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Painful Heat Reveals Hyperexcitability of the Temporal Pole in Interictal and Ictal Migraine States

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During migraine attacks, alterations in sensation accompanying headache may manifest as allodynia and enhanced sensitivity to light, sound, and odors. Our objective was to identify physiological changes in cortical regions in migraine patients using painful heat and functional magnetic resonance imaging (fMRI) and the structural basis for such changes using diffusion tensor imaging (DTI). In 11 interictal patients, painful heat threshold + 1°C was applied unilaterally to the forehead during fMRI scanning. Significantly greater activation was identified in the medial temporal lobe in patients relative to healthy subjects, specifically in the anterior temporal pole (TP). In patients, TP showed significantly increased functional connectivity in several brain regions relative to controls, suggesting that TP hyperexcitability may contribute to functional abnormalities in migraine. In 9 healthy subjects, DTI identified white matter connectivity between TP and pulvinar nucleus, which has been related to migraine. In 8 patients, fMRI activation in TP with painful heat was exacerbated during migraine, suggesting that repeated migraines may sensitize TP. This article investigates a nonclassical role of TP in migraineurs. Observed temporal lobe abnormalities may provide a basis for many of the perceptual changes in migraineurs and may serve as a potential interictal biomarker for drug efficacy.

Keywords: DTI, fMRI, headache, pain, temporal lobe

Introduction

Migraine is a common cause of headache and features an array of multisensory symptoms. The acute phase of migraine is well characterized clinically and consists of pain usually affecting one side of the head and has accompanying symptoms that include sensitivity to light, sound, and odors (Charles 2009). During and between migraine attacks, other features may include gastrointestinal (Boyle et al. 1990; Aurora et al. 2006), autonomic (Peroutka 2004; Melek et al. 2007), and psychological changes (Lanteri-Minet et al. 2005; Hamelsky and Lipton 2006; Radat et al. 2009). While the triggering mechanisms of migraine are not clearly defined, some abnormality in brain function may form the basis of repeated attacks (Weiller et al. 1995; Bahra et al. 2001; Welch et al. 2001; Afridi, Matharu, et al. 2005; Rocca et al. 2006; Moulton et al. 2008), which in turn may induce additional changes in brain function. Such changes may be observed in the interictal (i.e., between attacks) migraine brain.

Perhaps related to the multisensory symptoms that accompany migraine attacks, a number of studies have suggested that the interictal migraine brain may have altered functional processing of sensory information. Evidence of altered brain function include altered pain modulation (Sandrini et al. 2006), brain metabolism (Kim et al. 2009), visual evoked responses (Afra et al. 2000; Backer et al. 2001; Coppola et al. 2007), auditory evoked responses (Wang et al. 1996; Afra et al. 2000; Ambrosini et al. 2003), somatosensory evoked responses (Lang et al. 2004), motor excitability as induced by transcranial magnetic stimulation (Afra et al. 1998), and nociceptive processing (Katsarava et al. 2003; de Tommaso et al. 2005, 2007; Di Clemente et al. 2007). Neurochemical and structural evidence suggests that interictal migraine patients have altered levels of neurotransmitters (Prescot et al. 2009), brain morphology (Welch et al. 2001; Rocca et al. 2006; DaSilva et al. 2007; Valfre et al. 2008; Kim et al. 2009), occupancy of 5HT-1A receptors (Lothe et al. 2008), and brain vasculature (de Hoon et al. 2003). Taken together, most of the data suggest a "dys-excitable" brain (Stankewitz and May 2009) in which a number of functional abnormalities may be preconditioned and show fulminate manifestation in the migraine state.

Though alterations in sensory, emotional, and autonomic function have been reported previously during the interictal period, few reports outside of electroencephalography have evaluated brain changes following a noxious thermal stimulus (Valeriani et al. 2003; de Tommaso et al. 2005, 2007). These EEG studies suggest that interictal migraine patients have reduced cortical habituation to noxious laser stimuli, as well as a reduced capacity for diffuse noxious inhibitory control to modulate pain. Note that heat pain thresholds in episodic migraine patients during the interictal phase do not appear different from those observed in healthy controls (Burstein et al. 2000).

Functional magnetic imaging (fMRI) studies of migraine often compare patients during attacks versus at rest, but the interictal phase (i.e., between attacks) may not be a suitable negative baseline control due to the abnormalities in cortical structure and processing as described above. In Experiment 1, we used a stressor in the form of noxious heat to evaluate brain activation patterns in a cohort of patients with acute intermittent migraine during their interictal period and compared these with age–gender–matched controls. We hypothesized that migraine patients versus healthy controls have increased cortical responses in sensory, emotional, and autonomic regions in response to perceptually similar noxious heat (pain threshold +1°C) applied to the face. In interictal migraine patients, we found that the temporal lobe showed significantly increased activation, particularly in the anterior temporal pole (TP) and entorhinal cortex (EC). The TP

exhibited increased functional connectivity in structures related to pain processing in interictal migraine patients relative to controls. Based on Experiment 1, we hypothesized that these medial temporal lobe areas would show further activation during a migraine attack. Therefore, in Experiment 2, we implemented a region of interest (ROI)–based analysis on a separate group of 8 migraineurs during their attack versus interictal phase. The TP showed increased activation to painful heat during migraine attack. In Experiment 3, we used diffusion tensor imaging (DTI) to consider the connectivity of the TP with a potential nociceptive trigeminothalamic pathway. Structural tractography results indicated that the TP has extensive white matter connections with the pulvinar nucleus, a structure in the posterior thalamus implicated with sensitization during migraine attacks (Burstein et al. forthcoming). These functional and structural results indicate that the temporal lobe, and in particular the TP, may have a hitherto undiscovered role in migraine.

Materials and Methods

Experiment 1: Painful Heat fMRI Activation in Interictal Migraine Patients versus Healthy Controls

Using fMRI, we recorded blood oxygen level–dependent (BOLD) responses to heat stimuli in 11 episodic migraine patients. Scans were collected to measure responses to noxious heat (pain threshold +1°C). Stimuli were applied to the forehead on the affected side (as reported during an attack). The identical protocol was repeated in 11 age–gender–matched control subjects, and the side tested corresponded to that in the matched migraine patients.

Subjects

Episodic migraine patients (8 females, 3 males; 42·5 ± 11·9 years old; Table 1) were free of neurological and other sensory dysfunctions, although 2 patients were taking antidepressants. Six of the patients in the study had acute intermittent migraine without aura (<15 headache days/month) as defined by the International Headache Society (Olesen 2004). The IHS definition for migraine without aura consists of the occurrence of more than 5 headache attacks that fulfill the following criteria: 1) attacks lasting 4–72 h when untreated/unsuccessfully treated; 2) featuring at least 2 of the following characteristics: unilateral, pulsating, moderate-to-severe pain intensity, and aggravation by/causing avoidance of routine physical activity; 3) featuring nausea/vomiting and/or photophobia/phonophobia; and 4) the attack cannot be attributed to any other disorder. Five of the patients reported having migraines with aura, which were visual (n = 3), somatosensory (n = 1), or sensorimotor (n = 1) in quality. During screening, one patient reported that menstruation was a trigger for her migraine. The majority of these migraine patients experienced 1–2 migraines per week. Subjects were not having a migraine attack at least 72 h prior to testing. In addition, no patient had a migraine precipitated during or on the day following the baseline scan. Though patients were not surveyed days after their scan, the possibility that they could have an imminent impending attack seems unlikely given that no sensory differences were detected between the migraine and healthy subjects in this study. Subjects verbally rated the pain intensity of their average migraine as a 5 or higher on a 0–10 scale, with 10 being the most intense pain imaginable. For those patients taking daily medications (e.g., preventive as opposed to acute medications to abort the attack), patients abstained from taking their migraine medications (Supplementary Table 1) for one dosing interval (12–24 h) prior to their scheduled scan session to control for acute dosing effects. Age- and gender-matched healthy subjects (8 females, 3 males; 42·3 ± 11·9 years old) were also tested. This study was approved by the McLean Hospital Institutional Review Board and met the scientific and ethical guidelines for human research of the Helsinki Accord (http://ohsr.od.nih.gov/guidelines/helsinki.html). All patients and subjects provided written informed consent to participate in this study.

