Published in final edited form as:
Pain. 2012 February ; 153(2): 444–454. doi:10.1016/j.pain.2011.11.006.

Sex similarities and differences in pain-related periaqueductal gray connectivity

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Abstract

This study investigated sex similarities and differences in pain-related functional connectivity in 60 healthy subjects. We used functional magnetic resonance imaging and psychophysiological interaction analysis to investigate how exposure to low vs high experimental pain modulates the functional connectivity of the periaqueductal gray (PAG). We found no sex differences in pain thresholds, and in both men and women, the PAG was more functionally connected with the somatosensory cortex, the supplemental motor area, cerebellum, and thalamus during high pain, consistent with anatomic predictions. Twenty-six men displayed a pain-induced increase in PAG functional connectivity with the amygdala caudate and putamen that was not observed in women. In an extensive literature search, we found that female animals have been largely overlooked when the connections between the PAG and the amygdala have been described, and that women are systematically understudied with regard to endogenous pain inhibition. Our results emphasize the importance of including both male and female subjects when studying basic mechanisms of pain processing, and point toward a possible sex difference in endogenous pain inhibition.

Keywords

Amygdala; Functional connectivity; Gender; Periaqueductal gray (PAG); Psychophysiological interaction; Sex difference

1. Introduction

Pain experiences are shaped by a combination of cultural, psychological, and biological factors. Because the incidence of pain disorders is higher in women, with longer duration and severity [43, 130], sex differences in pain have been a focus of extensive research. These studies find that women are more often diagnosed with chronic pain disorders such as migraine, complex regional pain syndrome, fibromyalgia, irritable bowel syndrome, temporomandibular disorder, and whiplash-associated disorder [34, 58, 139]. The

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The authors have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2011.11.006.

pathophysiologic process of central sensitization is thought to be common to all of these disorders. Thus, gaining a greater understanding of the central mechanisms underlying this sex difference is a crucial next step for pain research [55].

The most studied endogenous pain modulatory system is the periaqueductal gray (PAG) and its descending projections to the rostral ventromedial medulla (RVM) [61, 90, 114]. Pain is modulated by the PAG through the RVM that directly communicates with nociceptive neurons in the dorsal horn of the spinal cord. The PAG receives direct projections from the hypothalamus and the limbic forebrain including the frontal neocortex, amygdala, and anterior cingulate cortex [2, 10]—regions involved in emotional and cognitive processing of pain. Given the crucial role of this descending pain control system, some investigators have hypothesized that its dysfunction, particularly dysfunction of the PAG, may be crucial to the development and maintenance of chronic pain states [3, 108].

Animal studies indicate differences in pain inhibition between male and female animals. The spinal endorphin/μ-opioid receptor analgesic system is sexually dimorphic in rats [56, 127]. Even though female rats have greater numbers of PAG to RVM output neurons [80], both morphine and pain induce more activation of PAG neurons projecting to the RVM in male rats [16, 78], and microinjection of morphine into the PAG produces less pain reduction in female rats [79]. These results suggest that distal projections of the PAG may be in part explaining sex differences in pain [80] and led us to speculate that there are similar sex-specific pain-evoked patterns of PAG connectivity in humans.

Previous functional magnetic resonance imaging (fMRI) studies on sex differences in pain reactivity indicate that men have greater pain activation of the somatosensory and insular cortex, and that women have higher medial prefrontal activation [35, 69, 93, 101, 126]. In addition to task-related fMRI, resting-state functional connectivity studies also indicate sex differences [15, 64]. For instance, using the PAG as a seed, we have found that men display higher connectivity to the uncus, the insula, and the prefrontal cortex, whereas women displayed higher PAG connectivity to the middle cingulate cortex [70].

As the key region in the endogenous pain modulation system, it is likely that the functional association between the PAG and other brain regions is changed when experiencing different levels of pain. We analyzed data from 3 previous experiments from our laboratory to investigate how midbrain connectivity changes when switching from low to high pain stimulation, and whether such changes in connectivity differ between men and women.

2. Materials and methods

2.1. Participants

Sixty healthy adults—34 women and 26 men—were included in the analysis (mean ± SD age 26 ± 4.7 years, range 20–45 years, no significant sex difference in age). To achieve an adequate sample size, we pooled data from 3 experiments [65, 67, 68] from our laboratory. The original aims of these experiments were similar (ie, to investigate the brain mechanisms of placebo, nocebo, and acupuncture analgesia). Each study began with 2 identical fMRI scans where heat pain stimuli of 2 different intensity levels were applied on the right forearm, all performed with the same male experiment leader (JK). These initial scans were completely identical across studies, and they were performed before any treatment was provided. Therefore, we believe that pooling these data together to achieve adequate statistical power for the present study is appropriate. The experiments were conducted with the written informed consent of each subject and approved by Massachusetts General Hospital's institutional review board.

2.2. Procedures for the delivery of noxious thermal stimuli

Pain was delivered to the right arm with a TSA-2001 thermal sensory analyzer with a 3 × 3 cm probe (Medoc Advanced Medical Systems, Rimat Yishai, Israel) running Covas software. All stimuli were initiated from a baseline resting temperature of 32 °C and increased to a target temperature. Each stimulus was presented for 12 s, including 2.5 s to ramp up toward the target temperature from baseline and to ramp down to baseline. The interstimulus interval ranged from 24 to 30 s. Subjective sensory pain ratings were collected after each pain stimulus [53].

