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Pain Relief Reverses Hippocampal Abnormalities in Trigeminal Neuralgia

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Abstract: **Chronic pain patients frequently report memory and concentration difficulties. Objective testing in this population points to poor performance on memory and cognitive tests, and increased comorbid anxiety and depression. Recent evidence has suggested convergence between chronic pain and memory deficits onto the hippocampus. The hippocampus consists of heterogenous subfields involved in memory consolidation, behavior regulation, and stress modulation. Despite significant studies outlining hippocampal changes in human and chronic pain animal models, the effect of pain relief on hippocampal abnormalities remains unknown. Trigeminal neuralgia (TN) is a chronic neuropathic pain disorder which is highly amenable to surgical interventions, providing a unique opportunity to investigate the effect of pain relief. This study investigates the effect of pain relief on hippocampal subfields in TN. Anatomical MR images of 61 TN patients were examined before and 6 months after surgery. Treatment responders (n = 47) reported 95% pain relief, whereas non-responders (n = 14) reported 40% change in pain on average. At baseline, patients had smaller hippocampal volumes, compared to controls. After surgery, responders' hippocampal volumes normalized, largely driven by CA2/3, CA4, and dentate gyrus, which are involved in memory consolidation and neurogenesis. We propose that hippocampal atrophy in TN is pain-driven and successful treatment normalizes such abnormalities.**

Perspective: ***Chronic pain patients have structural abnormalities in the hippocampus and its subfields. Pain relief normalizes these structural abnormalities and impacts patients in a sex-dependent manner.***

Key words: *Grey matter, cornu ammonis, dentate gyrus, hippocampal plasticity, orofacial pain, gamma knife surgery, memory, CNV.*

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Abbreviations: *AHN, Adult Hippocampal Neurogenesis; BEST, Bayesian Estimation Supersedes the t-test; BNI, Barrow Neurological Institute; CA, Cornu Ammonis; Cam-CAN, Cambridge Centre for Ageing and Neuroscience; CIHR, Canadian Institutes of Health Research; DG, Dentate Gyrus; GKRS, Gamma Knife Radiosurgery; ML HP, Molecular Layer of Hippocampus Proper; MRI, Magnetic Resonance Imaging; NRS, Numeric Rating Scale; SD, Standard Deviation; SGV, Subcortical Grey Volume; TN, Trigeminal Neuralgia; VOI, Volume of Interest.*

Introduction

Chronic pain adversely affects cognitive performance and significantly impacts the quality of life.[58,63] Chronic pain patients frequently experience poor memory and concentration, often accompanied by increased anxiety and depression.[3,8,14,15,23,35–37,40,57,64,66–68,74,75,82,85,90,102] The hippocampal formation consists of anatomically and functionally distinct subfields including the subiculum, *Cornu Ammonis* (CA1 − CA4), and dentate gyrus (DG). These subcortical regions play a significant role in memory formation,[51] emotional processing, and stress modulation.[103] In particular, prolonged exposure to stress, such as chronic neuropathic pain,[95] adversely affects memory, and this has been related to blunted hippocampal plasticity.[47–49,73,89]

Microstructural changes in the hippocampus have been reported in chronic pain conditions.[26,29,30,61,99] For example, studies using rodents with neuropathic pain demonstrated alterations in hippocampal gene expression profiles and blunted neurogenesis.[4,26,71,82] Similarly, hippocampal volumetric abnormalities have also been reported in other chronic neuropathic pain conditions including trigeminal neuralgia (TN).[39,71] TN is a debilitating chronic neuropathic facial pain disorder characterized by intense electric shock-like pain episodes.[12,20,42,54,107] TN has several unique features that distinguish it as an ideal model for the study of chronic pain: TN is largely unilateral; is severe in its nature; has stereotypical presentation among patients; and is not associated with other sensory deficits observed in other chronic pain disorders, such as numbness. Utilizing TN as a model, our group recently investigated the impact of chronic neuropathic pain on hippocampal subfields.[99] We reported atrophy in selected hippocampal subfields—with changes being positively related with pain duration.[99] These findings were in concordance with other studies which investigated the effect of chronic pain on the hippocampus and its subfields.[4,70,71,82]

Previous studies have found reversible changes in some structural brain abnormalities following effective pain treatments.[55,87] However, no previous study has identified reversible hippocampal alterations reported in chronic pain conditions. Given that prior efforts defined an effective treatment as a 20-40% improvement in pain ratings, it remains unknown whether complete pain resolution could affect hippocampal abnormalities. Uniquely, TN can offer valuable insight because it is one of the few pain conditions that are highly amenable to surgical interventions. Surgeries such as Gamma Knife Radiosurgery (GKRS) can result to complete TN pain resolution,[52,62,79] thereby permitting the investigation of a possible reversal of hippocampal abnormalities following pain relief.

Here, we aim to investigate the structure of the hippocampus and its subfields in TN patients before and after surgery to examine the effect of pain resolution on these structures. We hypothesize that pain relief will lead to an overall increase in hippocampal volume, and normalize previously observed abnormalities.[99] Furthermore, as neurogenesis is negatively affected in chronic pain conditions,[4,27] we hypothesize that pain relief will affect subfields important in neurogenesis, such as DG and CA4. Towards this goal, we plan to investigate structural magnetic resonance images (MRI) of TN patients before and after pain relief. Given that there are sex differences in hippocampal neurogenesis,[9,31,41,106] stress physiology,[72] and hippocampal subfields in TN patients,[99] we additionally, hypothesize that there will be sex differences after pain relief in TN patients.

Methods

Participants

Ethics

The University Health Network (UHN) Research Ethics Board approved this retrospective TN study. Patient data used in this study were analyzed retrospectively and no active participation. As such, individual patient consent was not required for this retrospective study. The UHN Research Ethics Board approved the recruitment of healthy controls and the image acquisition procedure. An individual written informed consent form was obtained from healthy individuals. All MRI scans were anonymized prior to any imagine analysis.

TN Patients

A total of 61 patients who was treated at Toronto Western Hospital in Canada were included in this study. Patients in this study met the following criteria: I) diagnosis of classical TN according to ICHD-3 criteria; II) GKRS treatment with no prior surgical interventions for TN; III) structural brain MRI prior to and 6 months after GKRS; IV) clinical follow-up 6 months after surgery. Patients with neurodegenerative disorders, TN secondary to multiple sclerosis, stroke, other chronic pain conditions, cranial tumors, and other neurological diseases were excluded from this study.

Images acquisition All T1-weighted images of TN patients were acquired with a 3 Tesla GE Signa HDx MRI scanner (General Electric, Boston, MA) fitted with an 8-channel head coil (fast-spoiled gradient echo, TE = 5.1 ms, TR = 12.0 ms, TI 300 ms, flip angle = 20°, voxel size = 0.86 mm × 0.86 mm × 1.00 mm, 256 × 256 matrix, field of view = 22 cm, 146 slices). It should be noted that TN patients scheduled for GKRS were generally scanned on the day of surgery. These images were used to guide the stereotactic surgery. However, in

some cases, due to limited scanner time availability, some scans only captured subcortical regions of interest. In these cases, all subcortical regions, including the entire hippocampus, were captured, and some cortical regions were lost.

Healthy Controls

To assess whether hippocampal abnormalities normalize after pain relief, 61 neurologically healthy individuals from the Cambridge Centre for Ageing and Neuroscience (Cam-CAN) dataset[88] were used as age- and sex-matched controls (age difference < 2 years). Exclusion criteria included: (1) depression, and (2) any report of pain. The ipsi- and contralateral sides for healthy individuals were determined based on their matched TN subjects: therefore, if a healthy subject was matched to a right TN patient, the right hemisphere was marked as ipsilateral. We used Cam-CAN dataset instead of healthy controls collected on site, as sex- and age-matched controls could not be recruited. The use of this control group was validated (see below).

Images acquisition All T1-weighted images of subjects from the Cam-CAN dataset were acquired with a 3 Tesla SIEMENS MAGNETOM TrioTim syngo MR B17 32-channel head coil (fast-spoiled gradient echo, TE = 2.99 ms, TR = 2250 ms, TI: 900 ms, flip angle = 9°, voxel size = 1.0 mm isotropic, 256 × 240 matrix, field of view =25.6 cm, 192 slices).

Healthy Controls Validation

To validate our approach to include Cam-CAN subjects in our analyses, we compared 76 healthy controls with T1 anatomical scans collected at Toronto Western Hospital and 76 age- and sex-matched (age difference < 1 year) neurologically healthy individuals from the Cam-CAN database. Both groups underwent the same processing pipeline as performed in the main analyses of this study (see below), including brain segmentation, parcellation, and hippocampal subfield segmentation using FreeSurfer 6.0. The volumetric results were compared at the group level using Wilcoxon test, to investigate their differences, as well as Bayesian Estimation Supersedes the t-test (BEST) test, to investigate their similarities.[53] All corrected p-values were above 0.05 in the Wilcoxon tests of the hippocampus and its subfields comparing the two groups. Additionally, the 95% Highest Density Interval of a true difference in means included zero in all BEST tests. As such, we showed that the hippocampus its subregions were statistically similar between the examined groups. Therefore, these two datasets, collected with different scanning protocols on different scanners, not only were not statistically different at the group level when comparing volumetric segmentations, but also statistically similar.

Automated Subcortical Segmentation

FreeSurfer 6.0 (https://surfer.nmr.mgh.harvard.edu/) was employed for subcortical segmentation[33] (including the hippocampus). Additionally, we used the Hippocampal Subfields Segmentation[44] protocol to automatically extract the volumetric values from 12 hippocampal subfields. Given recent evidence suggesting that the hippocampus has functionally meaningful subregions along its longitudinal axis,[1,6,76,91] we evaluated the volume of the head, body, and tail of the hippocampus using the FreeSurfer 6.0 developmental package.[84] Results were individually inspected for accuracy.

Surgical Intervention and Treatment Response

All patients underwent GKRS at Toronto Western Hospital, using an Elekta Perfexion system utilizing 4 mm collimators. One single fraction of 80 Gy was delivered to the 100% isodose to the cisternal segment of the symptomatic trigeminal nerve. To minimize the radiation effects, brainstem radiation was restricted to 15 Gy/mm^3.