Table 1
Subject demographics for Experiment 1—interictal migraine patients and controls

Patient no.	Sex	Age	Side	Threshold +1°C
1	F	30	L	48.7
2	M	57	L	48.3
3	F	57	L	43.7
4	F	44	L	50.0
5	F	57	R	49.5
6	M	49	L	47.0
7	F	29	L	49.6
8	M	35	L	48.2
9	F	28	R	42.6
10	F	33	R	50.0
11	F	49	L	48.8
Average	—	42.5 (SD 11.9)	—	47.9 (SD: 2.5)
Control no.	Sex	Age	Side	Thr+1°C
1	F	30	L	47.6
2	M	54	L	41.2
3	F	59	L	43.8
4	F	45	L	45.3
5	F	55	R	41.1
6	M	51	L	48.7
7	F	26	L	48.4
8	M	36	L	45.4
9	F	27	R	49.6
10	F	35	R	44.1
11	F	47	L	50.0
Average	—	42.3 (SD 11.9)	—	45.9 (SD: 3.2)

Stimuli

Temperatures were delivered using a 1.6 × 1.6-cm contact thermode (TSA-II; Medoc Advanced Medical Systems). Only the side of the face that was reported as sensitive during migraines by the patients was tested. The controls were matched to their corresponding migraine patient with regard to the side of the face tested. Heat pain thresholds were determined using an ascending method of limits. Subjects were presented with a 32 °C baseline temperature that increased 1 °C/s until they indicated their first detection of pain. Pain threshold was calculated as the average of 3 repetitions. Functional scans began with 40 s of the baseline temperature (32 °C) followed by three 15-s stimuli, each separated by 30 s. The rate of temperature change was 4 °C/s.

MR Acquisition

Imaging was conducted using a 3T Siemens Trio scanner with a quadrature head coil. T_1-weighted structural images were acquired using a 3D magnetization prepared rapid gradient echo (MP-RAGE) with established imaging parameters (Moulton et al. 2007). For functional scans, a gradient echo echo planar imaging (EPI) sequence with time echo (TE)/time repetition (TR) = 30/2500 was performed, with 74 volumes captured for each scan. Each functional scan consisted of 33 slices oriented in an oblique plane to match the brainstem axis. Slices were 3.5 mm thick with an in-plane resolution of 3.5 mm (64 × 64).

Image Analysis

Functional imaging data sets were processed and analyzed using scripts within FMRIB's Software Library (FSL, http://www.fmrib.ox.ac.uk/fsl) (Smith et al. 2004). The initial 2 volumes were removed from each of the functional scans to allow for signal equilibration. Visual screening of the functional volumes revealed that none of the subjects showed indications of gross movement (>1 voxel). The skull and other nonbrain areas were extracted from the anatomical and functional scans using FSL's script Brain Extraction Tool (BET). Motion correction using FMRIB's Linear Image Registration Tool (MCFLIRT) was performed on each functional scan. All volumes were mean-based intensity normalized by the same factor. The volumes were spatially smoothed with a 5-mm full-width at half-maximum (FWHM) filter, and a 75-s high-pass temporal filter was applied. These functional images were then coregistered with the anatomical images using FMRIB's

Linear Image Registration Tool (FLIRT), which uses an automated affine registration algorithm.

First-level fMRI analysis of single subject data was performed using FMRI Expert Analysis Tool using FMRIB's improved linear model (FEAT FILM), version 5.4, with local autocorrelation correction (Woolrich et al. 2001). The explanatory variables (EVs) for thermal stimuli were entered using the recorded temperature traces for each subject. Subjects were spatially normalized to the MNI152 brain for group analysis, and patients with right-sided migraines (n = 3) had their images flipped along the y-axis to correspond with the majority of the patients with left-sided migraine. The use of flipped brains in fMRI analysis is a well-described procedure in clinical pain studies (Maihofner et al. 2006; Pleger et al. 2006; Schweinhardt et al. 2006). This was also repeated in the 3 corresponding control subjects.

Group activation maps were generated by fMRI Expert Analysis Tool (FEAT) fMRIB's Local Analysis of Mixed Effects (FLAME). A mixed effects contrast analysis was performed to compare migraine versus control group activation. Statistical parametric maps were thresholded using Gaussian mixture modeling (GMM) (Pendse et al. 2009), a multiple comparisons-based analysis that has previously been used in the context of detecting activation in functional brain imaging (Becerra et al. 2006; Moulton et al. 2007; Moulton, Pendse, et al. 2009). A minimum cluster criterion of 7 voxels in original space (0.30 cm^3) was implemented to identify significant clusters. Single-trial averages were calculated using in-house programs (Moulton, Pendse, et al. 2009) in combination with functional time courses and ROIs defined by the contrast analysis.

Functional connectivity analysis was performed by whole-brain correlation of the average time course extracted from either the TP or EC ROIs, as defined by the GMM-thresholded contrast analysis. These functional ROIs were transformed from MNI152 standard space into each subject's native functional space, and the average time course for each ROI was calculated for each subject. The extracted average ROI time courses were smoothed using a Gaussian kernel whose kernel width was chosen automatically via leave-one-out cross-validation. This smoothing was performed to prevent correlations with noise in the raw average ROI time course. Correlation maps for each subject were generated based on these smoothed ROI time courses using FEAT FILM. The temporal derivative of the time course was not included as an EV. The results were spatially normalized to MNI152 space, and group analyses were performed using FEAT FLAME to generate separate correlation maps for the interictal migraine subjects and the healthy control subjects. FEAT FLAME was also used to contrast the functional connectivity parameter estimates of the 2 subject groups (interictal migraine—healthy controls). The group analyses results were thresholded using GMM.

Experiment 2: Painful Heat fMRI Activation in Migraine Patients: Attack versus Interictal Phase

We used fMRI-recorded BOLD responses to heat stimuli in 8 episodic migraine patients during their interictal phase and during a spontaneous migraine attack. For the attack scan, patients were scanned within 4 h of initiation of the migraine attack. For the interictal scan, subjects were not having a migraine attack at least 72 h prior to testing. In addition, no patient had a migraine precipitated during or on the day following the baseline scan. Though a specific ROI-based analysis is presented in this study, a separate article will present the whole-brain results of this cohort. Scans were collected to measure responses to noxious heat (pain threshold +1 °C). Stimuli were applied to the forehead on the affected side (as reported during an attack).

Subjects

Eight episodic migraine patients (5 females, 3 males; 44.6 ± 11.7 years old; Table 2) were recruited that were determined to have generalized allodynia, in that their pain detection thresholds on both face and hand were more than 3 °C lower during a migraine episode as compared with the interictal period. Seven of these patients had migraine without aura, while one patient had migraine with somatosensory aura. Four patients from Experiment 1 were included in this subject pool. The remaining 7 Experiment 1 patients were not included as they had no history of generalized allodynia nor did they return for a migraine attack scan. During screening, one patient reported that menstruation was a trigger for her migraine. The majority of these 8 subjects experienced 1–2 migraines per week. Subjects verbally rated the pain intensity of their average migraine as a 5 or higher on a 0–10 scale, with 10 being the most intense pain imaginable. Subjects were on a wide range of medications, including over the counter medicines such as Advil and Excedrin and physician-prescribed medications such as Imitrex or Zomig (Supplementary Table 2). For those patients taking daily medications (e.g., preventive as opposed to acute medications to abort the attack), patients abstained from taking their migraine medications for one dosing interval (12–24 h) prior to their scheduled scan session to control for acute dosing effects. The majority of the subjects had left side–affected migraine attacks, and the one subject who was right side affected was flipped to match as previously described in Experiment 1.

Table 2
Patient demographics for Experiment 2

Patient no.	Sex	Age	Side	Thr +1 °C (interictal)	Thr +1 °C (attack)
1[a]	M	57	L	48.3	41.6
2[a]	F	30	L	48.7	44.8
3[a]	F	44	L	50.0	49.5
4[a]	M	49	L	47.0	46.9
5	F	45	L	49.0	42.3
6	F	27	R	47.5	45.5
7	F	44	L	48.8	35.3
8	M	61	L	50.0	45.9
Average	—	44.6 (SD: 11.7)	—	48.7 (SD: 1.1)	44.0 (SD: 4.3)

[a]Patients also in Experiment 1.

Stimuli

Temperatures (pain threshold +1°C) were delivered as described above for Experiment 1. Pain thresholds were separately determined prior to both the interictal scan and the migraine attack scan.

MR Acquisition

Images were acquired with the same parameters as described above for Experiment 1.

Image Analysis

fMRI analysis was carried out using FSL. The prestatistical processing for each subject was conducted as described in Experiment 1. First-level fMRI analysis of single-subject data was performed for each of the interictal and migraine attack states using FSL FEAT and assuming a fixed-effects model, as described previously. Group-level activation maps were generated using a mixed-effects model, and the difference in brain activation between interictal and attack states was assessed by a voxelwise paired t-test. Statistical maps were thresholded based on GMM. A minimum cluster criterion of 7 voxels in original space (0.30 cm^3) was implemented to identify significant clusters. Significant voxels within ROIs for the TP and parahippocampal gyrus were specifically assessed.

Experiment 3: DTI in Healthy Subjects

The rationale for this white matter connectivity analysis was to determine whether nociceptive input could reach the TP through a trigeminothalamic pathway. One potential route for nociceptive information to be transmitted from the trigeminal nucleus is through the pulvinar nucleus, which has extensive white matter connections with the TP in nonhuman primates (Chow 1950; Simpson 1952; Siqueira 1965; Yeterian and Pandya 1989, 1991) and has also been related to the expression of allodynia and hyperalgesia during migraine attacks (Burstein et al. forthcoming). In order to evaluate the potential structural connectivity between the TP and the pulvinar nucleus of the thalamus, we performed DTI experiments in a separate group of healthy volunteers. We chose not to use the patient population for this experiment because they had ongoing or prior antimigraine therapy.