2.3. Calibration of noxious thermal stimuli

Before fMRI scanning, an ascending series of heat stimuli (increasing by 1 °C per stimulus) was applied on 2 areas on the right distal volar forearm (adjacent to the wrist) to identify individual temperatures settings corresponding to low pain (~5 on the 0–20 sensory scale) and high pain (~15). A random series of 4 high and 4 low pain stimuli were applied to the same areas of the forearm. Temperatures were adjusted if necessary to ensure that each individual's subjective ratings of high and low remained in the desired range.

2.4. The fMRI experiment

At least 3 days after pain testing and pain threshold determination, the individually calibrated pain stimuli were delivered in blocks during fMRI data acquisition. Each participant completed 2 fMRI runs with randomly timed pain sequences applied on the right distal forearm while the subjects were instructed to focus on a small black fixation cross in the center of a screen in front of them. The cross turned red at the onset of each stimulus and then turned black again when the temperature returned to baseline (ie, after 12 s). Next, after a delay of 4, 6, or 8 s, the Sensory Box Scale was displayed on the screen for 8 s, and subjects moved a cursor along the scale to indicate their subjective ratings. The interval between the end of the presentation of the rating scale and start of the delivery of the next pain stimulus ranged from 8 to 14 s, with an average of 12 s.

2.5. fMRI data acquisition

Brain imaging was performed with a 3-axis gradient head coil in a 3-T Siemens MRI system equipped for echo planar imaging. Because of a scanner upgrade, about half of the subjects (10 men and 18 women) were scanned with a 3-T head-only Siemens Allegra MRI system, and the other half (16 men and 16 women) were scanned with a 3-T whole-body Siemens Trio MRI system, with no significant difference in sex distribution between the scanners (P = .31, Fisher's exact test). The scanning parameters were identical and remained consistent across the 2 scanner versions to avoid any variance in data caused by parameter settings. Thirty axial interleaved slices (4 mm thick with 1-mm skip) parallel to the anterior and posterior commissure covering the whole brain were acquired with TR = 2000 ms, TE = 40 ms, flip angle = 90 degrees, and a 3.13 × 3.13 mm in-plane spatial resolution. A high-resolution 3D MPRAGE sequence for anatomic localization was also collected. Standard SPM5 [49] preprocessing included motion correction, spatial normalization to the Montreal Neurological Institute (MNI) template, spatial smoothing with an 8-mm Gaussian kernel, and high-pass temporal filtering (cutoff 128 s). The fMRI signal was then modeled by the general linear model.

2.6. Seed generation based on univariate general linear model effects

Midbrain activations, corresponding to the PAG region, were identified by the high pain > low pain contrast and by individual anatomy. For each participant, the time series were obtained for both fMRI runs by extracting the first eigenvariate ("volumes of interest" within SPM5) from a 3-mm radius sphere centered to encompass the right and left PAG

(MNI coordinates [MNI_{xyz}] right = 4, −26, −16, left = −4, −26, −16). The seed location was based on our previous resting state functional connectivity analyses [70]. We chose seeds lateral of the midline to avoid extracting signal from cerebrospinal fluid in the cerebral aqueduct. Extracted time series were adjusted for effects of interest by individual F contrasts. To identify individual PAG activity that showed some degree of pain relation, we lowered the statistical threshold in each individual until at least 5 voxels were found within 4 mm of the PAG coordinate defined from our previous resting state functional connectivity analyses [70]. This procedure resulted in an average individual activation threshold of $P = .17$ in men and $P = .35$ in women, with an average of 10 voxels extracted from both men and women for both the left and right PAG seed regions.

2.7. Psychophysiological interaction analysis

Psychophysiological interaction (PPI) analysis tests how much of the variance of BOLD signal can be explained by the interaction between signal in one seed region of interest (the physiological parameter) and an experimental variable (high or low pain) [48]. The seed time series was hemodynamically deconvolved [51] and, element by element, multiplied with the experimental (psychological) parameter (a term subtracting one condition from another, here high pain minus low pain (1–1)), resulting in the PPI interaction term. The first-level PPI design matrix included the interaction term, the psychological parameter, and the seed. Six motion-correction parameters were also included into the model to further account for possible movement-induced artifacts. The interaction regressor identifies voxels in the brain that display a difference in regression slope dependent on the seed time series and the experimental condition. The fit of this model is mapped into a contrast image for each participant, technically equivalent to a first-level univariate analysis. For each subject, PPI effects were estimated at each voxel, and contrast images (high pain > low pain) were produced. In the context of the present study, a positive PPI effect indicates that the regression slope indexing the relationship between the PAG and the identified regions is more positive in high pain than in low pain, whereas a negative PPI indicates the regression slope is more negative in high pain than in low pain.

2.8. Second-level PPI analysis of the bilateral PAG seeds

Individual PPI contrast images from the right and left seed were entered into a second-level mixed-effects analysis that used a factorial design including 3 factors (subjects, sex, and the PAG PPI effect for both functional runs). A critical cluster level of $P < .05$, familywise error (FWE) corrected for multiple comparisons encompassing >10 voxels was chosen as our significance criteria. To interpret the observed PAG PPI effects, we recalculated the PPI interaction term twice (after removal of one condition at a time from the psychological parameter—that is, (10) and (01) instead of (1–1)—and estimation of these explanatory PPI models revealed regressions of the PAG seeds in low and high pain conditions separately [87]. This post hoc analysis was performed separately for men and women, allowing us to disentangle the PPI interaction into its components and to plot the average beta values indexing the gradient of the regression slopes for men and women in both high and low pain. The 4 separate beta values (men and women, low and high pain) illustrate what factor or factors drive the PAG PPI effects.