Pain intensity and clinical outcomes were assessed before surgery, and at a 6-month post-treatment follow-up visit. Pain intensity was measured using two instruments: a Numeric Rating Scale (NRS)[45,80] and the Barrow Neurological Institute (BNI) scale.[81] The NRS was an 11-point scale, rated between 0 and 10, with the anchors: 0 = no pain and 10 = the worst imaginable pain. The BNI scale comprised five categories of pain for TN: class I—no trigeminal pain, no medication; class II—occasional pain, no medication; class III—some pain, adequately controlled with medication; class IV—some pain, not adequately controlled with medication; and class V—severe pain, no pain relief. In accordance to the previous literature,[43,56,96] patients who achieved >=75% reduction in pain (or complete pain resolution) on the NRS scale and score of I-III on the BNI scale at follow-up were classified as responders, whereas those who achieved <75% pain improvement on the NRS scale and score of IV-V on the BNI scale were classified as non-responders. There were seven patients that fit within the BNI III category but had somewhat less than 75% improvement of their pain with the NRS scale (please refer to Table 1). Each of these subjects was reviewed separately to determine whether they fit the category of responders or non-responders. Those who experienced a lower frequency of attacks after treatment, and had lowered their medication dose were considered as responders. The two non-responders in this group continued to experience frequent attacks and had in fact continued or increased their medication dose after an initial attempt to taper. All TN subjects' demographics are summarized in Table 1.

Subcortical Volume Correction

To account for head size differences in our participants, we employed the residual approach explained by Buckner *et al.*[18] Given that some participants did not have whole-brain MRI scans, we normalized the volume of the structures of interest using subcortical grey volume (SGV). As previously described,[18,83,99] we adjusted whole hippocampal volume using the residual method with the following formula:

Table 1. Trigeminal Subject Demographics

ID	Sex	Age	Laterality	Distribution	NRS		BNI		Medications		Group
					Pre	Post	Pre	Post	Pre	Post	
TN1	M	59	Right	V2, V3	10	0	V	III	CBZ	CBZ	Resp
TN2	M	79	Left	V2, V3	10	3	V	III	CBZ	CBZ	Resp†
TN3	M	70	Left	V1, V2, V3	10	3	IV	III	CBZ	CBZ	Resp†
TN4	M	53	Left	V2	10	0	IV	I	No med*	No med	Resp
TN5	M	71	Right	V2, V3	10	0	V	I	CBZ - GBP	No med	Resp
TN6	M	58	Right	V2	10	0	IV	I	CBZ	No med	Resp
TN7	M	63	Right	V3	10	0	V	III	CYM - BCL	CYM - BCL	Resp
TN8	M	31	Left	V2	10	0	IV	III	CBZ - BCL	CBZ - BCL	Resp
TN9	M	66	Left	V3	10	0	V	III	PGB - CBZ - BCL	CBZ	Resp
TN10	M	40	Right	V2, V3	10	0	IV	III	PGB - CBZ	PGB - CBZ	Resp
TN11	M	63	Left	V2, V3	7	0	V	I	PGB	No med	Resp
TN12	M	84	Right	V3	5	0	IV	I	TOL	No med	Resp
TN13	M	72	Right	V1, V2	10	0	IV	III	CBZ	CBZ	Resp
TN14	M	62	Right	V2, V3	8	0	IV	I	CBZ	No med	Resp
TN15	M	61	Right	V1, V2	9	0	V	I	PGB	No med	Resp
TN16	M	38	Right	V3	8	0	IV	III	CBZ - PGB	CBZ	Resp
TN17	M	73	Left	V1, V2, V3	8	0	IV	I	CBZ - GBP - TCA	No med	Resp
TN18	M	73	Right	V2, V3	8	2	V	II	GBP - HMO	No med	Resp
TN19	M	43	Left	V2	10	2	IV	III	CBZ	CBZ	Resp
TN20	F	82	Right	V2, V3	8	3	IV	III	CBZ - PGB - GBP	PGB	Resp†
TN21	F	69	Left	V2, V3	10	3	V	III	PGB	PGB	Resp†
TN22	F	65	Right	V1, V2, V3	10	3	V	III	GBP - CBZ	CBZ	Resp†
TN23	F	72	Left	V2	0	0	III	I	CBZ	No med	Resp
TN24	F	70	Right	V1	8	0	IV	I	CBZ	No med	Resp
TN25	F	74	Right	V3	10	0	V	I	No med	No med	Resp
TN26	F	56	Left	V3	10	0	IV	III	PGB - CBZ - TCA	PGB - CBZ	Resp
TN27	F	79	Right	V2	10	0	V	III	GBP	GBP	Resp
TN28	F	79	Left	V3	10	0	IV	III	CBZ	CBZ	Resp
TN29	F	60	Right	V2, V3	10	0	IV	II	PGB - CBZ	No med	Resp
TN30	F	67	Left	V3	10	0	V	I	GBP - CBZ	No med	Resp
TN31	F	49	Left	V1, V2, V3	10	0	V	I	PGB	No med	Resp
TN32	F	46	Right	V2	10	0	IV	III	CBZ - PGB	CBZ	Resp
TN33	F	55	Right	V2	10	0	V	I	No med*	No med	Resp
TN34	F	71	Left	V1, V2, V3	8	0	IV	III	CBZ	CBZ	Resp
TN35	F	68	Right	V1, V2	10	0	IV	III	CBZ	CBZ	Resp
TN36	F	61	Right	V1, V2, V3	10	0	V	II	PGB	No med	Resp
TN37	F	63	Right	V2, V3	8	0	IV	III	PGB	PGB	Resp
TN38	F	76	Right	V1, V2, V3	8	0	IV	II	GBP	No med	Resp
TN39	F	71	Left	V2, V3	8	0	IV	III	CBZ - GBP - BCL	CBZ	Resp
TN40	F	70	Left	V2, V3	9	0	V	II	No med*	No med	Resp
TN41	F	79	Left	V2	9	0	IV	I	GBP	No med	Resp
TN42	F	79	Right	V3	8	1	IV	III	PGB	PGB	Resp
TN43	F	74	Right	V2, V3	10	1	IV	III	GBP - CBZ	GBP - CBZ	Resp
TN44	F	70	Left	V2, V3	10	2	V	III	CBZ	CBZ	Resp
TN45	F	66	Left	V3	9	0	V	III	CBZ	CBZ	Resp
TN46	F	68	Right	V2, V3	8	0	IV	I	CBZ - GBP	No med	Resp
TN47	F	49	Left	NA	10	0	V	III	PGB	PGB	Resp
TN48	M	78	Right	NA	10	4	IV	IV	PGB - GBP	PGB - GBP	Non-Resp
TN49	M	63	Left	V3	10	4	IV	IV	CBZ	CBZ	Non-Resp
TN50	M	65	Left	V3	5	6	IV	IV	CBZ	CBZ	Non-Resp
TN51	M	73	Right	V2	10	7	IV	IV	GBP	GBP	Non-Resp
TN52	M	59	Right	V2	10	8	V	IV	CBZ	CBZ	Non-Resp
TN53	M	38	Left	V1, V2	10	9	V	V	PGB	PGB	Non-Resp
TN54	F	58	Right	V1, V2, V3	10	3	IV	III	CBZ	CBZ	Non-Resp†
TN55	F	81	Right	V2	10	3	IV	III	CBZ	CBZ	Non-Resp†
TN56	F	65	Left	V3	10	4	V	IV	GBP - ACV	GBP - ACV	Non-Resp
TN57	F	71	Right	V2, V3	10	4	V	IV	PGB	PGB	Non-Resp
TN58	F	68	Left	V2, V3	9	6	IV	V	GBP	GBP - ACV	Non-Resp
TN59	F	59	Right	V2, V3	10	6	V	IV	GBP - PGB	GBP	Non-Resp

(continued on next page)

Table 1. Continued

ID	Sex	Age	Laterality	Distribution	NRS		BNI		Medications		Group
					Pre	Post	Pre	Post	Pre	Post	
TN60	F	52	Right	V2, V3	10	6	IV	IV	CBZ	CBZ	Non-Resp
TN61	F	46	Right	V1, V2, V3	10	7	V	IV	No med*	No med*	Non-Resp

Distribution indicates the affected peripheral branches of the trigeminal nerve with (V1: ophthalmic branch; V2: maxillary branch; V3: mandibular branch). NRS corresponds to the 0-10 Numeric Rating Scale (Anchors: 0 = no pain; 10 = worst imaginable pain). BNI is Barrow Neurological Institute scale (class I: no trigeminal pain, no medication; class II: occasional pain, no medication; class III: some pain, adequately controlled with medication; class IV: some pain, not adequately controlled with medication; class V: severe pain, no pain relief). Groups are based on the pain relief and BNI scale 6 months after the surgical intervention (Resp: responders; Non-Resp: non-responders).
Abbreviations: M, male; F, females; CBZ, Carbamazepine; GBP, Gabapentin; BCL, Baclofen; LYC, Lyrica; PGB, pregabalin; TOL, Toradol; CYM, Cymbalta; HMO, Hydromorphone; TCA, Tricyclic Antidepressant; ACV, Anticonvulsant; No med, no medication.
*Indicates situation in which patients could not tolerate pharmacological treatments.
†Indicates patients that were reviewed in detail for their treatment response according to criteria outlined in section 2.3.

$$VOI_{adj} = VOI - b(SGV - SGV_{mean})$$

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 SGV, and the SGV_{mean} is the sample mean of the SGV. As such, this approach normalizes the hippocampal volume by removing the influence of the subcortical grey volume. All reported volumes are adjusted with this method.

To validate our approach to use SGV instead of total intracranial volume (ICV) to correct for individual hippocampal size, we performed a Pearson's correlation analysis between hippocampal size and SGV and ICV separately among 434 healthy subjects.