Table 3
Noxious heat activation in the interictal migraine patients

Brain region	Side	*z*-Statistic	*X* (mm)	*Y* (mm)	*Z* (mm)	Vol (cm^3)
Frontal						
Precentral	I	4.97	−30	−2	44	8.12
	I	3.98	−44	0	42	0.94
Superior_Medial	C	3.63	12	38	38	0.11
Middle	I	3.62	−20	24	50	0.25
	C	3.41	30	26	42	0.25
	C	3.41	32	38	24	0.14
Inferior_Triangular	C	3.58	38	32	0	0.11
Inferior_Orbital	C	3.52	42	40	−12	0.34
Superior	I	3.48	−14	16	56	0.18
	I	3.42	−12	22	56	0.10
Parietal						
Postcentral	I	4.28	−38	−28	42	2.08
	I	4.03	−42	−20	42	0.39
	I	3.65	−56	−16	28	0.22
	I	3.69	−34	−36	44	0.18
Supramarginal	I	3.54	−44	−42	24	0.18
	I	3.40	−58	−30	24	0.13
Inferior	I	4.00	−36	−42	50	1.61
	I	3.88	−52	−44	38	0.46
	I	3.48	−42	−52	36	0.11
Cingulum						
Anterior	M	4.23	0	30	24	3.30
Cingulate gyrus, anterior	*C*	*4.15*	*2*	*−14*	*28*	*1.82*
Insula						
Insula	C	3.95	40	20	4	0.76
	C	3.71	36	14	−12	0.22
Insula	*I*	*3.72*	*−38*	*−16*	*−8*	*0.10*
Subcortical						
Thalamus	C	3.56	10	−8	4	1.25
Brainstem/cerebellum						
Cerebellum_6	C	4.30	30	−54	−30	2.72
	I	3.60	−30	−60	−20	0.41
	C	3.45	14	−70	−20	0.22
Nucleus cuneiformis	*I*	*3.84*	*−12*	*−22*	*−14*	*1.05*
	I	*3.51*	*−6*	*−28*	*−20*	*0.14*
Principle sensory trigeminal nc	*C*	*3.48*	*8*	*−32*	*−10*	*0.24*
Vermis_8	C	3.46	4	−64	−42	0.21
Vermis_10	C	3.41	2	−48	−28	0.10
Cerebellum_9	C	3.41	14	−54	−56	0.30

Note: Brain regions were labeled based on the WFU_Pickatlas. Italicized brain regions were not identified by the WFU_Pickatlas and were identified using other atlases: the Harvard–Oxford (Flitney et al. 2007) and Cerebellar Atlases (Diedrichsen et al. 2009), both included with FSL; the "MRI Atlas of the Human Cerebellum" (Schmahmann et al. 2000) was used to identify cerebellar nuclei; and "Duvernoy's Atlas" (Naidich et al. 2009) was used to identify brainstem structures. C, contralateral; I, ipsilateral; M, midline.

Table 4
Noxious heat activation in the healthy control subjects

Brain region	Side	*z*-Statistics	*X* (mm)	*Y* (mm)	*Z* (mm)	Vol (cm^3)
Insula						
Insula	I	4.48	−34	14	6	75.81
	C	3.75	36	6	4	7.07
	C	3.39	44	18	−6	5.54
	C	3.36	38	18	−14	2.35
Frontal						
Precentral	I	4.29	−38	10	30	3.97
Inferior_Operculum	I	4.05	−44	14	32	7.50
	C	3.41	48	14	4	2.96
Supp_Motor_Area	I	3.89	−16	−2	64	2.08
	C	3.44	2	12	64	3.68
	I	3.31	−6	−4	66	0.98
Middle	C	3.79	34	26	48	1.61
	C	3.63	22	24	40	1.34
	C	3.45	34	26	40	1.74
	C	3.44	36	16	56	2.02
	I	3.50	−26	8	52	3.68
	I	3.39	−32	0	52	6.94
Superior	C	3.72	22	10	62	3.24
	I	3.61	−14	2	52	2.29
	C	3.57	20	10	50	4.35
	I	3.35	−22	8	68	2.82
Inferior_Operculum	C	3.68	48	14	34	8.58
Superior_Medial	C	3.37	12	56	28	1.62
	I	3.29	−12	24	58	2.22
Inferior_Triangular	C	3.38	50	16	20	4.38
Parietal						
Supramarginal	I	3.81	−60	−30	30	12.08
	C	3.73	58	−34	30	4.18
	C	3.65	58	−42	24	3.78
Postcentral	C	3.43	60	−16	30	4.87
Inferior	I	3.34	−54	−36	44	6.93
Temporal						
Superior	I	3.56	−52	4	−2	7.94
Pole_Middle	C	−3.33	42	8	−34	0.42
Cingulum						
Middle	C	3.50	16	−24	42	1.62
Occipital						
Rolandic_Operculum	C	3.27	40	−32	22	6.32
Subcortical						
Caudate	I	3.64	−10	2	12	0.30
	I	3.61	−10	−2	14	3.18
	I	3.48	−16	0	18	1.40
	I	3.37	−8	4	8	1.90
Brainstem/cerebellum						
Cerebellum_7b	C	0	16	−78	−48	7.92
Pontine nuclei	*I*	*3.72*	*−6*	*−24*	*−28*	*0.70*
Cerebellum_8	C	3.46	12	−62	−54	1.50
	I	3.45	−6	−60	−38	0.93
Substantia nigra	*I*	*3.43*	*−4*	*−24*	*-22*	*1.45*
	I	*3.34*	*−10*	*−22*	*−24*	*0.37*
Cerebellum_Crus2	I	3.30	−14	−74	−36	19.38
Superior colliculus	*M*	*3.28*	*0*	*−34*	*−8*	*0.75*

Note: Brain regions were labeled based on the WFU_Pickatlas. Italicized brain regions were not identified by the WFU_Pickatlas and were identified using other atlases: the Harvard–Oxford (Flitney et al. 2007) and Cerebellar Atlases (Diedrichsen et al. 2009), both included with FSL; the "MRI Atlas of the Human Cerebellum" (Schmahmann et al. 2000) was used to identify cerebellar nuclei; and "Duvernoy's Atlas" (Naidich et al. 2009) was used to identify brainstem structures. C, contralateral; I, ipsilateral; M, midline.

Subjects

We used DTI to evaluate white matter tracts in 9 healthy subjects (3 females, 6 males; 31.1 ± 12.5 years old). Subjects had no history of migraine or any type of chronic headache.

MR Acquisition

Imaging was carried out on a 3T Trio MR scanner (Siemens) using an 8-channel phased array head coil. For DTI, a single-shot twice-refocused EPI pulse sequence was used. The imaging parameters were TR = 7900 ms, TE = 92 ms, 5/8 partial Fourier, 3-fold sensitivity encoding acceleration, resolution = 1.75 × 1.75 × 2.5 mm^3, and a total of 50 axial slices to cover the entire cortex and cerebellum. A single nondiffusion-weighted (b = 0 s/mm^2) volume was collected, while 72 distinct diffusion-weighted volumes were collected at b = 1000 s/mm^2 (acquisition time ~10 min). Also, an MP-RAGE acquisition was used to collect T_1-weighted structural images.

Image Analysis

DTI analysis was carried out using FSL. The pre-statistical processing for each subject consisted of Skull stripping using BET and eddy current distortion correction. Head motion correction was performed using MCFLIRT to orient the images to a skull stripped nondiffusion-weighted reference volume. The data were also smoothed with a 5-mm FWHM spatial filter. The skull-stripped nondiffusion-weighted and MP-RAGE volumes were coregistered using an automated affine algorithm implemented by FLIRT.

Diffusion modeling and probabilistic tractography were carried out using the FMRIB Diffusion Toolbox (http://www.fmrib.ox.ac.uk/fsl/fdt), which allows the estimation of the most probable pathway from a seed mask to anywhere in the brain or a particular defined location (waypoint mask) using Bayesian techniques.

First, a diffusion tensor for each voxel was calculated using a least squares fit of the tensor model to the DTI data. From the diffusion tensors, the eigenvalues of each tensor, which represent the magnitude and direction of the 3 main diffusion directions, and fractional anisotropy (FA) values were calculated for each voxel. FA maps were created for each subject. To minimize confounds such as partial volume effects present near gray matter–white matter or ventricle–white matter borders, a minimum FA threshold of 0.2 was used to threshold the data.