3. Results

3.1. Behavioral and univariate fMRI results

There was no difference between men and women in the temperatures needed to evoke the target low or high pain ratings. A 2 × 2 analysis of variance revealed no significant main effect for sex, nor did an interaction for sex and stimulus level (main effect of sex; $F(1, 53) = 1$, $P = .31$, NS; sex × stimulus level interaction: $F(1, 53) = 0.82$, $P = .37$, NS). There was

also no difference between men and women regarding subjective ratings of high and low calibrated pain stimuli (2 × 2 analysis of variance, main effect of sex: $F(1, 53) = 1.1$, $P = .29$, NS; sex × stimulus level interaction: $F(1, 53) = 0.06$, $P = .801$, NS). Table 1 provides descriptive statistics of the temperatures and ratings. Furthermore, the PAG was activated in the high vs low pain condition (Table 2), but there were no significant sex differences in the magnitude of the PAG activation. Further details about the univariate effects of pain inductions have been provided previously [69].

There were no significant differences in the connectivity measures obtained by the 2 different scanners, consistent with our previous studies on the influence of scanner type [141]. All subsequent analyses thus disregarded scanner type as a factor.

3.2. PPI effects

The analyses of PPI effects during high pain vs low pain revealed significant results for several regions of the brain involved in pain processing. We report both common and sex-specific changes in functional connectivity of the PAG induced by the shift from low pain to high pain.

Both for the right and left PAG, there were extensive increases in functional connectivity (positive PPI effects) for high pain vs low pain and no significant decreases (Fig. 1). Significant positive PPI effects for the left PAG included the left somatosensory and motor cortex, the right medial frontal gyrus, the bilateral thalamus, cerebellum, and the brain stem. The right PAG exhibited similar positive PPI effects (Supplementary Table S1). We found no PPI effects to the middle and anterior cingulate at our significance threshold, but the midcingulate appeared at a more liberal threshold of $P < .001$ uncorrected. There was no significant ($P < .05$ FWE) difference between the connectivity of the left and the right PAG seed, and no significant sex × laterality interaction.

3.3. Sex similarities in PPI effects

The above main effect analysis included both men and women, and it is possible that some of the effects were driven by either men or women alone. To assess what regions displayed increased PAG connectivity at high pain present in both men and in women, a conjunction analysis was performed, where both men and women were required to display PPI effects above $P < .05$ FWE. This yielded a common network among men and women including the cerebellum, thalamus, and the somatosensory, motor, and premotor cortices (Fig. 2a and Table 3). To further understand the PPI effects, we decomposed the interaction for both men and women in the left cerebellum (MNI_{xyz} −26, −76, −28), the right thalamus (−14, −16, 18), the left medial supplemental motor area (−4, −12, 48), and in the left postcentral gyrus (−30, −32, 64) corresponding to the somatosensory region of the right forearm [103]. The results of this post hoc analysis are illustrated in Fig. 2b.

3.4. Sex differences in PPI effects

To investigate the possible differences in pain intensity-modulated PAG connectivity between men and women, the PPI effects for the left and right PAG were compared for male and female subjects. For the right PAG, there were no significant differences in PPI effects when comparing men and women. For the left PAG, however, there were several brain regions with significant differences in PPI effects, primarily in men showing greater PPI effects than women. The most robust distinction between men and women was observed in the left amygdala, a structure where men had significantly larger increases in functional connectivity than did women. In addition, men also had larger increases in PAG functional connectivity in the left thalamus, left precentral gyrus, right cuneus, right putamen, right supplemental motor area, and right caudate. The contrast of (women > men) showed that

women had larger increases in functional connectivity in the right supplemental motor area (Fig. 3a and Table 4).

To explore the effects driving the difference in connectivity between men and women during high and low pain, we disentangled the PPI interaction to illustrate the connectivity changes for the amygdala, left thalamus, right putamen, and right caudate by plotting beta values showing the relationship between PAG and time series of these regions separately. Fig. 3b illustrates the beta values indexing the influences between the PAG and effected regions in low and high pain, respectively. Fig. 4 illustrates the pain intensity-induced change in functional connectivity between the left PAG to left amygdala in a representative male and female subject.

4. Discussion

4.1. Findings

We investigated how pain intensity modulates connectivity of the PAG, and whether men and women recruit pain inhibitory systems differently. In both men and women, high pain increased PAG connectivity with thalamic, cerebellar, somatosensory, motor, and medial superior frontal regions—that is, via well-described anatomic pain-processing pathways [2, 4, 32, 72, 135]. A conjunction analysis of men and women revealed sex similarities in PPI effects, indicating a core network that is more functionally connected with the PAG in states of high pain vs low pain. We did not observe any significant differences between the left and the right PAG, but the connectivity changes were qualitatively more robust for the left PAG seed, consistent with right-sided pain being processed in the left hemisphere. We observed significant sex differences in functional connectivity of the PAG when subjects switched between low and high levels of pain. In men, higher pain led to an increased functional connectivity between the PAG and the amygdala and also between the PAG and the putamen. This effect was not present in women.

Our results suggest that pain intensity augments the difference between men and women in PAG to amygdala, caudate, and putamen connectivity, consistent with studies suggesting sex differences in the experience of pain arise from differences in emotional processing [115]. Anatomic investigations also support our findings by indicating that women have less pronounced midbrain white matter tracts [113]. In a postmortem Golgi-Cox staining study, human sexual dimorphisms in infants (ie, before societal influences) have also been reported in the raphe magnus nucleus [31]. Furthermore, measures of opioid binding potentials demonstrate that men have lower levels of l-opioid availability in the amygdala [147] and pain induces larger changes in μ-opioid receptor availability in the thalamus, ventral basal ganglia, and amygdala in men compared to women [148]. These results and ours suggest that the PAG-amygdala recruitment may be one of the mechanisms in which men and women differ in pain processing.