Volumetric Percent Change After Surgery

To assess sex effects in pain relief, we additionally calculated the percentage of volumetric change in the whole hippocampus using the following formula, in males and females:

$$Hippo_{change} = [(Hippo_{post-treatment} - Hippo_{pre-treatment})/ Hippo_{pre-treatment}]X100$$

Where $Hippo_{change}$ is the volumetric percent change after the surgery compared to the pre-surgery time point.

Statistical Analysis

All statistical analyses were conducted in R 3.5.1.[77] The non-parametric Wilcoxon test was used in our analyses for data that were not normally distributed. The statistical analyses include comparison of age between TN subjects and healthy controls, using a Student's t-tests; comparing hippocampal volumes pre- and post-surgery using paired Wilcoxon-test; comparing the pre- and post-surgery volume to healthy controls using Mann-Whitney U Test[65]; assessment of hippocampal volumetric percent change after treatment to pre-treatment time point using Wilcoxon singed-rank test (pre-treatment time point = no change baseline); comparison of sex differences in hippocampal changes after pain relief, using Wilcoxon signed-rank test.

All the reported p-values are corrected for multiple comparisons using Bonferroni's test with statistical analyses determined significant if $p < 0.05$.

Results

Subject Demographics

A total of 61 classical TN patients was included in this study (36F, 25M). All patients experienced unilateral facial pain (26L, 35R). All patients underwent GKRS as their first surgical treatment. The average pain duration prior to surgical intervention was 7.0 ± 7.8 years (mean ± SD, NRS scale). The average age at the time of surgery was 64.9 ± 12.0 years (F: 66.8 ± 10.1; M: 62.0 ± 14.1). Age was not statistically different between males and females (P = 0.14). The healthy cohort selected from the Cam-CAN dataset was 64.8 ± 12.1 years (36F: 66.8 ± 10.1; 25M: 62.0 ± 14.2). The age was not statistically different between the healthy and TN cohort (P = 0.99). Patient demographic information is detailed in Table 1.

Six months following the surgery, 47 patients were identified as responders (responder group), defined as at least 75% reduction in pain (including complete pain resolution) on the NRS scale and BNI sore of I-III. The average age for responders was 64.8 ± 12.1 (28F: 67.4 ± 9.7; 19M: 61.0 ± 14.4) and they reported 95% ± 11% improvement in pain on average after surgery. The remaining 14 patients were identified as non-responders, defined as less than 75% pain improvement on the NRS scale or BNI score of IV-V. Non-responders were 62.6 ± 11.9 years old on average at the time of surgery (8F: 62.5 ± 11.1; 6M: 62.7 ± 13.9) and reported a 40% ± 25% change in their pain after the surgical intervention.

SGV Strongly Correlates With Hippocampal Volume

A Pearson's correlation analysis among 434 healthy subjects from Cam-CAN dataset showed that the

hippocampus is correlated to total intracranial volume (ICV) by $R_{\text{Left Hippocampus - ICV}}$= 0.477 ($p < 0.001$), $R_{\text{Right Hippocampus - ICV}}$= 0.467 ($p$ <0.001) and to SGV by $R_{\text{Left Hippocampus - SGV}}$= 0.780 ($p < 0.001$), $R_{\text{Right Hippocampus - ICV}}$= 0.771 ($p$ <0.001). As such, our analyses showed that using SGV provides a more robust hippocampal volume normalization for head size than traditionally used ICV method.

Reversal of Structural Hippocampal Abnormalities with Pain Relief

The FreeSurfer 6.0[33] automated protocol delineated the volumetric values for the hippocampus. Hippocampal volume changes after surgery were determined for responders and non-responders, and were evaluated based on pain laterality (i.e., ipsilateral referring to the reported pain and surgical side; see Fig 1). In the responder group, the whole hippocampus volume increased bilaterally ($p_{\text{ipsilateral}} < 0.001$; $p_{\text{contralateral}}$ <0.001). In the non-responder group, the volumetric changes in the ipsi- and contralateral side were not statistically significant compared to pre-treatment ($p_{\text{ipsilateral}}$ = 0.10; $p_{\text{contralateral}}$ = 0.35). Furthermore, correlation analyses between pain reduction and hippocampal size change were not statistically significant ($r_{\text{ipsilateral}}$ = -0.063 $p_{\text{ipsilateral}}$ = 0.62, $r_{\text{contralateral}}$ = 0.030 $p_{\text{contralateral}}$ = 0.81). Similarly, correlation analyses between pain duration and volume changes in the responder cohort were not statistically significant ($r_{\text{ipsilateral}}$ = 0.007 $p_{\text{ipsilateral}}$ = 0.96, $r_{\text{contralateral}}$ = -0.127 $p_{\text{contralateral}}$ = 0.45).

Additionally, TN patients were compared to healthy individuals from the Cam-CAN database which showed hippocampus is bilaterally smaller in TN patients ($p_{\text{ipsilateral}} < 0.001$; $p_{\text{contralateral}}$ <0.001). As the number of subjects in the non-responder cohort was limited, we focused on investigating the effect of pain relief by analyzing the responder group. Our results showed that the responder cohort has significantly smaller ipsi- and contralateral whole hippocampus compared to healthy individuals ($p_{\text{ipsilateral}}$ = 0.006 $p_{\text{contralateral}}$ = 0.001) prior to the surgery. However, six months after GKRS and pain resolution, the whole hippocampus was not statistically different between those with TN and healthy individuals ($p_{\text{ipsilateral}}$ = 0.36 $p_{\text{contralateral}}$ = 0.15). The ipsi- and contralateral hippocampi were not asymmetric in neither TN (prior or after surgery) nor healthy individuals (all p values = 1). Results are summarized in Figure 2.

Hippocampal Subfields' Volume Normalize Following Pain Relief

In the responder cohort, the CA1, CA2/3, CA4, granule cell layer of the dentate gyrus (DG), molecular layer of hippocampus proper (ML HP), subiculum, and whole hippocampal body showed a significant bilateral volumetric increase compared to pre-surgery.

Presurgically, bilateral CA2/3, CA4, DG, and ML HP were smaller in TN patients compared to healthy controls. However, post-surgically, these subfields were no longer statistically different from healthy controls,

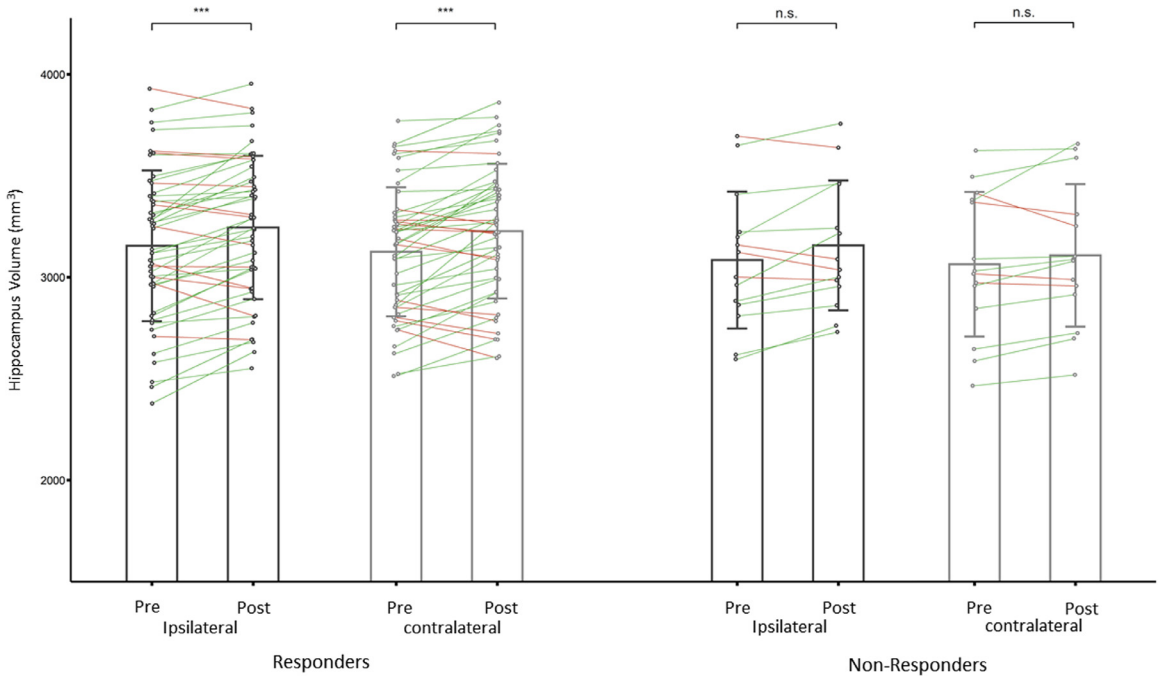

Figure 1. Hippocampal volumes in pre- and 6 months post-surgery in 47 responders and 14 non-responders TN patients. Wilcoxon-Paired Test was used for statistical analyses in pre- vs. post-surgery volumes (* $p < 0.05$, ** $P < 0.01$, *** $P < 0.001$). Lines connect the TN patients pre- and post-surgery. Black bars indicate ipsilateral results, whereas grey bars indicate contralateral results. Green lines indicate a volumetric increase from pre- to post-surgery and red lines indicated a volumetric decrease. Whole hippocampus: showing increased bilateral whole hippocampal volume in TN responders but not the non-responders 6 months after surgical intervention.

