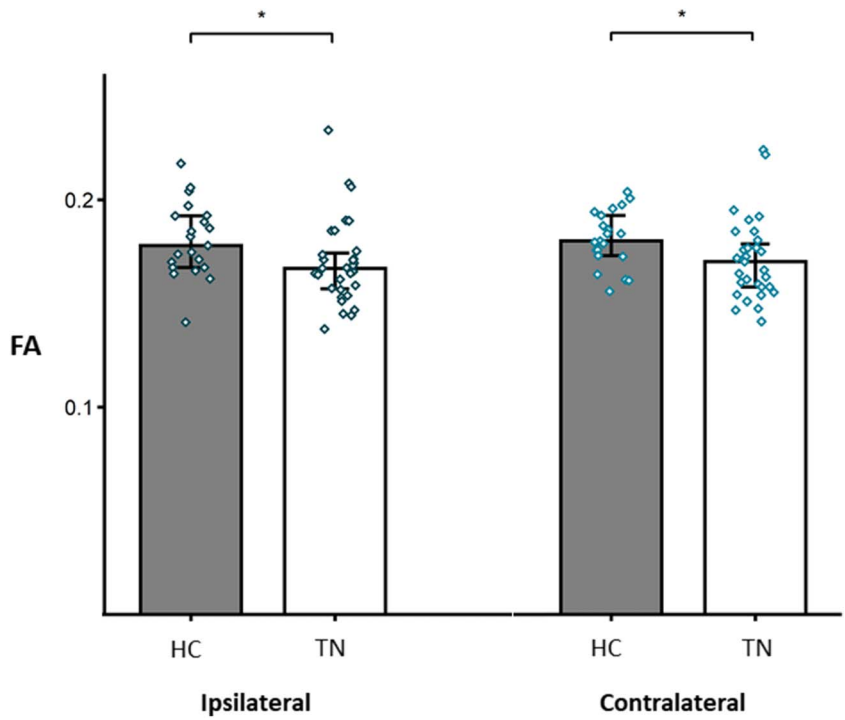

Figure 3. Hippocampal FA in 21 HCs (delineated by color bars) and 31 patients with right-sided TN (delineated by white bars). Each small diamond represents 1 subject. Ipsilateral refers to the right side of the brain and contralateral refers to the left side. Bars indicate the median value, and error bars delineate the spread between the 25th (Q1) and 75th (Q3) percentiles. The Mann–Whitney *U* test was used for comparing patients and controls (*$P < 0.05$). Patients with TN have bilaterally lower FA compared with healthy controls. FA, fractional anisotropy; HC, healthy control; TN, trigeminal neuralgia.

Table 4

Summary of corrected group comparisons between right-sided trigeminal neuralgia subjects and healthy controls.