For each subject, 2 masks were used: 1) TP mask—which was created from the group functional contrast map (P < 0.05,

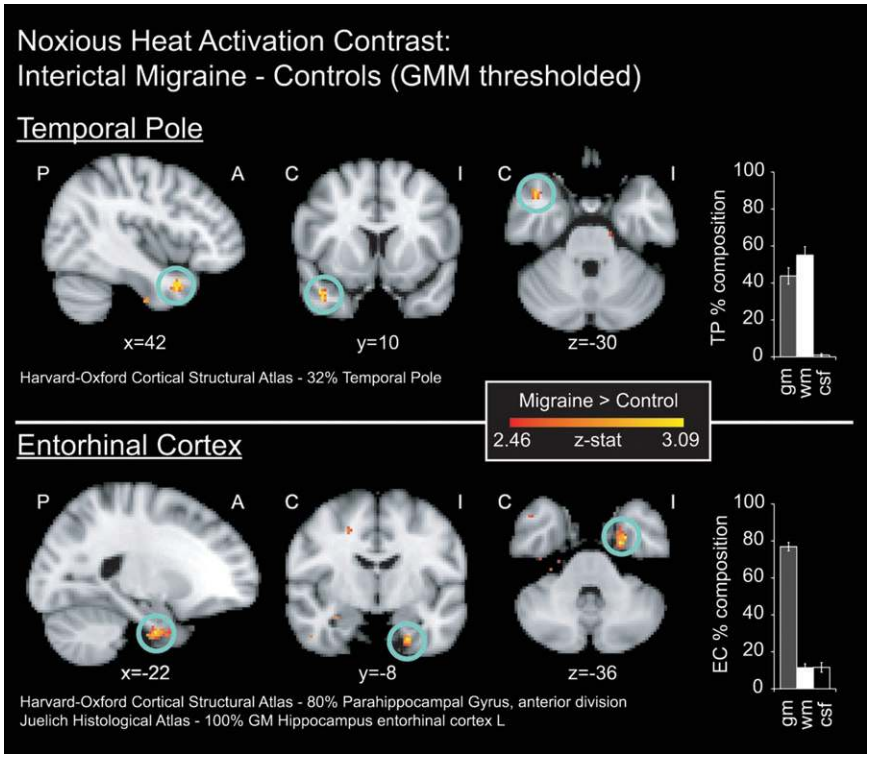

Figure 1. Interictal migraine patients ($n = 11$) versus healthy controls ($n = 11$) contrast analysis of noxious heat (pain threshold +1°C) activation. Areas with a significant contrast (determined by Gaussian Mixture Modeling) are indicated by red-to-yellow voxels. A minimum cluster criterion of 7 voxels in original space (0.30 cm^3) was implemented to identify significant clusters. The only clusters that showed a significant difference at this threshold level (blue circles) were the contralateral TP (maximum *z*-statistic: 3.32; volume: 0.35 cm^3) and the ipsilateral EC (maximum *z*-statistic: 3.16; volume: 0.77 cm^3), which both showed significantly increased responses to noxious heat in the interictal migraine patients. The bar graphs show the gray and white matter composition of the TP and EC. These bar graphs indicate that the TP and EC regions occur over gray matter and cannot be dismissed as white matter artifacts. Gray matter (GM) and white matter (WM) segmentation was performed using FSL FMRIB's Automated Segmentation Tool. Cerebrospinal fluid (csf) represents the percentage of the area that was not identified as GM or WM. The single-trial average graphs for TP and EC show the signal response to the application of noxious heat (gray area) in the interictal migraine patients (red) and control subjects (blue). A, anterior; C, contralateral; I, ipsilateral; P, posterior.

uncorrected). An affine transformation was used to transform this map from MNI152 space to each subject's anatomical space. 2) Pulvinar mask—which was defined for each subject in the anatomical space individually. Defining the boundaries of the pulvinar mask in each subject was guided by the subcortical segmentation of the brain using Freesurfer (http://surfer.nmr.mgh.harvard.edu) and a digital atlas of the human brain that is included with BrainNavigator (http://www.thehumanbrain.net/navigator, version 2.06).

Fiber tracking was initiated from all voxels within the TP seed masks to generate 5000 streamline samples, with a step length of 0.5 mm, maximum number of steps 2000, and a curvature threshold of 0.2. Tracking was constrained by the fractional anisotropic volumes. The dropping of the probability of connectivity with distance from the seed mask was also corrected for in estimating the pathways. In other words, instead of calculating the probability of connection between A and B (which decreases when the distance from A to B increases), this probability is multiplied by the expected length of the A to B connection.

The first analysis was performed with the aim of classifying the pulvinar voxels according to the probability of projection to the TP. For this analysis, the pulvinar mask was used as the seeding mask and the TP mask was designated as a classification target. For each subject, the probability maps were calculated and, similar to the previous analysis, were normalized to the product of the total number of estimated pathways and the pulvinar seed mask volume. The probability maps were calculated in each subject's anatomical space and were affine transformed to MNI space for group analysis. The probability maps were averaged across subjects, and the resulting average map was thresholded to exclude the lower 10% of values.

A second analysis was performed to determine the common/average pathway among all the subjects in this analysis. First, nonlinear registration was performed in order to coregister or align all FA images from all subjects to a predefined FA template image. The FSL-based FA template image, in the standard 1 × 1 × 1-mm^3 MNI152 space, was derived from an averaged data set of 58 FA maps from healthy male and female subjects. Using the tract-based spatial statistics (TBSS) tool (http://www.fmrib.ox.ac.uk/fsl/TBSS), the calculated nonlinear transformation was applied to the estimated pathways for each individual subject to coregister all the subjects to the standard 1 × 1 × 1-mm^3 MNI152 space to perform group-level analysis.

In order to average the subjects' pathways, the probability maps were normalized in the following way: for each subject, the size (volume) of the seed mask and the total number of estimated pathways were determined and the probability maps were scaled to the product of these 2 measures. The normalized probability maps were then thresholded to exclude pathways with probability less than 10% of the maximum probability in each subject. These maps were then binarized. These nonlinearly warped, normalized, thresholded, and binarized maps were then summed across the subjects to produce a group average probability map.

Results

Experiment 1: Painful Heat fMRI Activation in Interictal Migraine Patients versus Healthy Controls

Thermal Stimuli and Pain Ratings

The mean temperature applied to the interictal migraine patients during scanning was 47.9 ± 2.5 °C (standard deviation [SD]), while the healthy controls received 45.9 ± 3.2 °C

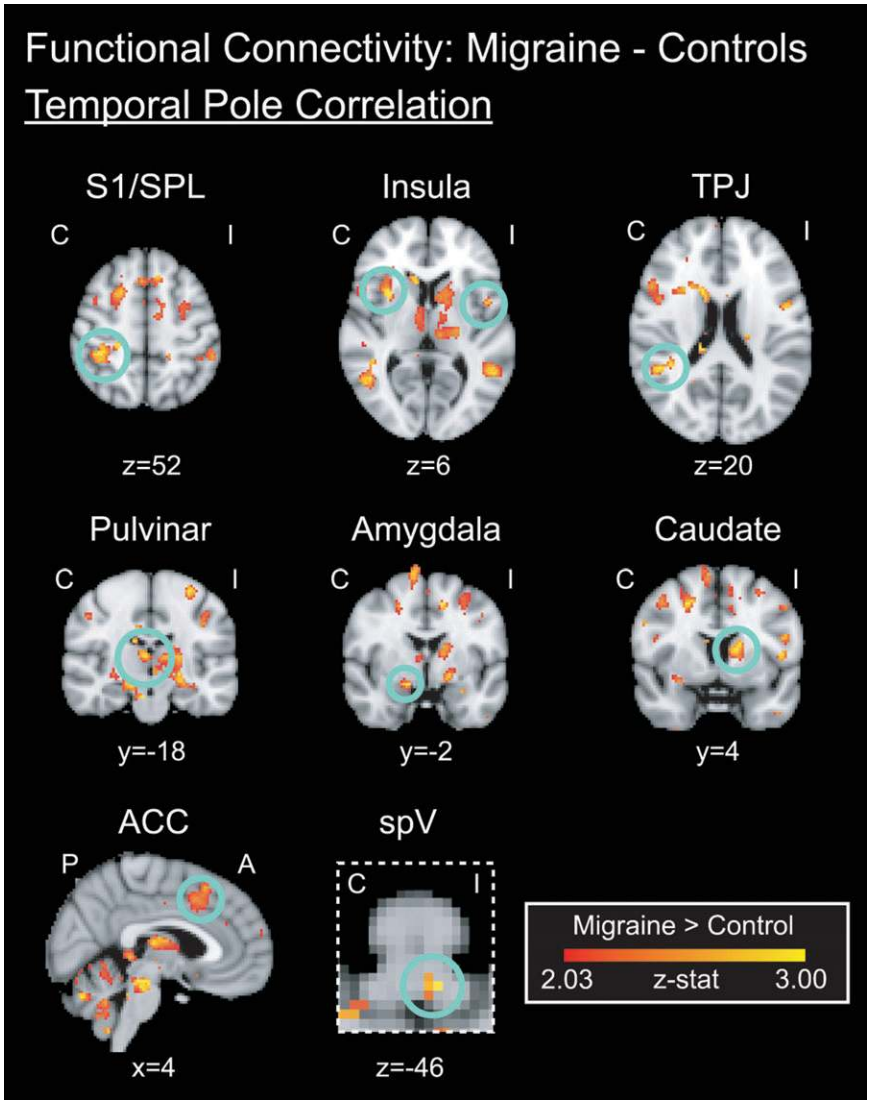

Figure 2. Functional connectivity contrast of the anterior TP during intermittent heat stimuli (pain threshold +1 °C) in interictal migraine patients—controls. The TP in interictal migraine patients has significantly enhanced functional connectivity within areas commonly activated by experimental pain, as well as in multimodal sensory processing areas. A, anterior; ACC, C, contralateral; I, ipsilateral: P, posterior, S1, primary somatosensory cortex; SPL, superior parietal lobe; spV, and TPJ, temporoparietal junction.