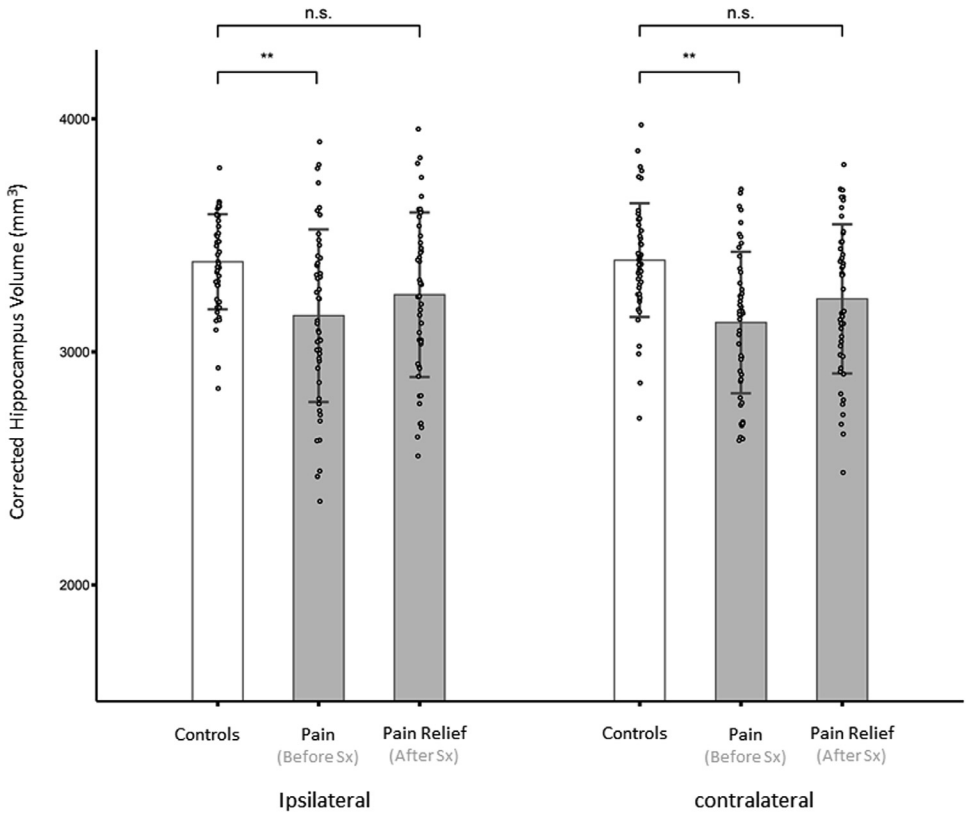

Figure 2. Automated hippocampal segmentation for 47 TN responders and their age- and sex-matched healthy controls. Results indicate bilateral smaller hippocampus in TN patients prior compared to healthy controls prior to the surgery. The volumetric differences are normalized after surgical intervention and pain relief. No asymmetry was observed in ipsi- and contra-lateral side of the hippocampus. All reported volumes are corrected for subcortical volume size (please refer to the method section). All p-values are corrected for multiple comparison using Bonferroni correction test (*$P < 0.05$, ** $P < 0.01$, *** $P < 0.001$).

indicating volumetric normalization after pain resolution. The same effect was observed on the contralateral CA1 and ipsilateral subiculum: they were statistically smaller in TN patients compared to healthy controls pre-surgery, but not post-surgery. Results are summarized in Table 2, Figure 3, and Figure 4.

Sex-dependent Changes in The Hippocampus

Both male and female TN responders showed a bilateral significant increase in the whole hippocampus volume after pain relief (see Fig 5). Following pain relief, male TN responders showed 1.68% $\pm$ 2.53 and 2.19% $\pm$ 3.43 increase on average on ipsi- and contralateral side, respectively, compared to pre-surgery time point. The volumetric increase was 4.27% $\pm$ 4.60 and 4.34 $\pm$ 4.63 in females TN responders on the ipsi- and contralateral sides, respectively. These sex-stratified analyses showed that female TN responders had a greater volumetric increase on average compared to males, which was significantly different on the ipsilateral side ($P = 0.031$).

Discussion

Increasing animal and human evidence point to the role of the hippocampus in chronic pain[2,4,6,26,60,70,82] yet little are known about the significance or possible dynamic nature of the reported hippocampal abnormalities. TN, a robust, unilateral pain syndrome with a substantial likelihood of surgical pain relief presents an ideal model to study possible pain-related hippocampal abnormalities. In our previous study of the hippocampus in TN, we demonstrated that the hippocampal subfields CA1, CA4, ML HP, and DG[99] are bilaterally smaller in untreated patients. In the current study, we showed that subregions responsible for neurogenesis and memory consolidation, demonstrate a bilateral increase in volume. Furthermore, our results indicated that the whole hippocampus, its body, CA4, ML HP, DG subfields are normalized to expected healthy control levels after the resolution of pain. We further demonstrated that the normalization or volume-recovery highlights sex-specific hippocampal plasticity in TN with a greater volumetric increase in females compared to males. Our work directly fits with important studies pointing to decreased hippocampal volumes associated with chronic stress,[16,59,78] as well as evidence for smaller hippocampal volumes in chronic pain patients with hypothalamic-pituitary-adrenal (HPA) axis hyperactivity.[97,98] Our study highlights key subfields that are vulnerable to the effects of chronic pain, and points that successful treatment can lead to recovery and normalization. Additionally, it is plausible to assume that recovery of many symptoms commonly associated with pain, such as

Table 2. Summary of Hippocampal Subfield Changes After Surgical Intervention in the Responder Cohort

Subfield	Laterality	Normalized volume (mm^3) ± SD			Corrected P-value			Subfield volume normalized after treatment
		TN pre	TN post	Healthy	TN pre vs. post	TN pre vs. healthy	TN post vs. healthy	
CA1	ipsi	586 ± 80	602 ± 77	623 ± 53	0.006†	0.326	1	
	contra	577 ± 57	594 ± 60	626 ± 59	0.024*	0.004†	0.615	✓
CA2/3	Ipsi	189 ± 32	200 ± 32	214 ±26	0.002†	0.003†	0.907	✓
	contra	186 ± 28	200 ± 29	215 ± 31	<0.001‡	<0.001‡	0.486	✓
CA4	Ipsi	233 ± 34	246 ± 33	253 ± 18	<0.001‡	0.011*	1	✓
	contra	229 ± 25	244 ± 28	255 ± 27	<0.001‡	<0.001‡	1	✓
ML HP	Ipsi	513 ± 64	531 ± 64	559 ± 36	<0.001‡	<0.001‡	0.465	✓
	contra	507 ± 51	527 ± 56	559 ± 45	<0.001‡	<0.001‡	0.304	✓
GC ML DG	ipsi	270 ± 38	283 ± 39	291 ± 23	<0.001‡	0.017*	1	✓
	contra	265 ± 30	281 ± 34	294 ± 30	<0.001‡	<0.001‡	1	✓
Pre-Sub	ipsi	277 ± 39	277 ± 36	297 ± 27	1	0.271	0.072	
	contra	278 ± 40	278 ± 37	293 ± 34	1	1	1	
Subiculum	ipsi	390 ± 46	401± 44	431±37	0.011*	0.001†	0.068	✓
	contra	391 ± 44	400 ± 46	429±38	0.026*	0.001†	0.042*	
Para-Sub	ipsi	61 ± 13	59 ± 13	58±10	1	1	1	
	contra	60 ± 12	59 ± 12	59±11	1	1	1	
Head	ipsi	1612 ± 223	1631 ± 221	1690 ± 137	1	1	1	
	contra	1580 ± 184	1608 ± 191	1700 ± 136	0.872	0.028*	0.602	✓
Body	ipsi	1078 ± 128	1114 ± 119	1162 ± 74	0.002†	0.013*	1	✓
	contra	1080 ± 108	1113 ± 101	1156 ± 99	0.009†	0.047*	1	✓
Tail	ipsi	506 ± 83	516 ± 85	521 ± 59	1	1	1	
	contra	505 ± 69	515 ± 71	523 ± 62	1	1	1	

Wilcoxon-Paired Test was used for statistical analyses in pre- vs. post-surgery volumes, and Mann-Whitney U Test was used for comparing the pre- and post-surgery volumes to healthy controls. All reported volumes are corrected for subcortical volume. All p-values are corrected for multiple comparison using Bonferroni correction. Abbreviations, CA, cornu ammonis; ML-HP, molecular layer of hippocampus proper; GC-ML-DG, granule cell and molecular layer of the dentate gyrus; Pre-Sub, pre-subiculum; Para-Sub, para-subiculum.
*p < 0.05
†p < 0.01
‡p < 0.001).

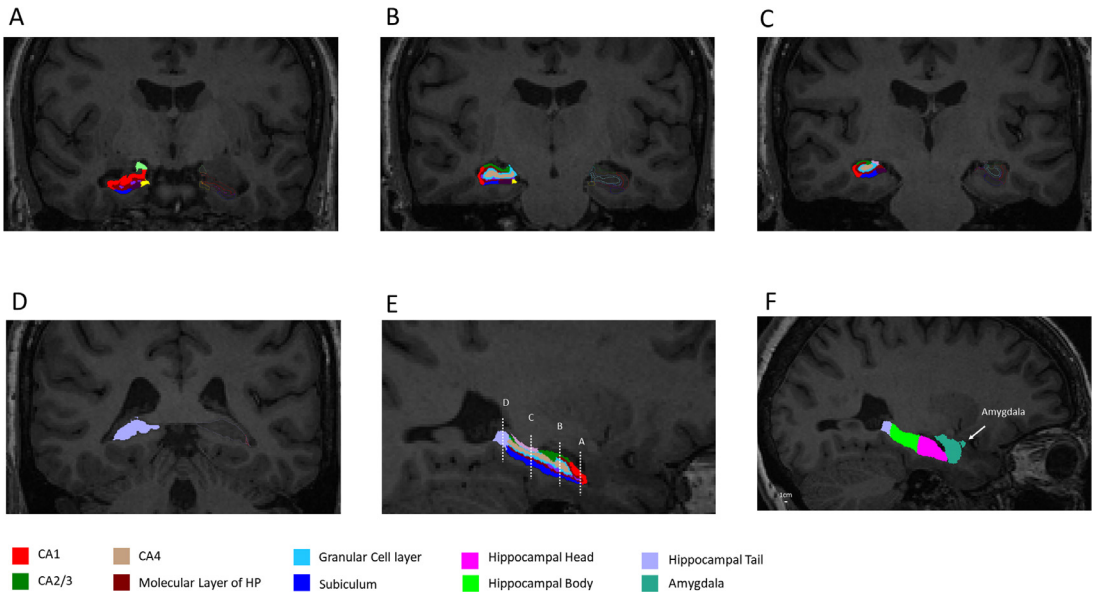

Figure 3. Automated hippocampal subfields segmentation for 47 TN responders and their age- and sex-matched healthy controls using FreeSurfer 6.0 and its developmental package. Hippocampal segmentation for an MRI scan delineated by FreeSurgery 6.0. A-D are coronal views. E and F are sagittal view.