Region	Side	Fractional anisotropy			Mean diffusivity		
		TN (mean ± SD)	Controls (mean ± SD)	Corrected *P* values	TN (mean ± SD)	Controls (mean ± SD)	Corrected *P* values
Structural subregions							
Hippocampus	Ipsi	0.1696 ± 0.0204	0.1804 ± 0.0177	0.02*	0.001085 ± 0.000081	0.001081 ± 0.000088	0.88
	Contra	0.1708 ± 0.0195	0.1808 ± 0.0135	0.01*	0.001056 ± 0.00008	0.001064 ± 0.000085	0.68
CA1	Ipsi	0.1511 ± 0.0200	0.1618 ± 0.0215	0.28	0.001099 ± 0.00011	0.001096 ± 0.00010	>0.99
	Contra	0.1553 ± 0.0233	0.1640 ± 0.0148	0.076	0.001051 ± 0.000084	0.001039 ± 0.000075	>0.99
CA2/3	Ipsi	0.1890 ± 0.0377	0.2029 ± 0.0393	>0.99	0.001227 ± 0.000139	0.001212 ± 0.00017	>0.99
	Contra	0.1886 ± 0.0329	0.2196 ± 0.0331	0.006**	0.001188 ± 0.000144	0.001153 ± 0.000134	>0.99
CA4	Ipsi	0.1586 ± 0.0329	0.1713 ± 0.0236	0.052	0.001005 ± 0.000083	0.000983 ± 0.000077	>0.99
	Contra	0.1560 ± 0.0243	0.1787 ± 0.0196	0.0011**	0.000982 ± 0.000081	0.000962 ± 0.000072	>0.99
Subiculum	Ipsi	0.1476 ± 0.0167	0.1533 ± 0.0142	0.76	0.00094 ± 0.000068	0.000949 ± 0.000075	>0.99
	Contra	0.1513 ± 0.0153	0.1490 ± 0.0142	>0.99	0.000889 ± 0.000053	0.000929 ± 0.000076	0.53
Functional subregions							
Head	Ipsi	0.1558 ± 0.0168	0.1620 ± 0.0192	>0.99	0.001066 ± 0.000093	0.001061 ± 0.000087	>0.99
	Contra	0.1566 ± 0.0181	0.1616 ± 0.0156	>0.99	0.001025 ± 0.000081	0.001008 ± 0.000069	>0.99
Body	Ipsi	0.1805 ± 0.0312	0.1978 ± 0.0219	0.04*	0.001118 ± 0.000090	0.001131 ± 0.000103	>0.99
	Contra	0.1811 ± 0.0240	0.2035 ± 0.0190	<0.001***	0.001087 ± 0.000094	0.001124 ± 0.000113	>0.99
Tail	Ipsi	0.1885 ± 0.0244	0.2016 ± 0.0232	0.56	0.001075 ± 0.000117	0.001053 ± 0.000116	>0.99
	Contra	0.1918 ± 0.0273	0.1935 ± 0.0269	>0.99	0.001086 ± 0.000134	0.001125 ± 0.000146	>0.99

CA, cornu ammonis; TN, trigeminal neuralgia.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

4. Discussion

Although there has been increasing interest in understanding the role of the hippocampus in the pathophysiology of chronic pain, little is known about the relationship between hippocampal microstructure and macrostructure and how these are affected in chronic pain.[3,5,8,80] This important gap interfaces with the observation that patients with chronic pain frequently present with functional changes, such as alterations in memory, that can be related to the hippocampus. This study was undertaken with the hypothesis that hippocampus microstructure is a sensitive metric to relay early alterations and may provide a crucial link between aberrant neurogenesis in response to chronic pain and volumetric changes.[33,34,37,70,81,94] Subregion and longitudinal axis analyses identified that patients with TN have hippocampal diffusivity alterations in multiple structural and functional domains. First, we discovered subregion-specific reductions in FA, specifically contralateral subregions CA2/3 and CA4 and bilateral hippocampal body. These subregions are crucial in memory, concentration, and the process of neurogenesis which may further explain cognitive abnormalities in chronic pain.[12,26,49] In addition, we observed that hippocampal diffusivity metrics were affected by age and sex,[36,43] with subfield-specific reduction in FA seen chiefly in female patients with TN. These results contribute to growing evidence of sex-specific differences in TN that potentially relate to sex differences in physiologic stress response.[36,43,73] A third indicates that the reduction of FA in the hippocampi of patients with TN is correlated with age. Taken together, we observe that hippocampal diffusivity alterations provide insight into abnormal hippocampal microstructure in chronic pain. Collectively, our results and other studies focusing on the role of the hippocampus in chronic pain help illustrate the relationship between pain, possible macro and microstructural abnormalities, and pave the way for greater focus on mechanistic evaluation of these abnormalities to enhance novel treatment options.

