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The missing link: enhanced functional connectivity between amygdala and visceroceptive cortex in migraine

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Abstract

Background—Migraine is a neurovascular disorder, in which altered functional connectivity between pain-modulating circuits and the limbic system may play a role. Cortical spreading depression (CSD), which underlies migraine aura induces C-fos expression in the amygdala. The role of CSD, and amygdala connectivity, in migraine without aura (MwoA) is less clear and may differentiate migraine from other chronic pain disorders.

Results—Amygdala connectivity in both migraine with aura (MWA) and MWoA was increased to the visceroceptive insula relative to healthy subjects and two other chronic pain conditions not associated with CSD: trigeminal neuralgia (TGN) and carpal tunnel syndrome (CTS).

Conclusion—The observed increased connectivity within the limbic/viscerosensory network, present only in migraineurs, adds to the evidence of a neurolimbic pain network dysfunction, and may reflect repetitive episodes of CSD leading to the development of migraine pain.

Keywords

migraine; cortical spreading depression; amygdala; insula; neurolimbic pain network

Introduction

It is widely accepted that migraine is a primary brain dysfunction resulting from activation and sensitization of the trigeminovascular pain pathway. Cortical spreading depression (CSD), the underlying mechanism of aura, has been proposed as one of the factors triggering trigeminal nociceptors (1). Several studies have shown that CSD-like phenomena may also underlie the pathophysiology of migraine without aura (MWoA)(2), and that both migraine with aura (MWA) and MWoA may be triggered by CSD: CSD block is indeed a property shared by all anti-migraine medicines, irrespective of the presence of aura (3). The link between CSD and headache in humans, however, remains not completely elucidated.

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Although direct evidence in the clinical setting for increased activity of trigeminal neurons is lacking, imaging studies have reported interictal brain abnormalities in migraineurs in subcortical and brainstem regions involved in somatosensory processing and pain modulation. These findings expand the well-accepted concept of central sensitization to include the role of subcortical-driven cortical hyperexcitability (4) in the pathogenesis of migraine. We previously established the presence of interictal dysfunction of limbic-brainstem connectivity through the periacqueductal gray (PAG), which was related to the frequency of migraine attacks (5). Whether our findings can be interpreted as a brain signature of migraine, or are shared by other chronic pain conditions is still debated.

The amygdala is an essential element of the limbic system, and may play a more important role in migraine than previously thought. Interestingly, a recent rodent study (6) demonstrated that a single episode of CSD, unlikely to elicit pain, induced c-fos expression in the amygdala, as well as behavioral responses consistent with amygdala activation. In humans, Stankewitz et al. (7) recently demonstrated sensitization of the amygdala during migraine attack. Sensitization of the amygdala by repeated episodes of CSD could play a role in the development and chronification of migraine pain.

The present study evaluated interictal amygdala functional connectivity in migraineurs compared to healthy subjects. We examined whether both MWA and MWoA would present increased connectivity between the amygdala and the viscerosensitive network, which would support the theory of episodes of ‘silent CSD’ in MWoA. In order to test whether increased amygdala/viscerosensitive connectivity was specific to migraine and not simply related to recurrent episodes of pain, we also evaluated resting connectivity in chronic pain patients suffering from carpal tunnel syndrome (CTS) and trigeminal neuralgia (TGN).

Methods

Twenty-two subjects with migraine (20 females, age (mean±SD) = 31.2±7.6 years; disease duration= 14.8±8.8 years, range 1-30 years), 11 with MWA, and 11 with MWoA, as defined by the International Headache Society (HIS) diagnostic criteria, were included in the study. All patients were migraine free for at least 72 hours at the time of MRI. Twenty healthy subjects (16 females, age =29.8±6.5 years) with no history of migraine or other headache types, and free from any medical condition and medication were included as migraine controls. Eleven CTS patients, (10 females, age= 36.7 ±7.7 years; disease duration= 3.27±2.15 years, range 1-9 years), and 11 controls, (9 females, age= 42.0±8.2 years) as well as 9 TGN patients (5 females, age= 61.2±21.4 years; disease duration= 5.61±2.93 years, range 1-9 years) and 9 controls, (6 females, age= 46.4±8.6 years). The 9 patients fulfilled IHS diagnostic criteria for classical TGN, complaining of unilateral electrical shock-like pain lasting few seconds, occurring spontaneously or triggered by light mechanical stimulation of the face and without any other sensory/neurological abnormality.

Between-group comparisons of correlation effect size were performed between each group and their matched controls. Age was included as a nuisance regressor for the TGN vs. Controls comparisons due to significant differences in mean age between these groups.