Abbreviations: CA, cornu ammonis; ML-HP, molecular layer of hippocampus proper; GC-ML-DG, granule cell and molecular layer of the dentate gyrus.

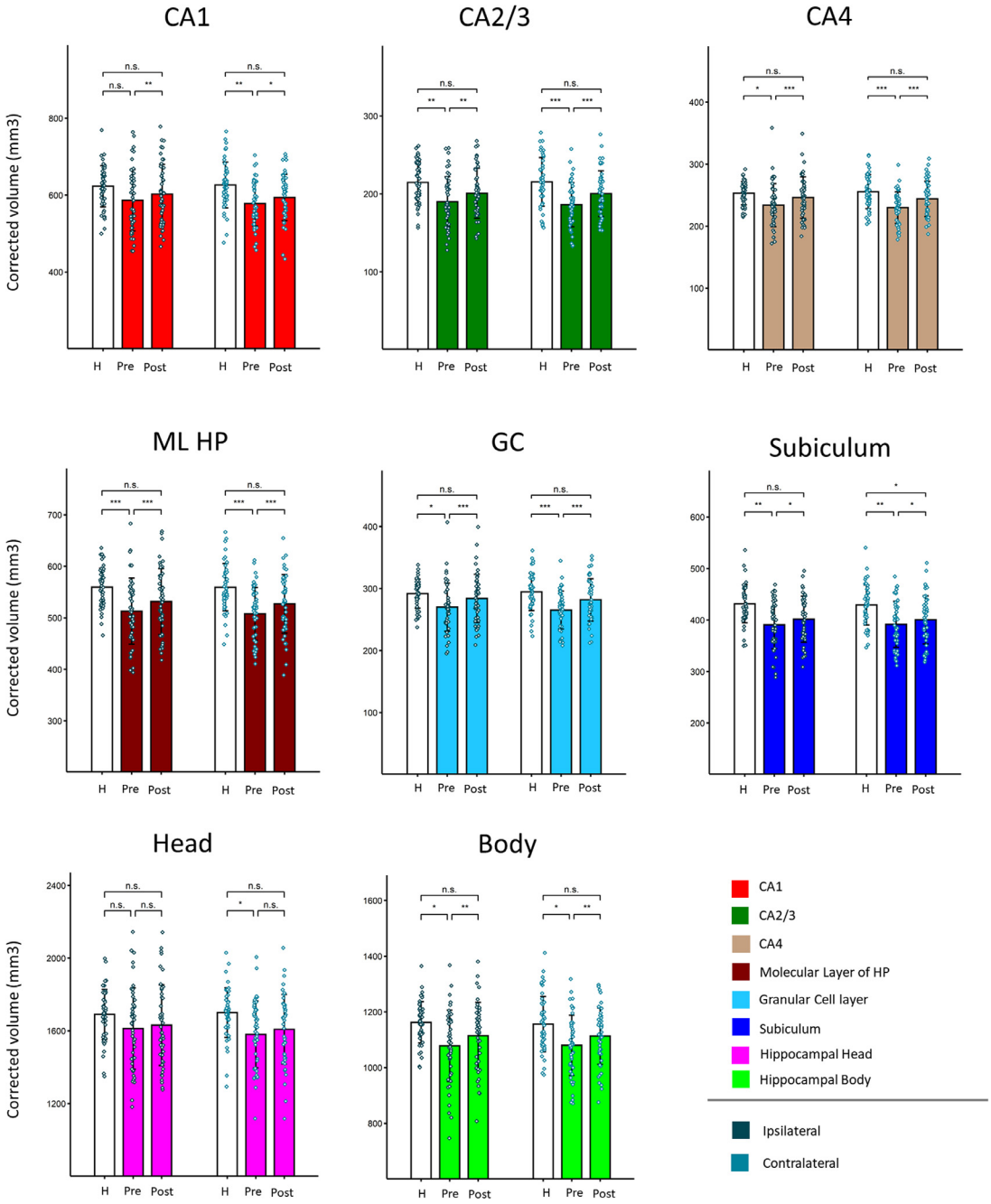

Figure 4. Hippocampal subfields change after pain relief. Wilcoxon-Paired Test was used for statistical analyses in pre- vs. post-surgery volumes, and Mann-Whitney U Test was used for comparing the pre- and post-surgery volumes to healthy controls. All reported volumes are corrected for subcortical volume size (please refer to the method section). All p-values are corrected for multiple comparison using Bonferroni correction. (*$P < 0.05$, ** $P < 0.01$, *** $P < 0.001$).

Abbreviations: CA, cornu ammonis; ML-HP, molecular layer of hippocampus proper; GC-ML-DG, granule cell and molecular layer of the dentate gyrus.

difficulty with concentration, decreased focus, and routinely reported mental fatigue[23,57,85] may in fact relate to the recovery and normalization of hippocampal structures.

Bilateral Increase in the Hippocampus and its Subregions Following Pain Resolution

The findings of our current study revealed that hippocampal volume recovers after pain relief in the responder cohort (see Fig 1). However, this increase is not observed in the non-responder cohort, who still suffer from persistent TN attacks. The recovery in responders suggests that pain relief could reverse the volumetric and microstructural abnormalities previously seen in the hippocampus. This is important to ponder when considering older individuals who are prone to cognitive decline characterized chiefly by hippocampus atrophy.[5,46,69]

Our findings demonstrated bilateral volumetric increase and normalization in hippocampal subregions including the CA2/3, CA4, ML HP, DG, and subiculum (see Fig. 4). These hippocampal subfields are involved in various roles including behavioral regulation, stress,

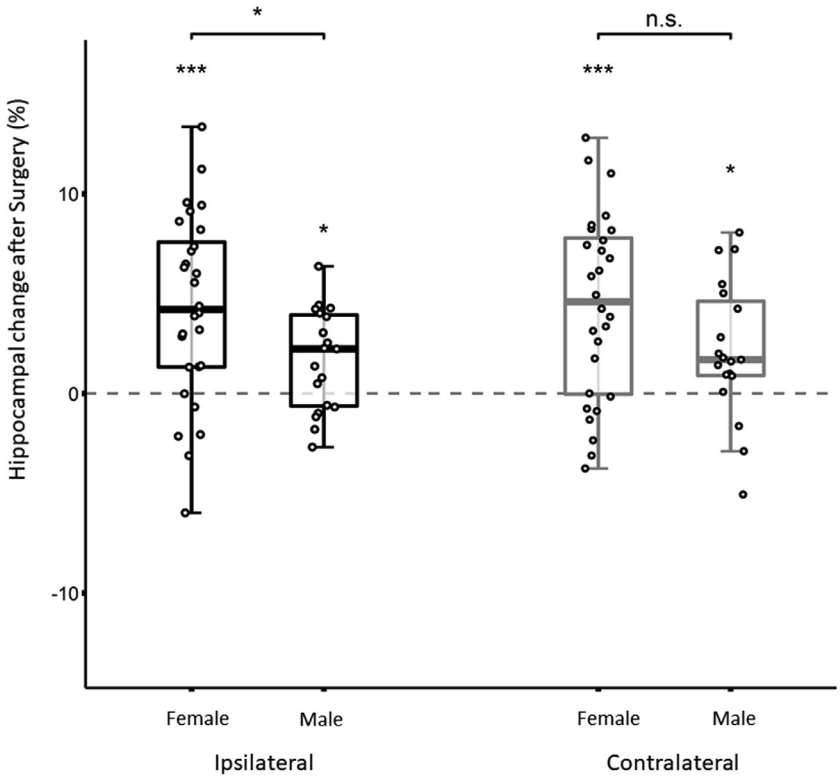

Figure 5. Hippocampal segmentation stratified by sex in the responder cohort. Subfield volume changes are calculated as: $VOI_{change} = [(VOI_{post\text{-}treatment} - VOI_{pre\text{-}treatment})/VOI_{pre\text{-}treatment}] \times 100$. Wilcoxon test is used for statistical analyses (*$P < 0.05$, ** $P < 0.01$, *** $P < 0.001$). Black bars indicate ipsilateral results, whereas grey bars indicate contralateral results.

and shaping chronic pain experience.[7,13,92,94] Morphological changes including atrophy in hippocampal CA3 pyramidal neurons have been observed in stress-induced situations.[25,101,105] As such, our results suggest pain relief which is followed by reduced TN attacks could reverse the changes in the CA3 hippocampal subfield. The hippocampus has complex afferent and efferent connections to diverse brain regions including the entorhinal cortex, cingulate cortex, prefrontal cortex, anterior thalamic nucleus, and hypothalamic mammillary bodies. Both the sensory afferent pathway (through the perforant pathway) and the efferent outputs (through the fornix) directly innervate the CA1 hippocampal subregion.[28,86,104] Here, we show a bilateral increase in CA1 subfield volume after pain relief in the responder cohort. This confirms our hypothesis that pain relief leads to increased neuroplasticity in the hippocampal region.

Neurogenesis Could Explain the Hippocampal Volume Recovery

As demonstrated in Figure 4, CA4 and DG, two hippocampal subfields involved in neuronal plasticity and neurogenesis, bilaterally increased in size, and normalized after pain resolution in TN responders. Grey matter plasticity can be due to changes in both neuronal and non-neuronal cells, including neurogenesis, gliogenesis, synaptogenesis, and other neuronal morphological changes.[108] Previous studies have reported altered adult hippocampal neurogenesis (AHN) in animal models of chronic pain.[34,100] Specifically, several studies have reported that neuropathic pain negatively affects neurogenesis[22,24,82,93], and other persistent pain conditions are related to decreases in AHN.[4,26,70] In line with these previous findings, the current study and our previous investigation reported significant bilateral volume loss in the CA4, DG, and ML HP in TN patients – all of which considered primary hippocampal subfields involved in AHN.[99]

As such, our current study provides a new line of evidence for hippocampal plasticity in chronic neuropathic conditions such as TN. Although it is not possible to pinpoint which mechanisms – neurogenesis, gliogenesis, or synaptogenesis – have caused the GM normalization, evidence suggests that the volume increase could be partially driven by neurogenesis. However, future studies are required to investigate the specific mechanisms underlying the positive effects of pain relief on AHN.