4.2. Limitations

The PAG has a broad range of functions [10], and we here interpret increased functional connectivity as part of an endogenous analgesic system, but without direct evidence by, for example, naloxone administration [41, 125] or measures of PAG opioid receptor availability [147]. Directionality and/or causality cannot be inferred from PPI analyses, and PPI effects do not necessarily imply direct anatomic connections. Moreover, the regions used as seeds are approximation of the PAG, with limited resolution [76].

We did not observe any sex difference in PAG to RVM connectivity, as has been reported in the animal literature [56, 78–80], possibly as a result of the difficulty of imaging brain stem regions [95]. Moreover, we did not observe any significant differences in pain ratings or

temperatures. Although our sample size was among the largest fMRI studies on pain to date, sample sizes of >41 subjects per group may be necessary to achieve power to also detect pain experience differences [116].

Structural imaging indicates that widespread areas of the cortical mantle are thicker in women than in men [22], particularly in the posterior medial wall [82]. Men have larger volumes, relative to cerebrum size, in the amygdala and hypothalamus [52, 102]. We did not control for sex and/or individual differences in brain morphology, other than by normalization of the individual anatomy to a standard template. There may be residual differences in volumes that contribute to the observed sex effects, as gray matter volume may influence functional connectivity measures [33, 131].

We did not control for gender identification [134], stage of menstrual cycle, or use of oral contraceptives. There is evidence that gonadal hormones influence amygdala function [144] and pain processing. For example, estrogens influence central l-opioid function in the amygdala [40, 124] and the PAG [123]. We made the assumption that gonadal hormone levels would be randomly distributed across the 34 studied women.

4.3. General discussion

The anatomic connections between the amygdala and the PAG have been described with multiple methods in multiple species (Table 5). We found no study investigating amygdala to PAG connections that reported similarities or differences between the sexes. Indeed, the absolute majority of studies only included male animals or made no mention of sex. See also Mogil and Chanda [91] for a review on the lack of female animals in basic science.

Several recent human fMRI studies indicate that manipulation of endogenous pain inhibition through a range of methods (eg, placebo, acupuncture, anticipation, distraction) exert their analgesic effect by activating the PAG (Table 6). Also in these studies, significantly ($P = .007$) more men have been studied and sex differences have received limited attention. In the studies indicating PAG involvement, significantly ($P = .003$) more men than women were studied, while this is not the case ($P = .83$) for studies indicating no PAG involvement or PAG deactivation. The difference in sex composition of studies finding the PAG and studies not finding the PAG was also significant, with more male subjects in the studies finding PAG involvement ($P = .037$). Although direct conclusions are difficult to draw from this literature search, there seems to be a dire need to describe the projections of the PAG in female animals. Moreover, women are less studied in human pain imaging, and studies that use mostly men seem to be more successful in demonstrating PAG involvement in pain modulation.

The perception, expression, and tolerance of pain are influenced by a variety of nonbiological processes, such as gender disparities in work, economy, daily living, social life, and expectations [12]. Male gender norms might be regarded to dictate that men should be able to tolerate pain, whereas feminine norms are more permissive of pain expression [94]. In healthy individuals, acute anger arousal triggers endogenous opioid release that reduces subsequent responsiveness to pain, an effect that is more pronounced in men [19]. Furthermore, expressing anger in direct physical or verbal ways has been associated with higher opioid analgesia in men and lower opioid analgesia in women [18]. Men may also have more anxiety related to pain [50]. Recent experimental studies point toward a greater placebo response on pain unpleasantness in men than in women [5], whereas no sex differences were reported in dental pain placebo analgesia [7].

Given the critical role of the amygdala in expression of anxiety, fear, and anger, it is tempting to speculate that stress, fear, and aggression in pain management contribute to the

enhanced male recruitment of the PAG-amygdala inhibition circuitry in the present study. In line with this, behavioral studies indicate that stress may induce hypoalgesia in men, but hyperalgesia in women [111], and in a study on stress-induced analgesia, stress-induced opioid modulation of pain was detected in women but not men [47]. However, we did not inquire how stressful the pain induction was, subjects' identification with gender norms, or what coping strategies the subjects engaged in.

In chronic pain, the tendency to express and suppress anger predicts poor treatment outcomes in men but not in women [20], and men with chronic pain have a higher association between pain unpleasantness and pain-related emotions such as frustration than do women [117]. Clinical studies suggest that women require more morphine after surgery to achieve a similar degree of analgesia compared with men [6, 25], but women and men generally show similar analgesic responses to morphine in experimental studies [43, 44], yet women tend to use less morphine in patient-controlled analgesia [27]. In light of the results of the present study, further studies on sex differences in PAG-amygdala connections may yield important insights for both pharmacological and psychological interventions in chronic pain.

In the popular media, and sometimes also in the scientific literature, subtle findings of sex differences are exaggerated and overinterpreted [14, 45, 62], a phenomenon that has been recognized for over a century [128]. The effect size of the sex differences in PAG-amygdala connectivity in the present study was substantial (ie, Cohen's $d = 0.69$) for average difference across the voxels in the amygdala cluster, and our sample size was larger than most previous neuroimaging studies. However, it is important to note that the present study also revealed a substantial overlap between men and women. We thus emphasize that the observed sex differences, while substantial, need to be replicated in studies controlling for factors such as gender identification, menstrual cycle, and oral contraceptives.