Migraine subjects and controls underwent anatomical and functional scanning on a Siemens 3T Tim Trio scanner with a 32-channel Siemens head-coil. Single-shot echo planar images (resolution=3×3×3 mm; 47 slices; repetition time/echo time [TE] = 3000/30 milliseconds; flip angle=90 degrees; 160 volumes) were acquired for functional resting state. CTS subjects and controls underwent anatomical and functional scanning on a Siemens 3T Tim Trio scanner equipped with a 32-channel Siemens head coil. Gradient echo BOLD images (resolution=3.125×3.125×3.6mm; 32 slices; TR/TE = 2000/30 milliseconds; flip angle=90

degrees; 180 volumes) were acquired for functional resting state. TGN subjects and controls underwent anatomical and functional scanning on a Siemens 3T Verio scanner with a 12-channel Siemens head coil. Single-shot echo planar images (resolution = 3.91×3.91 × 3mm; 40 slices; repetition time [TR]/echo time [TE] = 3000/30 milliseconds; flip angle=90 degrees; 150 volumes) were acquired for functional resting state.

Structural data were collected as described previously (5). Functional data were processed using FSL as described previously (5), including motion correction, spatial smoothing with 5mm full width half maximal Gaussian kernel, and a temporal high-pass filter. Because the amygdala region is highly susceptible to physiological noise caused by e.g. breathing and heart rate, MELODIC Independent Component Analysis (ICA) was performed in order to identify and remove noisy components due to scanner-related and physiological artifacts from the 4D fMRI data. Nonlinear registration using FMRIB's Nonlinear Image Registration Tool (FNIRT) was applied between the subject's structural and the standard space (the Montreal Neurological Institute (8) 2mm brain). The right and left amygdala, manually selected in standard space based on the anatomy, were selected as seeds (peak MNI coordinates: left X,Y,Z= −22, −4, −18; right X,Y,Z=20, −4, −18; with 3mm radius). Average time courses were extracted from these seeds using FSL's featquery function. The preprocessed time series were then fitted with a linear model consisting of a regressor representing the extracted time courses. The spatially normalized effect size and standard error volumes served as input to a mixed effects group analysis in FSL FEAT. The modeled group effect size and standard error were then divided to produce a volume whose voxels were t scores, subsequently transformed to Z scores. Images for each group were thresholded using clusters determined by $Z > 2.57$ ($p < 0.005$, uncorrected).

Results

The frequency of migraine attacks per month was similar in MWA and MWoA (MWA: 2.5±1.4; MWoA 4.1±4.0, p=0.2), and both groups had similar disease duration in years (MWA: 14.2±9.6; MWoA 15.4±6.8, p=0.76). Disease duration was however greater in migraineurs compared with CTS and TGN ($p<0.05$).

Analysis of resting state fMRI data showed that when comparing all migraineurs with controls, there was increased connectivity between the left and the right amygdala and the anterior insula, as well as with secondary somatosensory cortex (SII) and thalamus (see Table 1). Although it was more marked in migraineurs with aura, both MWA and MWoA showed increased connectivity between the amygdala and the insula when compared to matched controls; this was however not the case in the TG and CTS groups when compared to their respective controls (Figure 2).

Discussion

Our data demonstrate that migraineurs, independently from the presence of aura, show interictal abnormal functional connectivity between the amygdala and viscerosensory areas including the thalamus, anterior insula, and SII. Other groups of patients suffering from chronic pain, including non-migraine headache pain, did not present increased connectivity between the amygdala and the visceroceptive cortex.

The insula is an important component of the limbic system, receiving input from the thalamus and relaying efferent information to the cingulate and prefrontal cortices. It is involved with interoception and the perception of pain, through integration from somatosensory and visceral sensory modalities. Penfield demonstrated in the 1950's that direct electrical stimulation of the insula during surgery induced abdominal pain, nausea,

and alterations in gastric motility, as well as somatic sensations described as tingling or numbness in the face, hand, arm and tongue, but as described by Mazzola et al. (8) in 20 years of careful exploration of the human cortex via stimulation of the cortical surface, Penfield did not identify any “pain cortical area”. Interestingly, electrical stimulation of restricted areas of the human insular cortex can elicit a highly unpleasant headache (9). The insula is activated during migraine attacks (10), and interictal MR spectroscopy measures have revealed increased levels of excitatory glutamate in the insula of migraineurs (11). The parietal operculum, which contains SII, is another key region involved in the processing of visceral information.

In the animal model, CSD triggers a cascade of events leading to local neurogenic inflammation of the meninges (1), followed by activation of nociceptors located in the perivascular space of the meninges, and finally by the activation of neurons in the brainstem trigeminocervical complex (Sp5C) (12), and a single episode of CSD is sufficient to lead to c-fos expression of the ipsilateral amygdala and cortex (6). Activation of the amygdala is involved in long-lasting peripheral hypersensitivity induced by inflammation in the absence of tissue injury (13).

There are dense projections from Sp5C to the somatosensory cortex and the insula, relayed by the ventrobasal and posterior thalamic nuclei, respectively, and CSD initiated in the insula induces facilitation of meningeal-evoked response without affecting cutaneous nociceptive responses (12), indicating the important influence of the insula and the somatosensory cortices on the interoceptive inputs within the trigeminocervical complex, that could contribute to the development of migraine pain. In addition, dense insular projections to the amygdala have been described in rodents, and Shi and Cassel (14) have demonstrated that the anterior insula is an interface between the posterior insular cortex and the motor cortex, and is also connected with motor-related amygdala regions.