Axial Segmentation Reveals Hippocampal Body is Affected After Pain Relief

Our results demonstrated that the hippocampal body bilaterally increased in size in the responder cohort and is volumetrically normalized to the level of healthy controls (see Fig 3 and Fig 4). Furthermore, the hippocampal head showed contralateral volumetric normalization

after pain relief. These changes are important considering recent studies that showed a functional gradient along the longitudinal axis of the human hippocampus.[11,21,76] These subregions have distinct structural and functional connectivity, and subserve different behaviours.[1] In a recent meta-analysis of hippocampal abnormalities in chronic pain, Ayoub *et al.* reported that the right anterior hippocampus showed consistent abnormalities across studies. Furthermore, they tested the resting-state functional connectivity of this region in a large cohort of chronic low-back pain patients and found reduced connectivity to the medial prefrontal cortex in these patients compared to healthy individuals.[6] Although the hippocampus is involved in various functions, there is evidence that the anterior hippocampus is involved in gist memory, in other words in encoding contextual cues.[32] In the context of aversive stimuli, the anterior hippocampus has been associated with anxiety and fear-like behaviors.[17,19] The posterior hippocampus, on the other hand, is involved in fine-grained memory encoding and recall, amongst other functions.[10,32,50] Our results support the idea that the anterior hippocampus may be involved in nociception and can be affected by nociceptive input.

Sex Differences in Response to Pain Relief

Our study demonstrates that the bilateral hippocampal volume increase is seen in both males and females after pain relief (Fig 5). However, females showed a larger increase on average compared to males — especially on the hippocampus ipsilateral to TN pain where volumes were statistically greater than in males. Previous studies have delineated that there are sex differences in the adverse effects of stress on cognitive tasks and neurogenesis.[106] For example, Hillerer *et al.* have reported sex-dependent neurogenesis under chronic stress.[41] In prolonged stress conditions, females showed a reduction in neurogenesis compare to males, suggesting stress exposure has a greater impact on females compared to male.[41] Interestingly, our previous TN study reported females but not males suffer from bilateral hippocampal volume atrophy.[99] These results suggest that pain relief – which generally closely correlates with reduced stress – has a more significant impact on females than males. Considering that neurogenesis in females is more severely impacted by chronic stress, it is possible that pain relief re-establishes neurogenesis to a greater extent in females than males. As our study is the first investigation of the effect of pain relief on the hippocampus and its subfields, future studies are required to further delineate the mechanisms behind sex responses in pain relief.

Future Directions and Study Limitations

The onset of TN is usually after age 50 and the TN cohort investigated in the current study has an average age of 64.9 $\pm$ 12.0 years. Therefore, we were limited by the number of age-matched healthy controls collected on-site and had to utilize the Cam-CAN online dataset. We considered the potential impact of different imaging protocols and scanners, however, we ultimately found little evidence for that.

In the current study, the number of non-responders who did not experience pain relief after the treatment was relatively small. As such, we were statistically limited and had to focus on the responder cohort for subfield and sex-dependent analyses.

The severity of TN pain patients suffering from requires the patients to use pain medications and anticonvulsant drugs including carbamazepine, gabapentin, and pregabalin (please refer to Table 1). Although long-term use of antileptics could affect the hippocampal neuronal circuits,[38] no direct effect of these medications on the hippocampus has been reported and further investigation is required. It should also be noted that: I) given the severity of TN pain, it is not tenable to investigate a medication free population and TN studies are limited to control for the effect of medications, and II) albeit TN patients reduce their medications after GKRS, the majority still undergo pharmacological therapy and the effect of medications on the hippocampus is still present after surgery. Therefore, the findings in the current study reflect a typical TN population.

TN provides a unique opportunity to study the effect of pain relief on hippocampal abnormalities. However, few other pain conditions can be effectively treated as TN. As such, the findings of this study may be limited to TN patients and future studies are required to explore the hippocampal changes in other chronic pain conditions after treatment. Additionally, our study addresses the hippocampal changes after pain relief delineated by an MRI scan at 6 months post-GKRS. As such, the rate of recovery cannot be accurately calculated and future studies with multiple scans post-surgery are required to address this limitation. Although our study points to hippocampal recovery and possible cognitive function changes as the result, future studies are required to directly investigate this link.

Although our study did not report a statistically significant correlation between the amount of pain reduction and hippocampal size change, we note this is an important point to be investigated in future studies with a larger sample size and multiple scans after the surgery. Similarly, our analyses did not show any significant correlation between pain duration and volume changes. However, we hope future studies with a larger sample size would investigate this question and further explore sex difference and pain duration interactions.

References

1. Adnan A, Barnett A, Moayedi M, McCormick C, Cohn M, McAndrews MP: Distinct hippocampal functional networks revealed by tractography-based parcellation. Brain Struct Funct 221:2999-3012, 2016

2. Apkarian AV, Bushnell MC, Treede R-D, Zubieta JK: Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain 9:463, 2005

3. Apkarian AV, Hashmi JA, Baliki MN: Pain and the brain: Specificity and plasticity of the brain in clinical chronic pain. Pain 152:S49-S64, 2011

4. Apkarian AV, Mutso AA, Centeno MV, Kan L, Wu M, Levinstein M, Banisadr G, Gobeske KT, Miller RJ, Kessler JA, Sciences B, Radulovic J, Hen R, Kessler JA: Role of adult hippocampal neurogenesis in persistent pain. Pain 157:418-428, 2017

5. Apostolova LG, Dutton RA, Dinov ID, Hayashi KM, Toga AW, Cummings JL, Thompson PM: Conversion of mild cognitive impairment to alzheimer disease predicted by hippocampal atrophy maps. Arch Neurol 63:693-699, 2006

6. Ayoub LJ, Barnett A, Leboucher A, Golosky M, McAndrews MP, Seminowicz DA, Moayedi M: The medial temporal lobe in nociception. Pain 160:1245-1260, 2019

7. Bach DR, Hoffmann M, Finke C, Hurlemann R, Ploner CJ: Disentangling hippocampal and amygdala contribution to human anxiety-like behavior. J Neurosci 39:8517-8526, 2019

8. Bair M.J., Robinson R.L., Katon W., Kroenke K.: Depression and pain comorbidity: A literature review. Arch. Intern. Med. American Medical Association; page 2433–452003.

9. Bale TL, Epperson CN: Sex differences and stress across the lifespan. Nat Neurosci 18:1413-1420, 2015

10. Bannerman DM, Rawlins JNP, McHugh SB, Deacon RMJ, Yee BK, Bast T, Zhang WN, Pothuizen HHJ, Feldon J: Regional dissociations within the hippocampus - memory and anxiety. Neurosci Biobehav Rev 28:273-283, 2004

11. Beaujoin J, Palomero-Gallagher N, Boumezbeur F, Axer M, Bernard J, Poupon F, Schmitz D, Mangin JF, Poupon C: Post-mortem inference of the human hippocampal connectivity and microstructure using ultra-high field diffusion MRI at 11.7 T. Brain Struct Funct 223:2157-2179, 2018

12. Benoliel R., Heir G.M., Eliav E.: Neuropathic Orofacial Pain. In: Sharav Y., Benoliel R., editors. Orofac Pain Headache Elsevier Ltd; page 255–942008.

13. Berger SE, Vachon-Presseau É, Abdullah TB, Baria AT, Schnitzer TJ, Apkarian AV: Hippocampal Morphology Mediates Biased Memories of Chronic Pain, 166. Neuroimage Academic Press, 2018, pp 86-98

14. Berryman C, Stanton TR, Jane Bowering K, Tabor A, McFarlane A, Lorimer Moseley G: Evidence for working memory deficits in chronic pain: A systematic review and meta-analysis. Pain 154:1181-1196, 2013

15. Borsook D, Maleki N, Becerra L, McEwen B: Understanding migraine through the lens of maladaptive stress responses: A model disease of allostatic load. Neuron 73:219-234, 2012

16. Bremner JD, Randall P, Scott TM, Bronen RA, Seibyl JP, Southwick SM, Delaney RC, McCarthy G, Charney DS: Innis RB: MRI-based measurement of hippocampal volume in patients with combat- related posttraumatic stress disorder. Am J Psychiatry 152:973-981, 1995

17. Büchel C, Dolan RJ, Armony JL, Friston KJ: Amygdala-hippocampal involvement in human aversive trace conditioning revealed through event-related functional magnetic resonance imaging. J Neurosci 19:10869-10876, 1999

18. Buckner RL, Head D, Parker J, Fotenos AF, Marcus D, Morris JC, Snyder AZ: A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: Reliability and validation against manual measurement of total intracranial volume. Neuroimage 23:724-738, 2004

19. Cha J, Greenberg T, Song I, Blair Simpson H, Posner J, Mujica-Parodi LR: Abnormal Hippocampal Structure and Function in Clinical Anxiety and Comorbid Depression, 26. Hippocampus John Wiley and Sons Inc., 2016, pp 545-553

20. Chen DQ, DeSouza DD, Hayes DJ, Davis KD, O'Connor P, Hodaie M: Diffusivity signatures characterize trigeminal neuralgia associated with multiple sclerosis. Mult Scler 22:51-63, 2016

21. Dalton MA, McCormick C, Maguire EA: Differences in Functional Connectivity Along the Anterior-Posterior Axis of Human Hippocampal Subfields, 192. Neuroimage Academic Press, 2019, pp 38-51