(Table 1). The temperatures applied to the 2 groups were not significantly different from each other (Student *t*-test for unpaired data with equal variance, $t[20] = 1.58$, $P = 0.13$).

The "pain threshold +1°C" stimuli evoked on average a pain VAS rating of 5.4 ± 3.6 (SD) for the interictal migraine patients, while healthy controls reported 3.3 ± 3.4 (SD) on the 0–10 scale. The pain elicited by the "pain threshold +1°C" stimuli were not significantly different from each other (Student *t*-test for unpaired data with equal variance, $t[20] = 1.40$, $P = 0.18$).

Functional Activation and Contrast Maps

The group activation maps for the interictal migraine patients and healthy controls both showed widespread activation in response to the "pain threshold +1°C" stimuli (Tables 3 and 4). Areas that have previously been demonstrated to be active during the application of noxious thermal stimuli were active in both groups, including anterior cingulate cortex (ACC), bilateral insula, bilateral thalamus, bilateral primary somatosensory cortex, bilateral secondary somatosensory cortex, and bilateral cerebellum.

Contrast analysis of the interictal migraine versus control group revealed significant differences in only 2 areas: increased activation in migraine patients in the contralateral TP and within the ipsilateral parahippocampal gyrus (Fig. 1) centered on the EC, based on the Juelich Histological Atlas (Eickhoff et al. 2007). Subthreshold changes were identified in several regions (Supplementary Figure 1 and Table 3), including increases in pulvinar nucleus and the periaqueductal gray and decreases in the dorsolateral prefrontal cortex (DLPFC).

Functional Connectivity Analysis

For both TP and EC seed masks, significantly increased functional activity was observed in the interictal migraine patients. Increased functional connectivity with the TP was revealed in the temporoparietal junction, as well as areas associated with the processing of pain such as the ACC, insula, primary somatosensory cortex, spinal trigeminal nucleus (spV), amygdala, caudate, and pulvinar nucleus (Fig. 2 and Table 5). Significantly enhanced functional connectivity with the ipsilateral EC in migraine patients was identified in the DLPFC, ACC,

Table 5
Areas with increased TP functional connectivity in interictal migraine patients versus healthy controls

Brain region	Side	*z*-Statistics	*X* (mm)	*Y* (mm)	*Z* (mm)	Vol (cm^3)
Frontal						
Superior	I	3.43	−10	20	56	4.26
Inferior_Operculum	C	3.18	54	18	10	1.70
	C	3.17	50	20	10	2.53
Supp_Motor_Area	I	3.18	−14	−2	50	2.43
	I	3.12	−8	12	64	0.28
Inferior_Triangular	C	3.14	54	22	10	0.14
Precentral	I	2.95	−30	−18	62	2.18
Parietal						
Inferior	C	3.30	38	−38	52	2.89
	I	2.92	−50	−32	40	2.08
Occipital						
Rolandic_Operculum	I	3.10	−46	2	8	0.27
Temporal						
Middle	C	3.31	48	−54	0	0.75
	C	2.99	50	−56	4	0.58
	I	2.97	−52	−50	4	0.74
	C	2.96	46	−56	6	0.29
Fusiform	I	3.24	−30	−46	−18	0.46
	I	3.23	−34	−44	−20	1.09
Parahippocampal	I	3.17	−30	−40	−10	0.23
Superior	C	3.06	46	−44	20	0.91
	C	3.02	52	−20	2	0.11
	C	2.93	44	−42	4	0.26
Inferior	I	2.92	−42	−44	−14	0.29
Insula						
Insular cortex	*C*	*3.32*	*32*	*12*	*6*	*1.07*
Insula	C	3.10	36	28	−4	0.57
	C	3.03	36	28	0	0.79
Subcortical						
Thalamus	I	3.45	−22	−22	−2	0.83
	I	2.94	−10	−14	14	3.48
	C	2.94	6	−16	12	0.66
Caudate	C	3.45	12	20	8	0.38
	I	3.06	−14	4	12	2.27
	C	3.03	12	10	18	0.62
	I	2.96	−14	2	16	0.34
Amygdala	*C*	*3.00*	*14*	*−2*	*−14*	*0.64*
Thalamus	C	2.95	6	−12	12	1.18
Pallidum	I	2.93	−18	−4	−6	0.51
Brainstem/cerebellum						
Emboliform nucleus	*C*	*3.33*	*10*	*−52*	*−30*	*1.33*
Substantia nigra	*C*	*3.26*	*6*	*−20*	*−22*	*0.43*
Cerebellum_8	I	3.24	−24	−60	−58	0.46
	I	3.23	−12	−60	−56	0.14
	I	3.04	−24	−54	−48	1.81
	C	2.92	22	−62	−50	0.21
	C	2.90	28	−54	−52	0.30
Cerebellum_Crus2	I	3.13	−6	−80	−42	0.37
Pontine nuclei	*I*	*3.12*	*−4*	*−28*	*−36*	*1.09*
Cerebellum_4_5	I	3.07	−26	−42	−28	1.46
	I	2.98	−18	−52	−20	3.68
Cerebellum_7b	I	3.00	−10	−76	−46	0.74
Vermis IX	*M*	*2.97*	*0*	*−60*	*−46*	*1.52*
spV	*I*	*2.96*	*−4*	*−40*	*−46*	*0.03*
Vermis_7	C	2.95	4	−72	−30	0.49
Nucleus cuneiformis	*C*	*2.94*	*4*	*−26*	*−24*	*0.10*
Cerebellum_9	C	2.92	12	−44	−48	0.09
Dentate nucleus	*I*	*2.90*	*−14*	*−46*	*−36*	*0.16*

Note: Brain regions were labeled based on the WFU_Pickatlas. Italicized brain regions were not identified by the WFU_Pickatlas and were identified using other atlases: the Harvard-Oxford (Flitney et al. 2007) and Cerebellar Atlases (Diedrichsen et al. 2009), both included with FSL; the "MRI Atlas of the Human Cerebellum" (Schmahmann et al. 2000) was used to identify cerebellar nuclei; and "Duvernoy's Atlas" (Naidich et al. 2009) was used to identify brainstem structures. C, contralateral; I, ipsilateral; M, midline.

principle sensory trigeminal nucleus/main sensory nucleus (MSN), spV, and putamen (Fig. 3 and Table 6).

Experiment 2: Painful Heat fMRI Activation in Migraine Patients: Attack versus Interictal Phase

The mean temperature (pain threshold +1°C) applied to the migraine patients during scanning of their interictal phase was 48.7 ± 1.1 °C (SD), while during their attacks they received 44.0 ± 4.3 °C (Table 2). The temperatures applied for pain threshold +1°C during the migraine attacks were significantly lower than during the interictal phase (Student paired *t*-test, $t[7] = 3.05$, $P < 0.05$). For migraine patients, the "pain threshold +1°C" stimuli evoked on average a pain VAS rating of 6.8 ± 2.8 (SD) for the during the interictal phase, while during the attack phase patients reported 7.4 ± 2.5 (SD) on the 0–10 scale. The pain elicited by the "pain threshold +1°C" stimuli were not significantly different between the 2 phases (Student paired *t*-test, $t[7] = 0.34$, $P = 0.74$).

ROI-based contrast analysis of the migraine attack versus interictal phase revealed that migraine patients showed significantly increased activation in contralateral anterior TP and ipsilateral parahippocampal gyrus during migraine attack versus interictal phase (Fig. 4). The evaluation of other brain regions revealed with the ictal versus interictal migraine contrast will be the subject of a separate study.

Experiment 3: DTI in Healthy Subjects

Strong TP connectivity within the pulvinar nucleus is indicated by a group average probability map in which the pulvinar voxels are classified according to the probability of projection to the TP (Fig. 5*A*). White matter connections between the TP and pulvinar are clearly defined in skeletonized maps and 3D renderings of the average-group probability map (Fig. 5*B*,*C*). The pathways are bilateral and continue their path from the thalamus to the prefrontal cortex. These results together suggest that there are white matter pathways connecting the TP to the pulvinar nucleus.