4.1. Reduced fractional anisotropy in trigeminal neuralgia hippocampal subfields

DTI metrics, specifically FA and MD, serve as indicators of water diffusion barriers, providing valuable insights into the microarchitecture of the hippocampus,[17,24,58] may occur earlier and more accurately predict disease progression than macrostructural volumetric analyses.[47,70,94] This has been observed in other conditions but has not been previously reported in pain. For instance, in Alzheimer disease, hippocampal macrostructural abnormalities occur relatively late, while MCI progression may be better predicted by DTI-derived metrics, such as FA and MD, at earlier time points.[70,93,94]

It is argued that the breakdown of cellular microstructure within the hippocampus leads to fewer barriers for diffusion in all directions, and thus, water molecules are able to diffuse more freely, leading to decreased FA and increased MD.[57] We demonstrated that FA is reduced in patients with TN hippocampi with no significant difference in MD (**Table 4**). This indicates that hippocampal microstructure is differentially impacted in TN where the diffusion directionality is hindered while overall diffusivity is relatively unimpeded. Our study highlights the utility of DTI to help characterize disorders that affect the hippocampus. Fractional anisotropy and MD profiles may delineate the impact on the hippocampus. For example, FA is reduced and MD is increased in both epilepsy and Alzheimer disease.[7,30,35,52,65,82] These results highlight the utility of DTI metrics to provide insight into underlying TN pathophysiology and impact on the hippocampus. This study further elaborates on hippocampal abnormalities detailed in molecular and volumetric studies.

Recent functional MRI studies have identified different activation through the functional subregions of the hippocampus. Ayoub et al.[8] reported that anterior hippocampus has abnormally lower activity in chronic pain and reduced connectivity to the medial prefrontal cortex in patients with chronic pain compared with healthy controls. Similarly, prior studies have indicated that memory processes involving the encoding of individual items or objects tend to activate the more central or middle regions (body) of the hippocampus.[11,53]