22. Dellarole A, Morton P, Brambilla R, Walters W, Summers S, Bernardes D, Grilli M, Bethea JR: Neuropathic pain-induced depressive-like behavior and hippocampal neurogenesis and plasticity are dependent on TNFR1 signaling. Brain Behav Immunol 41:65-81, 2014

23. Dick BD, Rashiq S: Disruption of attention and working memory traces in individuals with chronic pain. Anesth Analg 104:1223-1229, 2007

24. Dimitrov EL, Tsuda MC, Usdin TB, Cameron HA, Dimitrov EL: Anxiety- and depression-like behavior and impaired neurogenesis evoked by peripheral neuropathy persist following resolution of prolonged tactile hypersensitivity. J Neurosci 34:12304-12312, 2014

25. Duman RS, Malberg J, Thome J: Neural plasticity to stress and antidepressant treatment. Biol Psychiatry 46:1181-1191, 1999

26. Duric V, McCarson KE: Persistent Pain Produces Stress-like Alterations in Hippocampal Neurogenesis and Gene Expression. J Pain 7:544-555, 2006

27. Eisch AJ, Petrik D: Depression and hippocampal neurogenesis: A road to remission? Science 338:72-75, 2012

28. Empson RM, Heinemann U: The perforant path projection to hippocampal area CA1 in the rat hippocampal-entorhinal cortex combined slice. J Physiol 484:707-720, 1995

29. Ezzati A, Zammit AR, Lipton ML, Lipton RB: The relationship between hippocampal volume, chronic pain, and depressive symptoms in older adults. Psychiatry Res - Neuroimaging 289:10-12, 2019

30. Ezzati A, Zimmerman ME, Katz MJ, Sundermann EE, Smith JL, Lipton ML, Lipton RB: Hippocampal subfields differentially correlate with chronic pain in older adults. Brain Res 1573:54-62, 2014

31. Falconer EM, Galea LAM: Sex differences in cell proliferation, cell death and defensive behavior following acute predator odor stress in adult rats. Brain Res 975:22-36, 2003

32. Fanselow MS, Dong HW: Are the Dorsal and Ventral Hippocampus Functionally Distinct Structures? Neuron 65:7-19, 2010

33. Fischl B: FreeSurfer. Neuroimage 62:774-781, 2012

34. Grilli M: Chronic pain and adult hippocampal neurogenesis: Translational implications from preclinical studies. J Pain Res 10:2281-2286, 2017

35. Grisart J, Van Der Linden M, Masquelier E: Controlled processes and automaticity in memory functioning in fibromyalgia patients: Relation with emotional distress and hypervigilance. J Clin Exp Neuropsychol 24:994-1009, 2002

36. Grisart JM, Van der Linden M: Conscious and automatic uses of memory in chronic pain patients. Pain 94:305-313, 2001

37. Gureje O, Von Korff M, Kola L, Demyttenaere K, He Y, Posada-Villa J, Lepine JP, Angermeyer MC, Levinson D, de Girolamo G, Iwata N, Karam A, Luiz Guimaraes Borges G, de Graaf R, Browne MO, Stein DJ, Haro JM, Bromet EJ, Kessler RC, Alonso J: The relation between multiple pains and mental disorders: Results from the World Mental Health Surveys. Pain 135:82-91, 2008

38. Haneef Z, Levin HS, Chiang S: Brain graph topology changes associated with anti-epileptic drug use. Brain Connect 5:284-291, 2015

39. Hayes DJ, Chen DQ, Zhong J, Lin A, Behan B, Walker M, Hodaie M: Affective circuitry alterations in patients with trigeminal neuralgia. Front Neuroanat 11, 2017

40. De Heer EW, Gerrits MMJG, Beekman ATF, Dekker J, Van Marwijk HWJ, De Waal MWM, Spinhoven P, Penninx BWJH, Van Der Feltz-Cornelis CM: The Association of depression and anxiety with pain: A study from NESDA. PLoS One 9, 2014

41. Hillerer KM, Neumann ID, Couillard-Despres S, Aigner L, Slattery DA: Sex-dependent regulation of hippocampal neurogenesis under basal and chronic stress conditions in rats. Hippocampus 23:476-487, 2013

42. Hodaie M, Coello AF: Advances in the management of trigeminal neuralgia. J Neurosurg Sci 57:13-21, 2013

43. Hung PSP, Tohyama S, Zhang JY, Hodaie M: Temporal disconnection between pain relief and trigeminal nerve microstructural changes after Gamma Knife radiosurgery for trigeminal neuralgia. J Neurosurg 1-9, 2019

44. Iglesias JE, Augustinack JC, Nguyen K, Player CM, Player A, Wright M, Roy N, Frosch MP, McKee AC, Wald LL, Fischl B, Van Leemput K: A Computational Atlas of the Hippocampal Formation Using Ex vivo, Ultra-High Resolution MRI: Application to Adaptive Segmentation of in vivo MRI, 115. Neuroimage Academic Press Inc., 2015, pp 117-137

45. Jensen MP, McFarland CA: Increasing the reliability and validity of pain intensity measurement in chronic pain patients. Pain 55:195-203, 1993

46. Kälin AM, Park MTM, Chakravarty MM, Lerch JP, Michels L, Schroeder C, Broicher SD, Kollias S, Nitsch RM, Gietl AF, Unschuld PG, Hock C, Leh SE: Subcortical shape changes, hippocampal atrophy and cortical thinning in future Alzheimer's disease patients. Front Aging Neurosci 9, 2017

47. Kim EJ, Pellman B, Kim JJ: Stress effects on the hippocampus: A critical review. Learn Mem 22:411-416, 2015

48. Kim JJ, Diamond DM: The stressed hippocampus, synaptic plasticity and lost memories. Nat Rev Neurosci 3:453-462, 2002

49. Kim JJ, Lee HJ, Welday AC, Song EY, Cho J, Sharp PE, Jung MW, Blair HT: Stress-induced alterations in hippocampal plasticity, place cells, and spatial memory. Proc Natl Acad Sci U S A 104:18297-18302, 2007

50. Kjelstrup KG, Tuvnes FA, Steffenach HA, Murison R, Moser EI, Moser MB: Reduced fear expression after lesions of the ventral hippocampus. Proc Natl Acad Sci U S A 99:10825-10830, 2002

51. Knierim JJ: The hippocampus. Curr Biol 25:R1116-R1121, 2015

52. Kondziolka D, Zorro O, Lobato-Polo JE, Kano H, Flannery TJ, Flickinger JC, Lunsford LD: Gamma Knife stereotactic radiosurgery for idiopathic trigeminal neuralgia. J Neurosurg 112:758-765, 2010

53. Kruschke JK: Bayesian estimation supersedes the t test. J Exp Psychol Gen 142:573-603, 2013

54. Leclercq D, Thiebaut JB, Héran F: Trigeminal neuralgia. Diagn Interv Imaging 94:993-1001, 2013

55. Lewis GN, Parker RS, Sharma S, Rice DA, McNair PJ: Structural brain alterations before and after total knee arthroplasty: A longitudinal assessment. Pain Med 19:2166-2176, 2018

56. Li ST, Pan Q, Liu N, Shen F, Liu Z, Guan Y, Sindou M, Burchiel KJ: Trigeminal neuralgia: What are the important factors for good operative outcomes with microvascular decompression. Surg Neurol 62:400-404, 2004

57. Ling J, Campbell C, Heffernan TM, Greenough CG: Short-term prospective memory deficits in chronic back pain patients. Psychosom Med 69:144-148, 2007

58. Loeser JD, Melzack R: Pain: An overview. Lancet 353:1607-1609, 1999

59. Logue MW, van Rooij SJH, Dennis EL, Davis SL, Hayes JP, Stevens JS, Densmore M, Haswell CC, Ipser J, Koch SBJ, Korgaonkar M, Lebois LAM, Peverill M, Baker JT, Boedhoe PSW, Frijling JL, Gruber SA, Harpaz-Rotem I, Jahanshad N, Koopowitz S, Levy I, Nawijn L, O'Connor L, Olff M, Salat DH, Sheridan MA, Spielberg JM, van Zuiden M, Winternitz SR, Wolff JD, Wolf EJ, Wang X, Wrocklage K, Abdallah CG, Bryant RA, Geuze E, Jovanovic T, Kaufman ML, King AP, Krystal JH, Lagopoulos J, Bennett M, Lanius R, Liberzon I, McGlinchey RE, McLaughlin KA, Milberg WP, Miller MW, Ressler KJ, Veltman DJ, Stein DJ, Thomaes K, Thompson PM, Morey RA: Smaller hippocampal volume in posttraumatic stress disorder: A Multisite ENIGMA-PGC Study: Subcortical volumetry results from posttraumatic stress disorder consortia. Biol Psychiatry 83:244-253, 2018

60. Maleki N, Becerra L, Brawn J, McEwen B, Burstein R, Borsook D: Common hippocampal structural and functional changes in migraine. Brain Struct Funct 218:903-912, 2013

61. Mansour AR, Farmer MA, Baliki MN, Apkarian AV: Chronic pain: The role of learning and brain plasticity. Restor Neurol Neurosci 32:129-139, 2014

62. Martínez Moreno NE, Gutiérrez-Sárraga J, Rey-Portolés G, Jiménez-Huete A, Martínez Álvarez R: Long-Term Outcomes in the treatment of classical trigeminal neuralgia by gamma knife radiosurgery: A retrospective study in patients with minimum 2-year follow-up. Neurosurgery 79:879-887, 2016

63. Mazza S, Frot M, Rey AE: A comprehensive literature review of chronic pain and memory. Prog Neuro-Psychopharmacology Biol Psychiatry 87:183-192, 2018

64. McCarberg B, Peppin J: Pain pathways and nervous system plasticity: Learning and memory in pain. Pain Med 20:2421-2437, 2019

65. McKnight P.E., Najab J.: Mann-Whitney U Test. In: Weiner I.B., Craighead W.E., editors. Corsini Encycl Psychol Hoboken, NJ, USA: John Wiley & Sons, Inc.; page 1−12010.