In conclusion, we found evidence for substantial modulation of PAG connectivity induced by pain intensity. Both men and women showed increases in cerebellar, thalamic, somatosensory superior frontal connectivity to the PAG at high pain. We also observed sex differences in pain intensity-modulated connectivity of the PAG. Specifically, men seem to have more access to an amygdale-mediated recruitment of the endogenous pain inhibition system. We emphasize the importance of including both male and female subjects when studying the basic mechanisms of pain processing. A fuller description of the influence of sex and gender on recruitment of endogenous analgesia, and how emotive strategies associated with negative affect influence such coping with pain, may yield important clinical and therapeutic insights.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

C.L. received support from the International Association for the Study of Pain (IASP) Early Career Award and the Swedish Society for Medical Research (SSMF). J.C.B. received support from Ev. Studienwerk Villigst (Schwerte, Germany) and is an ERP scholar of the German National Academic Foundation. K.J. received support from SSMF and the Swedish Council for Working Life and Social Research (FAS). This work was supported by PO1-AT002048 to B.R. from National Center for Complimentary and Alternative Medicine (NCCAM), KO1AT003883 (NCCAM) and R21AT004497 (NCCAM), R03AT218317 from National Institute on Drug Abuse (NIDA), R01AT006364 (NCCAM) to Jian Kong, R01AT005280 (NCCAM) and R21AT00949 (NCCAM) to Randy Gollub, M01-RR-01066 and UL1 RR025758-01 for Clinical Research Center Biomedical Imaging Core from National Center for Research Resources (NCRR), and P41RR14075 for Center for Functional Neuroimaging Technologies (NCRR).

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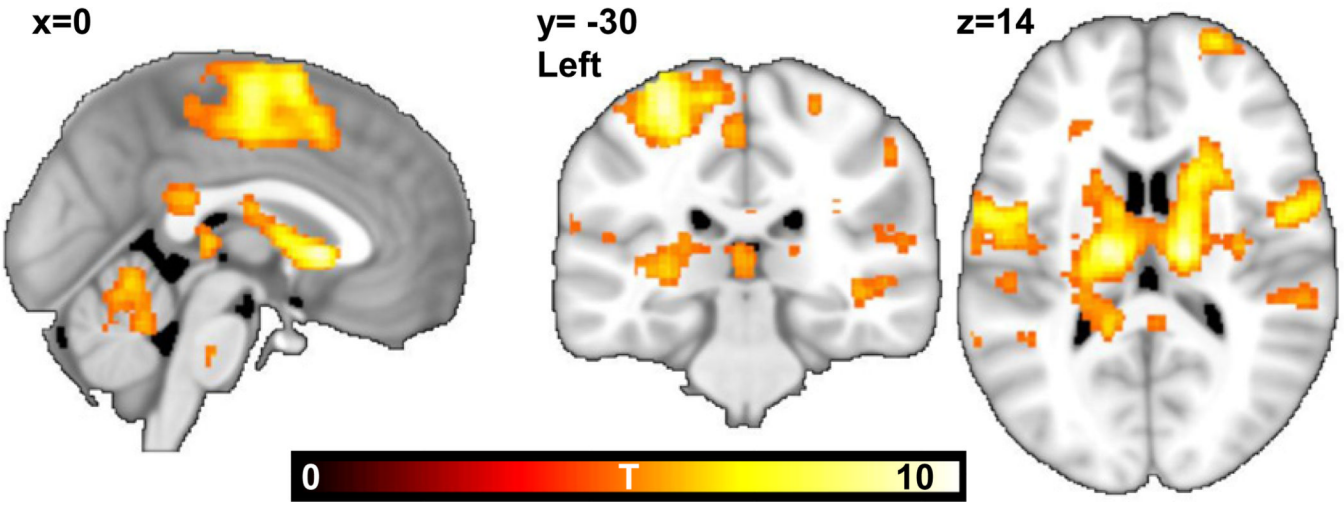

Fig. 1.

Areas displaying a change in connectivity with the left PAG seed at high pain as compared to low pain in all subjects (n = 60). Positive PPI effects are displayed on the MNI template at $P < .05$ FWE. The color scale denotes T values.