Discussion

The main findings of our study include: 1) an increase in the fMRI BOLD response during the interictal period in TP in migraineurs versus healthy controls in response to a thermal stimulus, which suggest that the this region is functionally different even outside of a migraine attack, 2) enhanced TP functional connectivity in migraineurs versus healthy controls (i.e., the parallel and correlated signal profile within voxels in different brain regions) contributing to the notion of overall alteration in neural processing in the interictal state, 3) a potential trigeminothalamic pathway through the pulvinar nucleus that may send nociceptive information to the TP, and 4) increase in fMRI BOLD signal during the ictal period (migraine attack) in TP that is in the same location as the activation pattern observed during the interictal period, suggesting that migraine attacks exacerbate or sensitize TP activation. As the stimuli were well balanced in terms of the temperatures applied and pain ratings between the patients and controls, brain regions normally associated with pain processing (e.g., anterior cingulate, insula, primary somatosensory cortex) did not show significant differences. We believe that these novel findings may contribute to some of the perceptual changes observed in migraine patients.

The Temporal Lobe and Pain Processing

A number of studies have shown activation in the temporal lobe following noxious stimuli, though typically reported in the hippocampus rather than the TP (Rosen et al. 1996; Derbyshire et al. 1997; Iadarola et al. 1998; Ploghaus et al. 2000; Becerra et al. 2001; Ploghaus et al. 2001; Bingel et al. 2002; Godinho et al. 2006). In migraine patients during their interictal phase, we observed

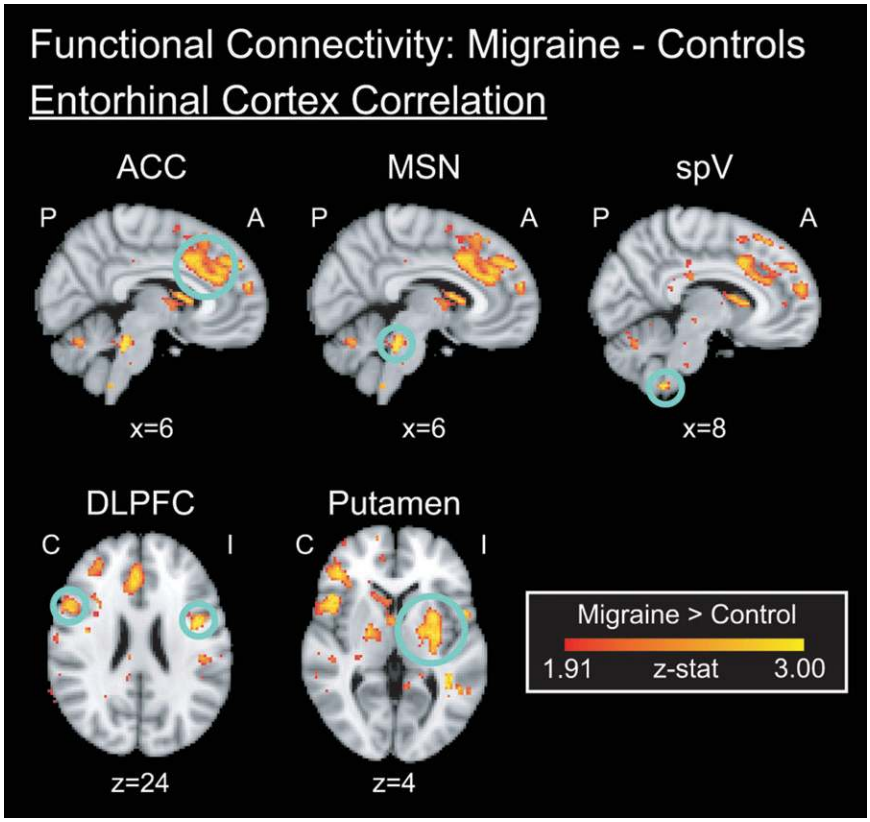

Figure 3. Functional connectivity contrast of the EC during intermittent heat stimuli (pain threshold +1°C) in interictal migraine patients—controls. Patients show significantly enhanced functional connectivity in areas related to the processing of innocuous and noxious stimuli and descending pain modulation. A, anterior; C, contralateral; I, ipsilateral; MSN, P, posterior, and spV, trigeminal nucleus.

significant changes in the TP as well as the EC in response to noxious heat. The role of the TP in pain processing is not well understood, but it has been suggested to play a role in assigning affective tone to short-term memories relating to pain (Godinho et al. 2006), which may be related to reports of impaired memory in migraine patients during the interictal period (Calandre et al. 2002; Vincent and Hadjikhani 2007). We interpret the enhanced TP excitability as sensitization that occurs in migraine patients even when not having a migraine attack.

The DTI tractography results suggest that a white matter pathway exists that may direct nociceptive information from the pulvinar nucleus to the TP. The pulvinar nucleus receives input from the dorsolateral spinothalamic tract (Apkarian and Hodge 1989) and the analogous trigeminothalamic tract (Rausell et al. 1992), which relays nociceptive information from primary afferent nociceptors innervating the face. Structural connectivity between the pulvinar nucleus and the TP has been previously described in primates (Chow 1950; Simpson 1952; Siqueira 1965; Yeterian and Pandya 1989, 1991) and has also been observed functionally in patients with TP epilepsy (Rosenberg et al. 2009). The structural connectivity between the TP and the pulvinar nucleus, which may receive nociceptive input, suggests the presence of an afferent pathway that could provide the substrate for functional changes in the TP in migraine patients.

The Temporal Pole and Migraine

The specific role for the TP in migraine is not known. Data supporting our finding of hyperexcitable temporal region in migraine include: 1) TP dysfunction in migraine patients relating to disrupted higher-order perceptual processes including vision (Antal et al. 2005; Granziera et al. 2006; Harle et al. 2006) and odor (Demarquay et al. 2008); 2) comorbidity of headache and epilepsy, particularly migraine and temporal lobe epilepsy (Lipton et al. 1994; Bigal et al. 2003; Ito et al. 2003; Vanmolkot et al. 2003; Kors et al. 2004; Yankovsky et al. 2005; De Simone et al. 2007; Kwan et al. 2008; Castro et al. 2009), and anterior temporal lobe resection in epileptic patients with migraine headaches relieves them of both their migraines and epilepsy (Yankovsky et al. 2005); 3) migraine imaging studies have shown increased temporal lobe activation during migraine attacks and aura (Weiller et al. 1995; Hall et al. 2004; Afridi, Giffin, et al. 2005; Afridi, Matharu, et al. 2005). Each of these points is discussed below.

Possibly related to its responsiveness to noxious heat, the TP is an associative multisensory area that also processes visual, odor, and auditory information (Moran et al. 1987; Bougeard and Fischer 2002; Clarke et al. 2002; Olson et al. 2007; Asari et al. 2008). In migraine patients, odor hypersensitivity during the interictal period has been correlated with greater attack frequency, a higher number of odor-induced migraines, and visual hypersensitivity (Demarquay et al. 2006). A positron emission tomography study using olfactory stimuli showed that in interictal migraineurs, the TP and the cuneus were the only brain areas with significantly greater activation than healthy controls (Demarquay et al. 2008). Increased TP activation with olfaction in migraineurs is of interest because odor perception is also disrupted in temporal lobe epilepsy (Grant 2005).

Table 6
Areas with increased EC functional connectivity in interictal migraine patients versus healthy controls