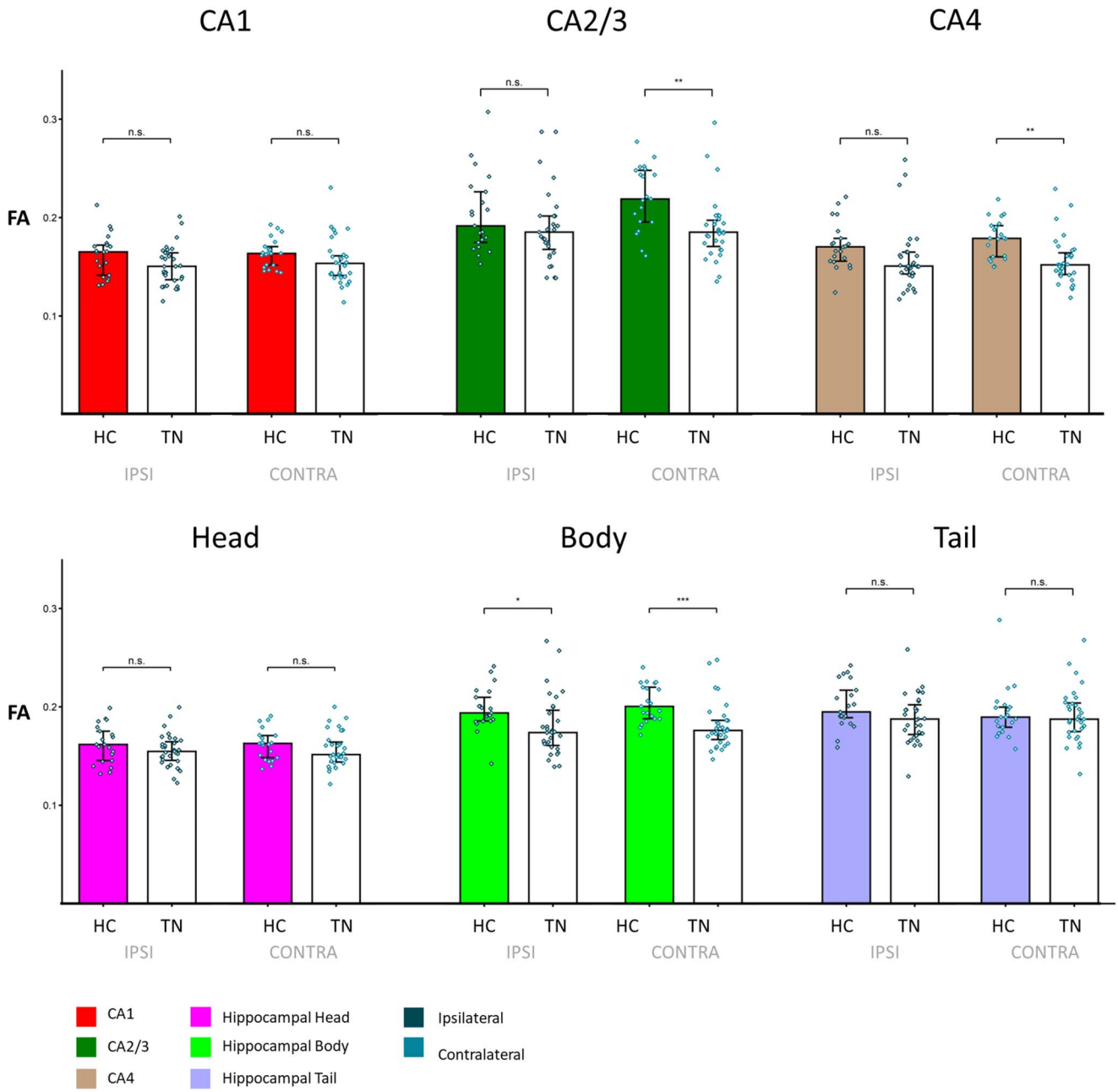

Figure 4. Hippocampal subfields FA in 21 HCs (delineated by color bars) and 31 patients with right-sided TN (delineated by white bars). Each small diamond represents 1 subject. Ipsilateral refers to the right side of the brain and contralateral refers to the left side. Bars indicate the median value, and error bars delineate the spread between the 25th (Q1) and 75th (Q3) percentiles. The Mann–Whitney *U* test was used for comparing patients and controls. All reported *P*-values are corrected for multiple comparison using Bonferroni correction (n.s. not statistically significant, $^{*}P < 0.05$, $^{**}P < 0.01$). CA, cornu ammonis; FA, fractional anisotropy; HC, healthy control; TN, trigeminal neuralgia.

Hence, our findings, illustrating bilateral FA reduction in the hippocampal body, may represent another manifestation of the reported memory deficits in individuals with chronic pain.

We also observe possible correspondence between diffusivity changes and previously reported volumetric changes.[92] For example, in this study, we report that FA is bilaterally affected in the whole hippocampus in female but not male patients with TN. In our previous study investigation hippocampal structure, we observed smaller hippocampi bilaterally in female but not male patients with TN. Similarly, this study reveals reduced FA in the contralateral CA4 among patients with TN, a region we previously identified as bilaterally smaller in patients with TN. These collective findings underscore possible microlevel and macrolevel changes within the hippocampus in individuals experiencing chronic pain.

Previous studies have shown that pain signals can be processed asymmetrically in the brain, particularly within the insula.[3,6,20,23] These findings highlight that the observed laterality in our study may reflect a similar phenomenon reported in previous research on pain laterality leading to downstream asymmetrical hippocampal diffusivity as a result of asymmetric pain processing. In addition, given the relatively young age of the TN cohort in this study, unilateral changes may precede bilateral hippocampal subfield abnormalities potentially observed in an older cohort.