CTS and TGN are two chronic pain conditions that do not evoke viscerоceptive sensations. In these two groups of patients, we did not observe increased connectivity between the amygdala and the insula or the SII cortices, further supporting the proposed linkage between CSD and enhanced amygdala connectivity.

This study is limited by the fact that we only had a limited number of participants in the groups of patients suffering from trigeminal neuralgia and from carpal tunnel syndrome, and also by the fact that data for these two groups of patients were acquired on different MRI scanners. However, when compared with controls acquired from identical scanners following the same protocols by controlling for gender and age, none of these groups exhibited increased amygdala-insula increased connectivity, as observed in migraineurs compared with controls. Another limitation is that our resting connectivity approach only offers indirect evidence of neural connectivity. However, our data do suggest altered connectivity in the pain-processing network as well as the involvement of a key structure of the limbic system: the amygdala. Our results support the concept of migraine being associated with a dysfunctional neurolimbic pain network (15).

While our findings do not constitute direct proof of the presence of CSD in MWoA, they strongly support the hypothesis that CSD-induced amygdala activation during repetitive episodes of migraine with and without aura consolidates connectivity within the viscerоceptive cortex, and that amygdala interactions with areas involved in interoception could play a role in the development of migraine symptoms.

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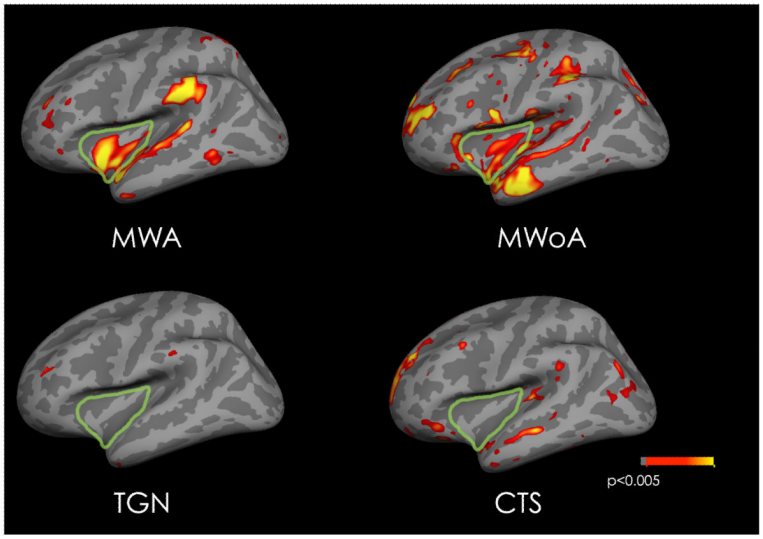

Figure 1.

Top and bottom panels: Statistical maps of connectivity between the amygdala and the rest of the brain ($p<0.005$, uncorrected), in MWA, MWoA, TGN and CTS. Although MWA exhibit the stronger connectivity between the amygdala and the insula, MWoA also present connectivity between these structures, whereas they are absent in TGN and CTS patients. The maps are displayed on the inflated cortical surface of the template FreeSurfer brain (fsaverage) on the lateral surface of the brain

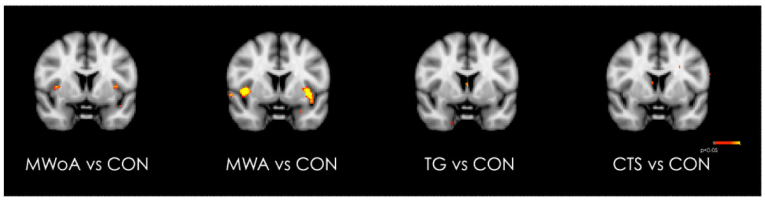

Figure 2.
Coronal section at the level of the insula at y=2 on the MNI average brain, showing the statistical maps of difference in connectivity with the amygdala between MWoA vs. matched controls, MWA vs. matched controls, TG vs. matched controls and CTS vs. matched controls. As in the direct maps of connectivity shown in Figure 1, one can see that both groups of migraineurs show connectivity between the amygdala and the insula, when compared with controls, whereas this is not the case in the two other groups.

Table 1

Peaks of increased connectivity clusters in MNI coordinates (z>2.3; minimum cluster size 44 voxels) between left (X,Y,Z= −22,−4,−18) and right amygdala (X,Y,Z=20, −4, −18) and the rest of the cortex in 20 migraineurs compared with 20 gender- and age-matched controls.

Region	Zmax	x	y	z
Insula	3.15	−36	6	4
	3.22	42	2	0
	3.02	−38	20	1
Parietal operculum/SII	3.04	−62	−34	24
Thalamus	2.75	10	−18	−4
Heschl's gyrus	2.79	46	−6	−12
Temporal pole	3.38	58	8	−4