Brain region	Side	*z*-Statistics	*X* (mm)	*Y* (mm)	*Z* (mm)	Vol (cm^3)
Cingulum						
Anterior	I	3.29	0	38	26	0.74
	C	2.94	4	30	24	0.54
	C	2.92	6	34	22	0.59
	C	2.85	6	24	26	0.72
Middle	C	3.00	6	12	38	0.66
	C	2.99	4	18	36	1.97
	C	2.92	4	40	30	0.98
Frontal						
Inferior_Triangular	C	3.25	46	18	2	3.98
	C	3.04	44	38	2	2.67
	C	2.85	50	14	22	0.45
Precentral	I	3.20	−42	0	24	1.35
	I	3.10	−34	−6	44	0.23
	C	2.92	46	2	46	1.71
	I	2.83	−40	0	50	0.42
Inferior_Operculum	C	3.11	54	12	26	1.35
	I	2.84	−48	6	28	0.67
Superior_Medial	I	3.10	0	28	52	2.26
	I	2.97	0	44	34	1.34
	I	2.97	2	42	40	0.78
	C	3.03	6	58	18	0.38
	C	2.86	14	58	12	0.88
	C	2.86	6	50	32	0.66
Superior	I	2.86	−18	20	56	2.43
Inferior_Orbital	C	2.99	50	22	−4	1.26
Middle	C	2.84	36	38	26	0.66
Temporal						
Fusiform	I	3.14	−40	−48	−14	0.43
	I	2.90	−32	−62	−16	1.28
Lingual	I	3.04	−24	−44	−4	0.46
	I	2.83	−24	−48	−4	0.49
Superior	C	2.87	60	−34	20	0.216
Occipital						
Rolandic_Operculum	I	3.05	−50	−22	20	0.568
	I	2.93	−48	4	8	0.624
	I	2.91	−50	2	12	0.432
	I	2.88	−44	4	12	0.44
Parietal						
Postcentral	I	2.97	−54	−18	18	0.24
	I	2.84	−44	−20	52	0.50
Supramarginal	I	2.93	−60	−28	30	0.10
	C	2.89	42	−34	40	1.10
	C	2.82	46	−32	44	0.42
Inferior	I	2.90	−54	−38	38	0.64
	C	2.85	44	−38	50	0.53
Insula						
Insular cortex	*I*	*2.83*	*−32*	*4*	*−14*	*1.01*
Subcortical						
Putamen	I	3.17	−28	−2	10	5.56
Brainstem/cerebellum						
Cerebellum_8	C	3.55	18	−50	−56	0.87
	I	3.45	−18	−66	−42	0.86
	I	2.93	−20	−58	−46	0.20
Principle sensory trigeminal nc	*C*	*3.39*	*6*	*−34*	*−28*	*0.58*
Left Crus II	*I*	*3.35*	*−14*	*−70*	*−36*	*1.22*
Cerebellum_9	C	3.32	16	−46	−56	0.14
	C	3.24	8	−46	−56	0.30
Globose nucleus	*I*	*2.93*	*−10*	*−60*	*−32*	*0.20*
Cerebellum_Crus1	C	2.90	14	−72	−30	1.23

Note: Brain regions were labeled based on the WFU_Pickatlas. Italicized brain regions were not identified by the WFU_Pickatlas and were identified using other atlases: the Harvard–Oxford (Flitney et al. 2007) and Cerebellar Atlases (Diedrichsen et al. 2009), both included with FSL; the "MRI Atlas of the Human Cerebellum" (Schmahmann et al. 2000) was used to identify cerebellar nuclei; and "Duvernoy's Atlas" (Naidich et al. 2009) was used to identify brainstem structures.C, contralateral; I, ipsilateral; M, midline.

A high prevalence of migraine is present in patients suffering from temporal lobe epilepsy (Deprez et al. 2007; De Simone et al. 2007). Removal of the anterior temporal lobe or the hippocampus in patients with comorbid temporal lobe epilepsy and migraine headaches results in the complete amelioration of migraine (Yankovsky et al. 2005). Like migraine, epilepsy has also been associated with abnormal functioning within the pulvinar nucleus (Rosenberg et al. 2006), which has also demonstrated extensive functional connectivity with the temporal lobe in patients with epilepsy (Rosenberg et al. 2009). Such data suggest that the association between epilepsy and migraine may be due to abnormal TP function.

Activation within the temporal lobe has previously been found during migraine attacks (Weiller et al. 1995; Afridi, Giffin, et al. 2005; Afridi, Matharu, et al. 2005) and aura (Hall et al. 2004). Temporal lobe activations have been tentatively attributed to the expression of phonophobia in auditory association cortices and visual abnormalities. We showed that in response to a heat stressor, the most prominent functional difference in the cortex between the interictal migraine brain and controls was hyperexcitability in the TP, which is further activated during a migraine attack. Note also that during the migraine attack, temperatures significantly lower than those used during the interictal state evoked increased TP activation. We propose that hyperexcitability of this multisensory region during both the interictal and ictal state may contribute to symptoms of migraine.

Another component of the temporal lobe that showed hypersensitivity to noxious heat in migraine patients is the EC, located in the ventromedial portion of the temporal lobe. It has connections to the hippocampus and various other cortical and subcortical structures and is best known as a component of the medial temporal lobe memory system (Eichenbaum and Lipton 2008). Aside from memory, the hippocampus is also involved in space location (Jeffery 2007) and exacerbation of pain by anxiety (Ploghaus et al. 2001). Not much is known about the EC in the context of migraine. However, electrical stimulation of the rhinal cortical regions produces emotional, dysautonomic features also known as "dreamy state syndromes" (Bartolomei et al. 2004). The EC relates to experiential syndromes and thus may be part of a brain process that is involved in the storage and retrieval of polymodal sensory information originating from the parietal association area (Sakai 2003). Given that migraine is painful, we assume that pain during the migraine state somehow involves the EC and repeated painful episodes. In this way, a hypersensitive state may be produced in the EC as we have observed in this study. In addition, the EC may elaborate the painful state based on prior experience (Casey and Tran 2006), which may be related to Hebbian conditioning.

Inferences of Brain State from Functional Connectivity of Temporal Lobe Structures

In this study, the TP shows enhanced functional connectivity within pain-related cortical structures and the temporoparietal junction in migraine patients. The function of the superior temporal lobe has previously been proposed to be dependent on coactivation with different functional networks (Hein and Knight 2008). As noted in Figure 2, a significant increase in functional connectivity for migraine patients occurred between the TP and a number of brain regions, including regions associated with sensory/discriminative (primary somatosensory cortex, posterior thalamus, posterior insula) and affective/motivational aspects of pain, including the anterior cingulate, anterior insula, amygdala, and basal ganglia (caudate). Functional connectivity represents a measure of signal correlation between 2 regions and does not imply any specific relationship to causation (Friston 1994). Thus, we cannot interpret the TP

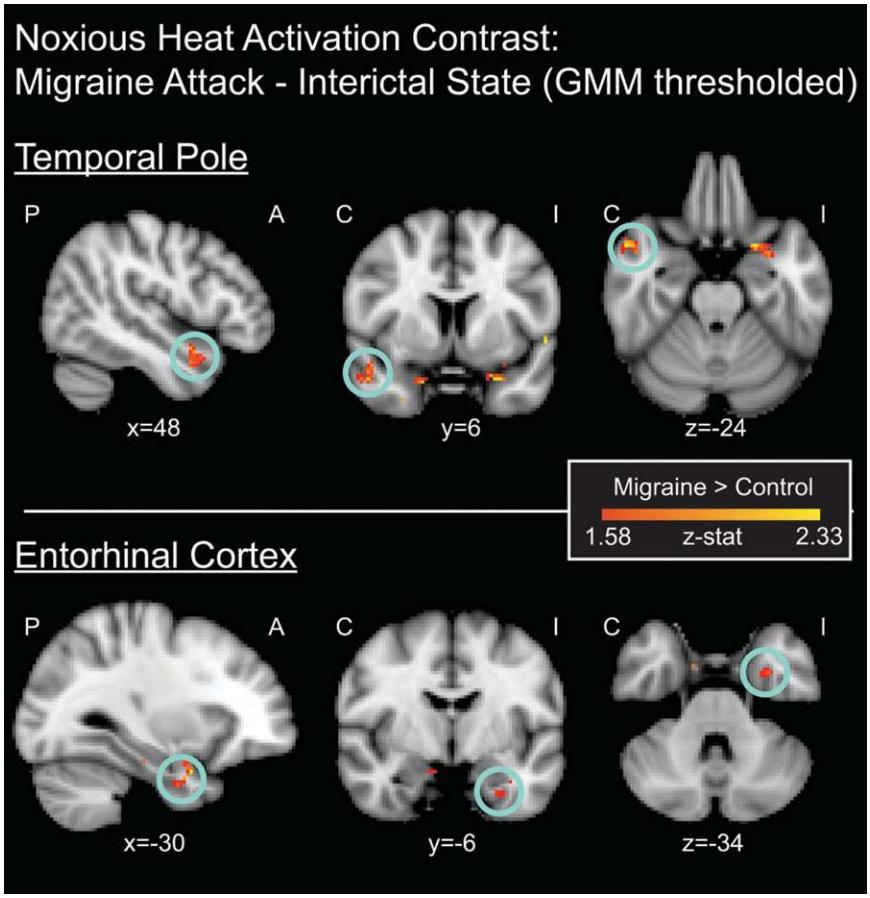

Figure 4. Migraine attack versus interictal state ($n = 8$ patients) contrast analysis of noxious heat (pain threshold +1°C) activation. Red-to-yellow voxels indicate areas with a significant contrast (determined by Gaussian mixture modeling) within the TP and the parahippocampal gyrus, as defined by the Harvard–Oxford Cortical Atlas as implemented by FSL. A minimum cluster criterion of 7 voxels in original space (0.30 cm^3) was implemented to identify significant clusters. Blue circles highlight the TP and EC regions with significant contrasts in Experiment 1. Both the TP (maximum *z*-statistic: 2.23; volume: 0.57 cm^3) and EC (maximum *z*-statistic: 2.57; volume: 0.54 cm^3) show significantly increased activation during a migraine attack. A, anterior; C, contralateral; I, ipsilateral; and P, posterior.

as a neural driver of alterations in other regions. Nevertheless, the correlation of signal patterns between the TP and these other regions in the interictal migraine state suggests the possibility that the brain state in these regions may be altered by repeated migraines. Certainly the posterior thalamus (Burstein et al. forthcoming), anterior cingulate (Obermann et al. 2009; Seifert et al. 2009), and basal ganglia (Becerra et al. 2006) have previously been implicated in central sensitization. These altered states may arise from altered Hebbian plasticity, in which repeated stimulation of specific receptors leads slowly to the formation of "cell assemblies" that can act as a self-contained system after stimulation has ceased (Hebb 2002). As such, the changes in brain function can become fulminant through alterations in synaptic strength, driven by repeated migraines.