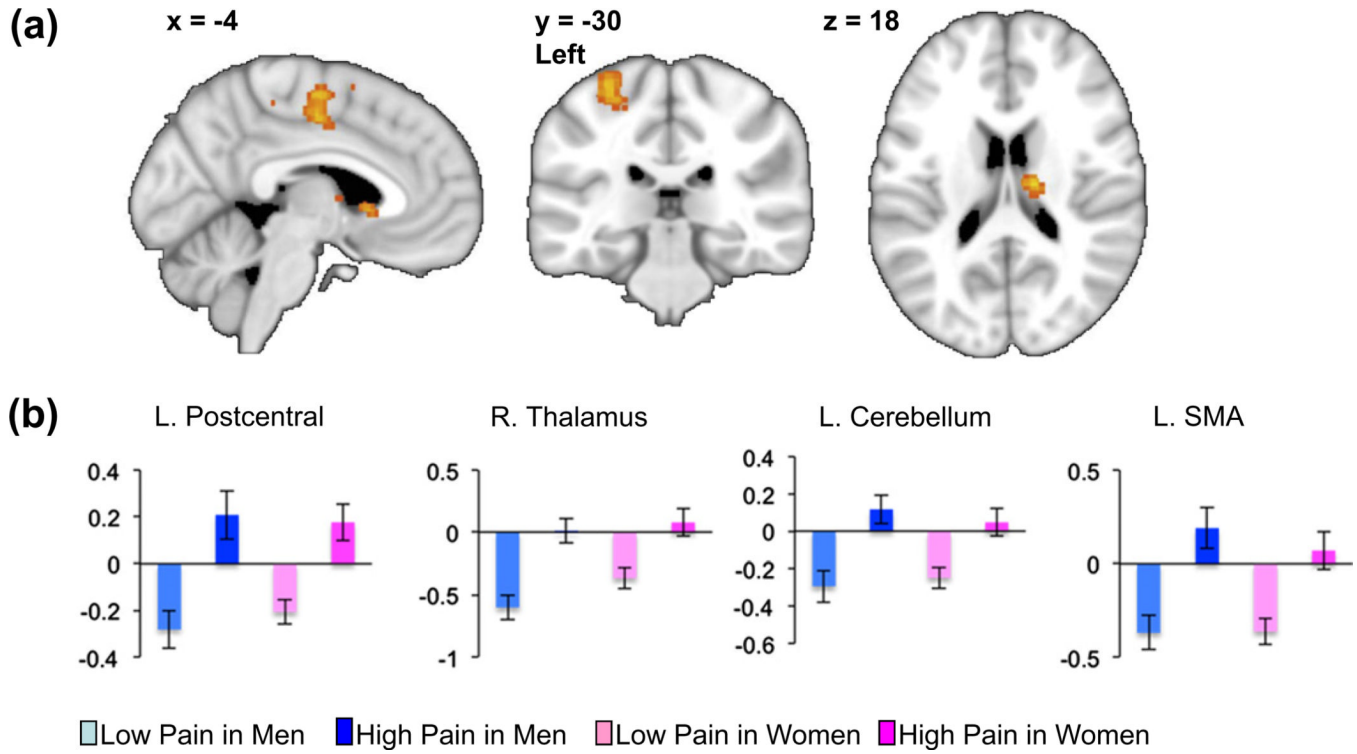

Fig. 2.

(a) Areas where men and women are alike in the way the connectivity with the PAG changes from low to high pain. Areas where the change in connectivity is at $P < .05$ FWE for both men and women are displayed in on the MNI template. (b) Box plots indicate the decomposed PPI effects for men and women during states of low and high pain for the left postcentral gyrus, the right thalamus, the left cerebellum and the left supplementary motor area (SMA).

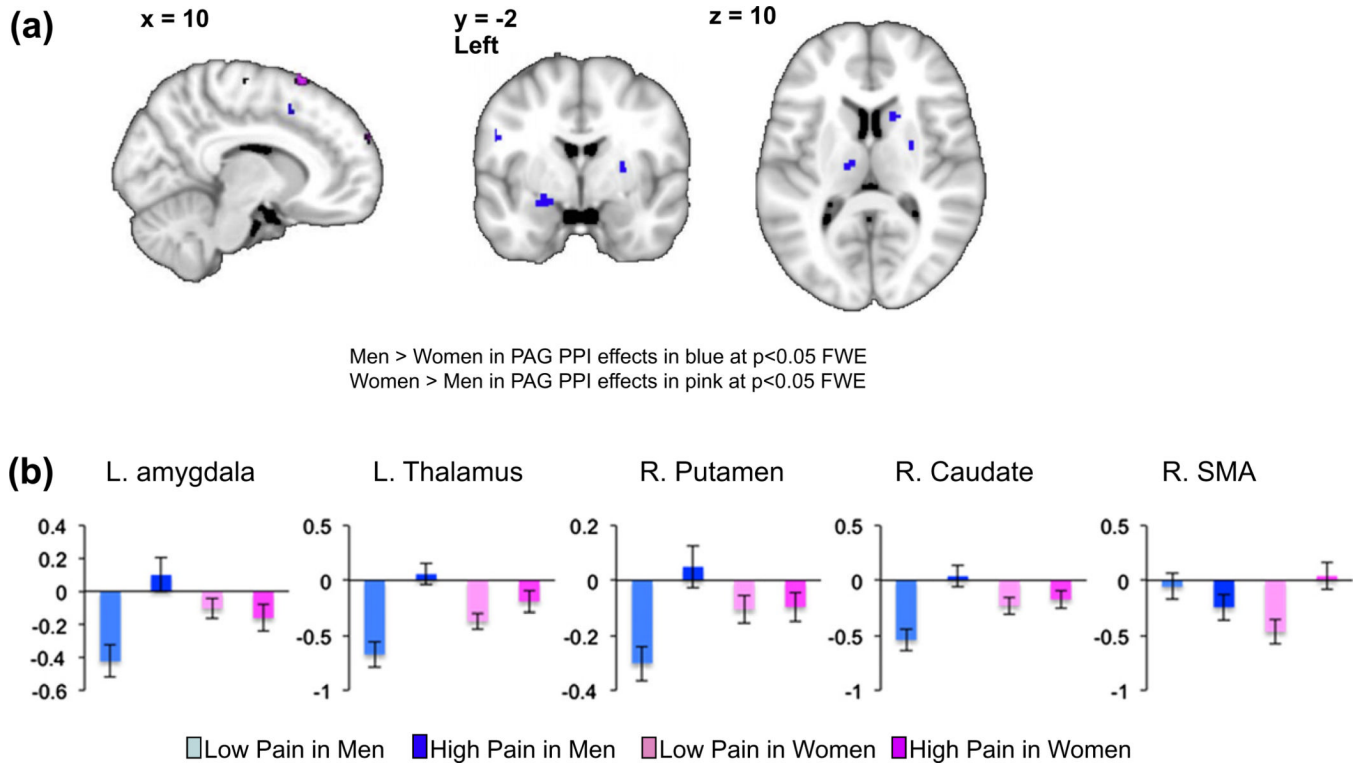

Fig. 3.