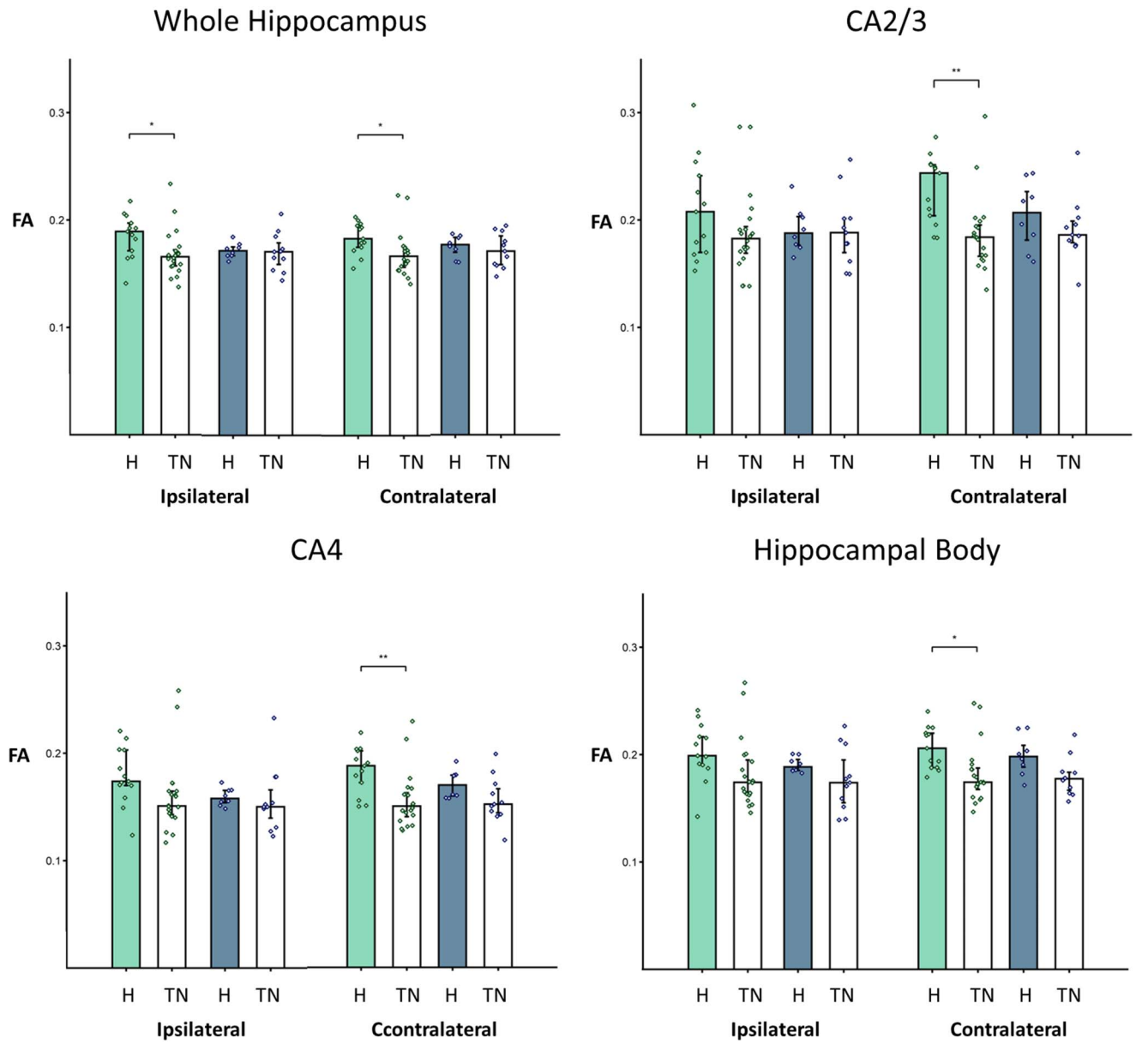

Figure 5. Hippocampal and its subfields FA stratified by sex in 21 HCs (delineated by color bars, 13 F, 8 M) and 31 patients with right-sided TN (delineated by white bars, 20 F, 11 M). Ipsilateral refers to the right side of the brain and contralateral refers to the left side. Bars indicate the median value, and error bars delineate the spread between the 25th (Q1) and 75th (Q3) percentiles. The Mann–Whitney *U* test was used for comparing patients and controls. All reported *P*-values are corrected for multiple comparison using Bonferroni correction (*$P < 0.05$, **$P < 0.01$). The results show sex-dependent differences in FA values in patients with TN. CA, cornu ammonis; FA, fractional anisotropy; HC, healthy control; TN, trigeminal neuralgia.