Similarly, the EC showed enhanced functional connectivity within the DLPFC, in addition to areas involved in processing noxious (ACC, spV, and putamen) and innocuous stimuli (MSN). The EC is the main gateway to the hippocampus and is associated with memory processing and has also been related to the exacerbation of pain due to anxiety (Ploghaus et al. 2001). The enhanced connectivity of the EC with the DLPFC has implications regarding a possible change in spatial attentional processing (Sakai and Passingham 2003) and in the descending modulation of nociceptive processing (Gear et al. 1999; Zubieta et al. 2001; Anderson et al. 2002; Bencherif et al. 2002; Lorenz et al. 2003). The increased functional connectivity in ACC, spV, putamen, and MSN suggests that information exchange between memory and heat stimulus processing may be enhanced in migraine patients.

An alternative interpretation for the differences relating to the EC between patients and controls is that the "EC" ROI may actually correspond to the location of the trigeminal ganglion. Considering that patients showed increased activation in this area on the side ipsilateral to stimulation (Fig. 1),and that one of the predominant theories on the basis of migraine is the sensitization of meningeal afferents in the trigeminal ganglion (Strassman et al. 1996; Bolay et al. 2002), this is an appealing interpretation. However, we believe that the spatial extent of the EC ROI minimally overlies the trigeminal ganglion, if at all, for the following reasons: 1) the ROI appears more lateral, posterior, and superior than our previous demonstrations of trigeminal ganglion activation (Borsook et al. 2003; Becerra et al. 2006; Moulton, Becerra, and Borsook 2009); (2) these previous observations of trigeminal ganglion activation were focal and were only a fraction of the spatial expanse of the ROI observed in this study; and (3) standardized probablistic atlases indicate that the ROI is within the cerebral cortex; the ROI is identified by the Juelich Histological Atlas (Eickhoff et al. 2007) as the EC of the hippocampus and by the Harvard–Oxford

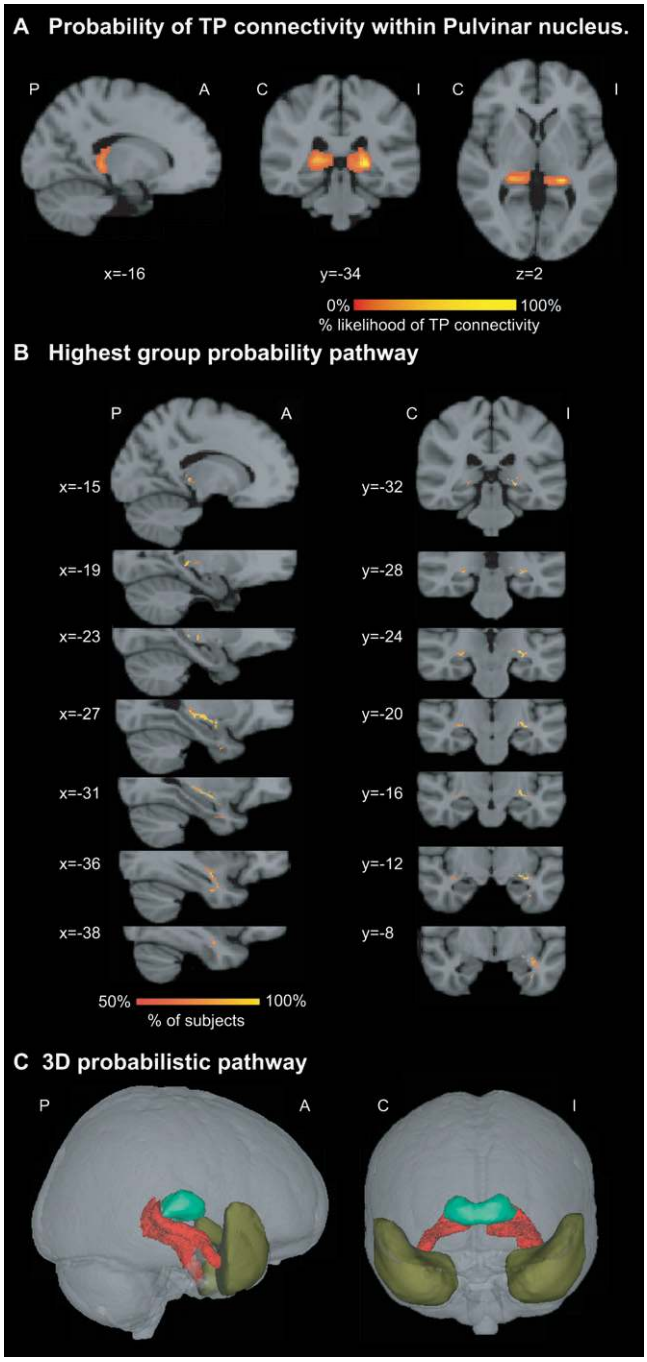

Figure 5. Group probability maps of white matter tracts connecting the TP and the pulvinar nucleus in the posterior thalamus based on the DTI tractography in 9 subjects. (*A*) Group probability of TP connectivity within pulvinar nucleus. The map represents the probability that voxels within the pulvinar nucleus have a connection to the TP (see Materials and Methods). (*B*) Group probability pathway connecting pulvinar nucleus and TP. The fact that there are common pulvinar voxels present in all the subjects with a maximum probability (yellow) strongly suggests that there is a connection between the TP and the pulvinar. The maps represent the probability of the presence of the pathways in at least 50% of the subjects to the maximum of presence in all subjects. (*C*) 3D rendering of the probabilistic pathway connecting TP and pulvinar nucleus. The probability map (red) is the same as shown in part (*B*). Pulvinar (green) and TP (olive) masks are shown here as well. Additionally, a projection from the pulvinar extends to the prefrontal cortex. A, anterior; C, contralateral; I, ipsilateral; and P, posterior.

Cortical Structural Atlas (Flitney et al. 2007) as the parahippocampal gyrus.

An obvious limitation of the design employed in this study is in its inability to conclusively resolve the preexisting versus acquired nature of the observed alterations. Conclusive resolution of this issue may require prospective and/or twin studies. Notwithstanding this limitation, the present work suggests that this temporal lobe abnormality exists but can only speculate as to whether it preexists or develops.

A common caveat in the study of migraine patients is the influence of chronic medication usage on their brain physiology. Patients may potentially have reduced cortical responsiveness to painful stimuli relative to healthy controls. However, several points reduce the likelihood of this confound: 1) 8 out of 11 patients were not taking preventative medications for their migraine, 2) patients taking preventative medications discontinued taking them one dosage cycle prior to imaging, 3) increased, not decreased, activation was detected in TP and EC in interictal patients relative to healthy controls, 4) the significant differences were localized specifically to these 2 regions and were not global as might be expected for a drug, and 5) the heterogeneity of the medications taken by the patients reduces the likelihood of a mass action of any one pharmacological mechanism influencing the fMRI signal. Another consideration is that intermittent use of acute migraine medications may have unknown long-term effects on nociceptive processing. Medications taken by the subjects (e.g., triptans) may also influence their sensitivity to noxious stimuli by acting upon the sympathetic nervous system (De Felice et al. 2010) but specific studies on their effects on fMRI activation are lacking.

Conclusions

In this report, we evaluated the whole-brain response to a thermal stressor to determine alterations in responses between the migraine brain during a pain-free (interictal) period and nonmigraine brain. Our data suggest that the temporal lobe is highly significantly affected by migraine. Other brain regions may have altered connectivity with the TP in the interictal migraine brain, including those related to sensory/discriminative aspects of pain, affective/motivational aspects of pain, cognition, and pain modulation. Furthermore, given our understanding of the TP's involvement in integration of complex behaviors, we suggest that some behavioral manifestations observed in migraine patients may stem from ictal driven changes. The strong white matter connectivity observed between the TP and the pulvinar nucleus not only suggests an overlap of the areas affected in both epilepsy and migraine (Rosenberg et al. 2006; Burstein et al. forthcoming) but also that experimental therapeutic approaches to treat temporal lobe epilepsy, such as chronic stimulation of the medial pulvinar nucleus (Rosenberg et al. 2009), may be useful in the treatment of migraine. The migraine brain may differ from the normal brain for a variety of reasons, including genetic factors as well as neuroplastic changes that occur with repeated migraine attacks.

Supplementary Material

Supplementary Tables 1–3 and Figure 1 can be found at: http://www.cercor.oxfordjournals.org/

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Notes

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