66. Mifflin K, Chorney J, Dick B: Attention and working memory in female adolescents with chronic pain and pain-free female adolescents. Clin J Pain 32:609-616, 2016

67. Moriarty O, McGuire BE, Finn DP: The effect of pain on cognitive function: A review of clinical and preclinical research. Prog Neurobiol 93:385-404, 2011

68. Moriarty O, Ruane N, O'Gorman D, Maharaj CH, Mitchell C, Sarma KM, Finn DP, McGuire BE: Cognitive impairment in patients with chronic neuropathic or radicular pain: An interaction of pain and age. Front Behav Neurosci 11, 2017

69. Mueller SG, Schuff N, Yaffe K, Madison C, Miller B, Weiner MW: Hippocampal atrophy patterns in mild cognitive impairment and alzheimer's disease. Hum Brain Mapp 31:1339-1347, 2010

70. Mutso AA, Petre B, Huang L, Baliki MN, Torbey S, Herrmann KM, Schnitzer TJ, Apkarian AV: Reorganization of hippocampal functional connectivity with transition to chronic back pain. J Neurophysiol 111:1065-1076, 2014

71. Mutso AA, Radzicki D, Baliki MN, Huang L, Banisadr G, Centeno MV, Radulovic J, Martina M, Miller RJ, Vania Apkarian A, Apkarian AV: Abnormalities in Hippocampal Functioning with Persistent Pain. J Neurosci 32:5747-5756, 2012

72. Naninck EFG, Hoeijmakers L, Kakava-Georgiadou N, Meesters A, Lazic SE, Lucassen PJ, Korosi A: Chronic Early Life Stress Alters Developmental and Adult Neurogenesis and Impairs Cognitive Function in Mice, 25. Hippocampus John Wiley and Sons Inc., 2015, pp 309-328

73. O'Keefe J, Dostrovsky J: The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. Brain Res 34:171-175, 1971

74. Oosterman JM, Derksen LC, van Wijck AJM, Veldhuijzen DS, Kessels RPC: Memory functions in chronic pain: Examining contributions of attention and age to test performance. Clin J Pain 27:70-75, 2011

75. Park DC, Glass JM, Minear M, Crofford LJ: Cognitive function in fibromyalgia patients. Arthritis Rheum 44:2125-2133, 2001

76. Poppenk J, Evensmoen HR, Moscovitch M, Nadel L: Long-axis specialization of the human hippocampus. Trends Cogn Sci 17:230-240, 2013

77. R Core Team: R: A language and environment for statistical computing., 2018. Available at: http://www.r-project.org/

78. Rahman MM, Callaghan CK, Kerskens CM, Chattarji S, O'Mara SM: Early hippocampal volume loss as a marker of eventual memory deficits caused by repeated stress. Sci Rep 6:1-15, 2016

79. Regis J., Tuleasca C., Resseguier N., Carron R., Donnet A., Gaudart J., Levivier M.: Long-term safety and effiacy of Gamma Knife surgery in classical trigeminal neuralgia: A 497-patient historical cohort study. J. Neurosurg. 1079−872016.

80. Rodriguez CS: Pain measurement in the elderly: A review. Pain Manag Nurs 2:38-46, 2001

81. Rogers CL, Shetter AG, Fiedler JA, Smith KA, Han PP, Speiser BL: Gamma knife radiosurgery for trigeminal neuralgia: The initial experience of the Barrow Neurological Institute. Int J Radiat Oncol Biol Phys 47:1013-1019, 2000

82. Romero-Grimaldi C, Berrocoso E, Alba-Delgado C, Madrigal JLM, Perez-Nievas BG, Leza JC, Mico JA: Stress increases the negative effects of chronic pain on hippocampal neurogenesis. Anesth Analg 121:1078-1088, 2015

83. Sanfilipo MP, Benedict RHB, Zivadinov R, Bakshi R: Correction for intracranial volume in analysis of whole brain atrophy in multiple sclerosis: The proportion vs. residual method. Neuroimage 22:1732-1743, 2004

84. Saygin ZM, Kliemann D, Iglesias JE, van der Kouwe AJW, Boyd E, Reuter M, Stevens A, Van Leemput K, McKee A, Frosch MP, Fischl B, Augustinack JC: High-resolution magnetic resonance imaging reveals nuclei of the human amygdala: manual segmentation to automatic atlas. Neuroimage 155:370-382, 2017

85. Schnurr RF, MacDonald MR: Memory complaints in chronic pain. Clin J Pain 11, 1995

86. Schultz C., Engelhardt M.: Anatomy of the Hippocampal Formation. In: Szabo K., Hennerici M.G., editors. Hippocampus Clin Neurosci S. Karger AG; 6−172014.

87. Seminowicz DA, Wideman TH, Naso L, Hatami-Khoroushahi Z, Fallatah S, Ware MA, Jarzem P, Bushnell MC, Shir Y, Ouellet JA, Stone LS: Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. J Neurosci 31:7540-7550, 2011

88. Shafto MA, Tyler LK, Dixon M, Taylor JR, Rowe JB, Cusack R, Calder AJ, Marslen-Wilson WD, Duncan J, Dalgleish T, Henson RN, Brayne C, Bullmore E, Campbell K, Cheung T, Davis S, Geerligs L, Kievit R, McCarrey A, Price D, Samu D, Treder M, Tsvetanov K, Williams N, Bates L, Emery T, Erzinçlioglu S, Gadie A, Gerbase S, Georgieva S, Hanley C, Parkin B, Troy D, Allen J, Amery G, Amunts L, Barcroft A, Castle A, Dias C, Dowrick J, Fair M, Fisher H, Goulding A, Grewal A, Hale G, Hilton A, Johnson F, Johnston P, Kavanagh-Williamson T, Kwasniewska M, McMinn A, Norman K, Penrose J, Roby F, Rowland D, Sargeant J, Squire M, Stevens B, Stoddart A, Stone C, Thompson T, Yazlik O, Barnes D, Hillman J, Mitchell J, Villis L, Matthews FE: The Cambridge Centre for Ageing and Neuroscience (Cam-CAN) study protocol: A cross-sectional, lifespan, multidisciplinary examination of healthy cognitive ageing. BMC Neurol 14, 2014

89. Shors TJ: Stressful Experience and Learning Across the Lifespan. Annu Rev Psychol 57:55-85, 2006

90. Sjogren P, Christrup LL, Petersen MA, Hojsted J: Neuropsychological assessment of chronic non-malignant pain patients treated in a multidisciplinary pain centre. Eur J Pain 9:453, 2005

91. Strange BA, Witter MP, Lein ES, Moser EI: Functional organization of the hippocampal longitudinal axis. Nat Rev Neurosci 15:655-669, 2014

92. Tajerian M, Hung V, Nguyen H, Lee G, Joubert LM, Malkovskiy AV, Zou B, Xie S, Huang TT, Clark JD: The hippocampal extracellular matrix regulates pain and memory after injury. Mol Psychiatry 23:2302-2313, 2018

93. Terada M, Kuzumaki N, Hareyama N, Imai S, Niikura K, Narita M, Yamazaki M, Suzuki T, Narita M: Suppression of enriched environment-induced neurogenesis in a rodent model of neuropathic pain. Neurosci Lett 440:314-318, 2008

94. Thompson JM, Neugebauer V: Cortico-limbic pain mechanisms. Neurosci Lett 702:15-23, 2019

95. Timmers I, Quaedflieg CWEM, Hsu C, Heathcote LC, Rovnaghi CR, Simons LE: The interaction between stress and chronic pain through the lens of threat learning. Neurosci Biobehav Rev 107:641-655, 2019

96. Tohyama S, Hung PSP, Zhong J, Hodaie M: Early postsurgical diffusivity metrics for prognostication of long-term pain relief after Gamma Knife radiosurgery for trigeminal neuralgia. J Neurosurg 131:539-548, 2018

97. Travis SG, Coupland NJ, Hegadoren K, Silverstone PH, Huang Y, Carter R, Fujiwara E, Seres P, Malykhin NV: Effects of cortisol on hippocampal subfields volumes and memory performance in healthy control subjects and patients with major depressive disorder. J Affect Disord 201:34-41, 2016

98. Vachon-Presseau E, Roy M, Martel MO, Caron E, Marin MF, Chen J, Albouy G, Plante I, Sullivan MJ, Lupien SJ, Rainville P: The stress model of chronic pain: Evidence from basal cortisol and hippocampal structure and function in humans. Brain 136:815-827, 2013

99. Vaculik MF, Noorani A, Hung PSP, Hodaie M: Selective hippocampal subfield volume reductions in classic trigeminal neuralgia. NeuroImage Clin 23:101911, 2019

100. Vasic V, Schmidt MHH: Resilience and vulnerability to pain and inflammation in the hippocampus. Int J Mol Sci 18, 2017

101. Watanabe Y, Gould E, McEwen BS: Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. Brain Res 588:341-345, 1992

102. Whitlock EL, Diaz-Ramirez LG, Glymour MM, Boscardin WJ, Covinsky KE, Smith AK: Association between persistent pain and memory decline and dementia in a longitudinal cohort of elders. JAMA Intern Med 177, 2017

103. Wingenfeld K., Wolf O.T.: Stress, memory, and the hippocampus. In: Szabo K., Hennerici M.G., editors. Hippocampus Clin Neurosci S. Karger AG; page 109−202014.

104. Witter M.P.: Connectivity of the Hippocampus. In: Cutsuridis V., Graham B., Cobb S., Vida I., editors. Hippocampal Microcircuits Springer New York; page 5−262010.

105. Woolley CS, Gould E, McEwen BS: Exposure to excess glucocorticoids alters dendritic morphology of adult hippocampal pyramidal neurons. Brain Res 531:225-231, 1990

106. Yagi S, Galea LAM: Sex differences in hippocampal cognition and neurogenesis. Neuropsychopharmacology 44:200-213, 2019

107. Zakrzewska JM, Linskey ME: Trigeminal neuralgia. BMJ 348, 2014. g474−g474

108. Zatorre RJ, Fields RD, Johansen-Berg H: Plasticity in gray and white: Neuroimaging changes in brain structure during learning. Nat Neurosci 15:528-536, 2012