4.2. Diffusivity differences point to microstructural and neuronal remodeling in the hippocampus

Our findings show that diffusivity is affected in contralateral CA2/3 and CA4 hippocampal subregions. Similarly, our previous study showed volumetric changes in the same subfields in patients with TN. These findings are significant considering the importance of these subregions in hippocampal neuroplasticity and neurogenesis, ultimately mediating cognitive and emotional functions.[48,75,95]

The CA3 subregion has extensive connection to entorhinal cortex, DG, and to CA1.[1,18] Together with the CA2 subregion, CA3 plays an integral role in memory formation and consolidation.[26,49,68] In addition, chronic pain adversely affects memory and concentration,[12,62] pointing to CA2/3 subregions. Considering that altered diffusivity is an indication for microstructural changes, the decreased FA in CA2/3 subregions could be another indication to memory and functional changes in patients with chronic pain.

The CA4, which includes the DG, is capable of neurogenesis and drives neuronal plasticity.[25] We previously showed that the CA4/DG are bilaterally smaller in patients with TN and recovered after pain relief.[73] In addition, other studies have reported that chronic pain negatively affects neurogenesis in the hippocampus.[5,71,80] Furthermore, the diffusivity is altered in DG of animal models following training for learning and memory.[13] Therefore, the decreased FA in CA4 subregion of patients with TN could be a marker for altered neuronal plasticity and neurogenesis. Additional studies are required to identify specific cellular changes.