(a) Areas where men and women differ in the way the connectivity of the PAG changes from low to high pain. Areas where the change in connectivity was higher in men are displayed in blue, areas where the connectivity change was higher in women are displayed in pink at a significance threshold of $P < .05$ FWE. (b) Box plots indicate the decomposed PPI effects for the amygdala, left thalamus, right putamen and the right caudate where men had larger PPI effects than women, and for the right supplemental motor area where women had larger PPI effects than men.

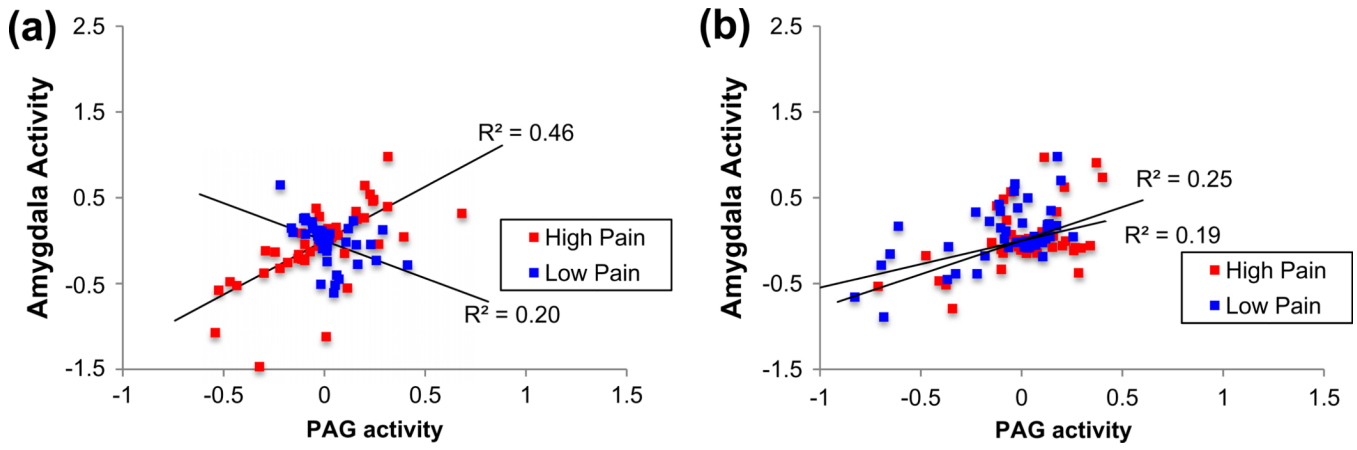

Fig. 4.
PPI effect in one representative male (a) and female (b) subject. Red squares indicate time series functional connectivity between the PAG seed and the amygdale during high pain; blue squares indicate the connectivity during low pain.

Table 1

Temperature needed to evoke low and high pain and subjective ratings in subjects with a 3 × 3 cm heat probe on the forearm

Subject	Mean temperature, °C, mean ± SD		Mean subjective rating, mean ± SD[a]	
	Low pain	High pain	Low pain	High pain
Male (n = 26)	46.2 ± 1.5	48.8 ± 1.0	4.6 ± 2.1	13.8 ± 1.8
Female (n = 34)	45.8 ± 1.6	48.4 ± 1.2	5.2 ± 2.8	14.2 ± 1.9
All	45.9 ± 1.5	48.6 ± 1.2	4.9 ± 2.5	14.0 ± 1.8

[a]Subjective rating is 0–20 on Gracely's pain intensity scale.

Table 2

Univariate PAG activations in response to thermal pain (n = 60) within a 4-mm spherical mask around the PAG.[a]

ROI	x	y	z	T value	No. of voxels	*P* (FWE corrected)
Right PAG	4	−26	−14	6.92	32	<.001
Left PAG	−2	−28	−16	7.59	32	<.001

[a]Seed locations are given in MNI coordinates. All results are corrected for multiple comparisons.

Table 3

Brain regions exhibiting higher functional connectivity (positive PPI) with the left and right PAG.[a]

Region	Peak			Cluster		Peak T value
	x	y	z	PFWE	Size	
Conjunction of men and women left PAG region						
Left postcentral gyrus	−30	−32	64	0.000	458	6.7
Left precentral gyrus	−32	−22	48			6.3
Left postcentral gyrus	−44	−10	46			5.9
Right caudate	2	14	0	0.000	119	6.7
Left caudate	0	4	4			5.3
Right thalamus	14	−16	18	0.000	52	6.5
Left supplemental motor area	−4	−12	48	0.000	273	6.4
Left supplemental motor area	−2	−10	58			6.2
Right cerebellum	18	−58	−24	0.000	103	5.9
Right cerebellum	28	−56	−30			5.2
Right supplemental motor area	2	4	64	0.000	82	5.9
Left cerebellum	−26	−76	−28	0.000	106	5.7
Left cerebellum	−20	−68	−26			5.3
Left cerebellum	−34	−62	−32			5.0
Left caudate	−14	22	04	0.004	16	5.5
Right rolandic operculum	58	−2	10	0.005	14	5.4
Conjunction of men and women right PAG						
Left middle cingulate	−2	−10	42	0.006	13	5.1

[a]Connectivity was assessed using the contrast “High pain > Low pain” in a conjunction analysis of 34 women and 26 men indicating sex similarities in functional connectivity changes present in both men and women. Peak regions are given in MNI coordinates. All results are corrected for multiple comparisons at $P < .05$ FWE with a 10-voxel-cluster size threshold. There were no significant negative PPI effects.