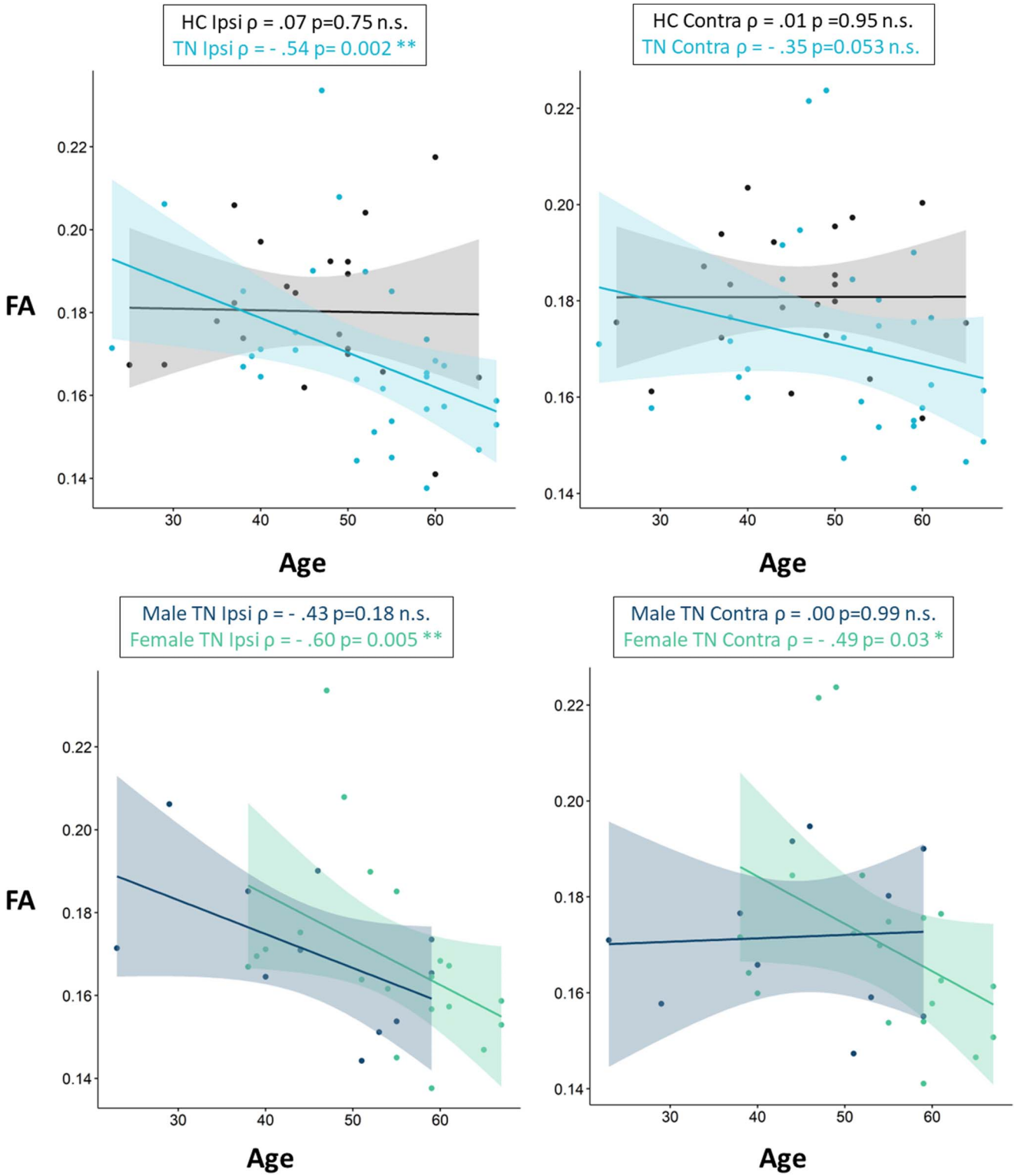

Figure 6. Correlation between whole hippocampal FA and age. The top 2 graphs present correlation in 21 HC and 31 patients with right-sided TN. Each dot represents 1 subject. The bottom 2 graphs present correlation in 31 patients with right-sided TN stratified by sex (20 F, 11 M). Spearman correlation was used in these analyses. Rho (ρ) and *P* values are reported individually for each graph (n.s. not statistically significant, $^{*}P < 0.05$, $^{**}P < 0.01$). Lines represent the best fitted linear model and shaded areas indicate the 95% confidence intervals. Line and confidence intervals are included solely for visualization purposes. The results show sex-dependent correlations between FA and age in female patients with TN. FA, fractional anisotropy; HC, healthy control; TN, trigeminal neuralgia.

4.3. Abnormal diffusion is primarily seen in female patients with trigeminal neuralgia

Our study demonstrates a sex-specific reduction in female TN hippocampal subfield FA (**Fig. 5**). Female patients with TN have significantly reduced FA in bilateral whole hippocampi and contralateral subregions CA2/3, CA4, and body. These results are congruent with our previous work which demonstrated a female TN-specific reduction in bilateral hippocampal subfield volumes.[92]

Sex-specific activation of the hypothalamic–pituitary–adrenal (HPA) axis may explain this difference. The HPA axis is a neuroendocrine system that regulates responses to acute and chronic physiologic stress by regulating cortisol secretion from the adrenal glands.[40,85] Prolonged exposure to cortisol is deleterious to hippocampal volume and structure.[63,98] Mouse models indicate sex-dependent effects in acute and chronic activation of the HPA axis.[9,38,45,64,96] Female patients, compared with male patients, have more robust response to acute stress indicated by elevated cortisol and delayed return to baseline following acute events.[9,38,45,96] Chronic pain can induce chronic stress and lead to maladaptive HPA axis function and decreased hippocampal volume.[67,91] Similarly, previous studies have implicated sex as a factor in hippocampal cognition and neurogenesis[100] and demonstrated sex-dependent reductions neurogenesis in the hippocampi following chronic stress.[41] Exaggerated exposure to chronic stress and reduced neurogenesis may explain the female driven reduction in FA in patients with TN.