Table 4

Sex differences in PPI effects for the left PAG in 26 male and 34 female subjects.[a]

Region	Peak			Cluster		Peak T value
	x	y	z	PFWE	Size	
Left PAG PPI effects, men > women						
Left amygdala	−22	−2	−12	0.000	58	6.4
Right cuneus	22	−60	38	0.001	36	5.9
Left thalamus	−12	−16	12	0.003	20	5.7
Right putamen	26	−6	8	0.005	14	5.5
Right supplemental motor area	8	12	50	0.005	15	5.4
Right caudate	14	14	8	0.002	26	5.4
Left precentral gyrus	−52	22	28	0.004	17	5.3
Left precentral gyrus	−56	4	22			5.1
Left PAG PPI effects, women > men						
Right supplemental motor area	10	20	68	0.007	11	5.7

[a]The contrast “High pain > Low pain” was used and cluster peak locations (x, y, z) are given in MNI coordinates. All results are derived from a statistical threshold of $P < .05$, FWE corrected for multiple comparisons with clusters encompassing >10 voxels. No significant sex differences in PPI effects were observed for the right PAG.

Table 5

Animal studies reporting PAG-amygdala connections with various methods.[a]

Species	*n*	Male (%)	Female (%)	Female vs male	Reference
Mouse	12	100	0		[132]
Rat	22	100	0		[11]
	55	100	0		[54]
	40	100	0		[118]
	20	100	0		[23]
	36	100	0		[106]
	12	100	0		[21]
	48	100	0		[26]
	6	000	0		[9]
	90	100	0		[84]
	–	000	0		[98]
	–	000	0		[46]
	–	000	0		[30]
	–	000	0		[29]
	–	000	0		[28]
	–	100	–		[63]
	70	“Males and females”	–	[92]	
	–	“Males and females”	–	[24]	
	20	–	–		[109]
	21	–	–	–	[59]
	162	–	–	–	[99]
	86	–	–	–	[71]
	–	–	–	–	[86]
Opossum	–	–	–	–	[77]
Guinea pig	73	100	0		[74]
Rabbit	13	“Males and females”	–	[100]	
	35	–	–	–	[88]
	67	–	–	–	[89]
Cat	5	“Males and females”	–	[122]	

Species	*n*	Male (%)	Female (%)	Female vs male	Reference
	26	–	–	–	[60]
	4	–	–	–	[86]
	10	–	–	–	[99]
	21	–	–	–	[71]
	1	–	–	–	[59]
Squirrel monkey	6	100	0		[38]
	12	–	–	–	[86]
Macaca fascicularis	9	–	–	–	[110
	18	“Males and females”	–		[2]
Macaca mulatta	9	–	–		[1]
	1	–	–	–	[59]
Human	8	100	0		[57]

[a]Ellipsis dots indicate not specified. Although we tried to be as systematic as possible in our literature search, some studies may be missing.

Table 6

Human studies on endogenous pain modulation.[a]

Manipulation	*n*	Male (%)	Female (%)	PAG	Male vs female	Reference
Placebo	9	100	0	↑[b]	–	[105]
	48	100	0	↑[c]	–	[41]
	14	100	0	↑[c]	–	[146]
	15	100	0	↑[d]	–	[137]
	40	100	0	_[d]	–	[73]
	19	79	21	↑[b]	–	[13]
	10	80	20	↔	–	[97]
	47	63[e]	37[e]	↑	None[e]	[136]
	16	56	44	↔	–	[66]
	20	45	55	↑[c]	–	[121]
	11	45	55	↔	–	[138]
	14	43	57	↔	–	[75]
	31	42	58	↔	–	[83]
	14	36	64	↔	–	[81]
Nocebo	13	38	62	↔	–	[65]
Offset analgesia	15	47	53	↑	–	[140]
	12	0	100	↑[f]	–	[36]
Stress	21	48	52	↔	–	[142]
	14	0	100	↔[g]	–	[119]
Distraction	7	86	14	↑	–	[133]
	9	67	33	↑	–	[129]
Control over pain	16	69	31	↔	–	[120]
Hyperalgesia	12	50	50	↑	–	[143]
Allodynia	12	100	0	↑	–	[85]
Pain vs nonpain	28	50	50	↑[c]	Male > female[h]	[148]
Anticipation	12	50	50	↑	–	[42]

Manipulation	*n*	Male (%)	Female (%)	PAG	Male vs female	Reference
Acupuncture	16	50	50	↑[i]	–	[8]
	12	50	50	↔	–	[67]
	48	50	50	↑		[68]
	10	40	60	↑[i]	–	[96]
	15	47	53	↑[i,j]	–	[37]
	12	50	50	↑[i]	–	[145]
Hypnosis	8	62	38	↔[k]	–	[112]
DBS of PAG	16	81	19	↑[l]	–	[104]
Running	10	100	0	↔[c]	–	[17]
HNCS	22	100	0	↑	–	[125]
Spontaneous fluctuation	16	100	0	↑	–	[107]
Somatic vs visceral	10	50	50	↔	–	[39]
Total	674	62	38	Significantly more men studied, $P < .01$		

[a] Although we tried to be as systematic as possible in our literature search, some studies may be missing.

[b] Placebo increased rostral ACC to PAG connectivity.

[c] μ-Opioid receptor binding potential.

[d] TMS of dlPFC disrupts placebo analgesia.

[e] Personal communication.

[f] No amygdala involvement.

[g] PAG activation correlated to chronic stress scores in pain and no pain.

[h] Greater μ-opioid activation in male amygdala.

[i] No pain induction.

[j] Increased PAG resting state connectivity.

[k] Possible nonsignificant increase in PAG.

[l] Analgesia and altered heart rate variability with deep brain stimulation.