4.4. Hippocampal changes and accelerated brain aging in trigeminal neuralgia

We demonstrate that TN age, but not control age, is significantly negatively correlated with FA in the whole ipsilateral hippocampus (**Fig. 6**). Previous studies have examined the association between age and diffusivity metrics in the hippocampi of older adults. Anblagan et al. identified a reduction in hippocampi FA of older adults over time (2018). The hippocampus becomes increasingly susceptible to physiologic and environmental stress with age.[34,60,79,84,86] Increasing literature has associated chronic pain disorders with accelerated brain aging.[21,56,69] Hung et al. demonstrated that brain age is significantly increased compared with chronological age in chronic pain disorders including TN (2022). Interestingly, increased brain age among patients with TN was predominantly driven by female patients[43] as our study also identified a female-driven association between age and hippocampal FA (**Fig. 6**). Therefore, our collective findings suggest that chronic pain disorders, especially TN, are associated with female-driven brain structural and microstructural abnormalities. Furthermore, the FA decline in female patients with TN may provide an additional contributor to accelerated brain aging observed by Hung et al. in younger female patients with TN.[43]

Our study includes a relatively young cohort of patients with TN. Volumetric atrophy of the hippocampus has been associated with increasing age.[22] However, age-related hippocampal reductions in FA occurs among controls significantly older than utilized in our study.[2,76] We address possible age bias by demonstrating no significant difference in age between TN and controls and BEST analyses that demonstrate cohort ages are statistically similar. Therefore, we do not anticipate significant bias regarding age-related diffusion between cohorts.

4.5. Future directions and study limitations

TN pain severity may be medically or surgically treated. Medical treatment options include anticonvulsant medications including gabapentin, pregabalin, and carbamazepine (**Table 1**). Patients taking anticonvulsant medications occasionally report symptoms related to cognitive and memory issues[29]; however, no direct effect on the hippocampus has been established. Given the severity of TN pain, there are challenges in establishing a surgically and medically naive cohort. As such, our cohort represents a typical TN population. Future studies could investigate the significance of pain duration, age of onset, severity, and medication on diffusivity in a larger cohort.

This study was performed retrospectively. To determine the order of microstructural and macrostructural hippocampal abnormalities, a prospective study should be performed. Similarly, future studies may assess the association between cardiometabolic health and hippocampal structure.[89] This study did not identify any association between pain duration or severity and hippocampal diffusivity. However, there is dissonance in reporting pain onset and time of diagnosis, resulting in inconsistent assessment of true pain duration.

We note that the image acquisition parameters are different between retrospective control and patient cohorts, specifically the matrix and FOV in the T1 images and TR in the diffusion images. Regarding T1 images, these parameters translate into identical 1-mm isovoxel resolution while maintaining whole-brain coverage and therefore would not impact segmentation performance. Similarly for the DWI images, TN and healthy controls share the same b-value, resolution, gradients, TE, and FOV and are acquired on the same scanner. They have different TR values; however, previous studies have identified TE to be much more relevant to image comparison compared with TR.[46] Furthermore, region of interest–based analyses, including this study, have been reported to be more resilient to acquisition differences than voxel-based analyses.[72] Therefore, we do not anticipate significant imaging bias between our study groups.

We recognize the potential impact of subregion volumetric sizes in T1 on DTI diffusivity metrics. However, this study, given its limited number of subjects, does not provide sufficient statistical power to comprehensively address this question. We hope that a future study with a larger participant pool could effectively investigate this matter.

Disclosures

The authors have no conflict of interest to declare.

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