OXFORD

## PSYCHOLOGY, PSYCHIATRY, & BRAIN NEUROSCIENCE SECTION

# Brain Asymmetry in Pain Affective Modulation

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## Abstract

**Objective**. The aim of this study was to characterize the dynamic brain networks underlying the affective modulation of pleasant, unpleasant, and neutral image perception due to painful stimulations in healthy subjects. **Methods**. Forty volunteers, 20 men and 20 women, participated in this study. Brain activity was recorded by 64-channel electroencephalography. After data cleaning, brain functional networks were built through the use of the motif synchronization method. **Results**. We found that increased cerebral connectivity in the left hemisphere under the pain condition broke the connection symmetry. Both women and men showed homophilic connections (intrahemispheric), but women were more homophilic than men. The pain condition increased homophily in the left hemisphere, and emotions could modulate pain. The frontal, central, and left temporal regions showed homophilic variation, depending on the emotional stimulus. **Conclusions**. Pain and emotions altered brain activity. There was increased connectivity and homophily in the left brain hemisphere for the painful experience. The emotions modulated brain activity in the pain condition. Overall, the brain presented homophilic characteristics; homophily changed, depending on emotion or pain. The left brain hemisphere seems to be related to pain processing.

**Key Words**: Pain; Emotion; Brain Asymmetry; Affective Modulation of Pain; Brain Functional Network; Time-Varying Graphs

## Introduction

Pain is a complex multidimensional experience that involves several factors, including sensory, emotional, and physical factors. During pain perception, people automatically stop behaviors and thoughts in an attempt to look for mechanisms to cease the suffering [1]. They focus their attention on the pain region so that, when attention is diverted, it can modulate pain through selectivity mechanisms [2]. Emotions can be considered as a mechanism for attention selecting; thus, they can modulate pain [3]. This finding indicates that arousal evoked by

negative images increases pain, whereas the attention effect induced by neutral images has an opposite effect. Images with erotic or attack content are more effective for modulating pain than are neutral images, indicating that arousal also contributes to pain modulation [4]. Emotions can manage and regulate stimuli and attention mechanisms [5, 6] and, when the individual is in need of an effective response , influence the cognitive system that defines which stimuli should be given priority and for how long. Hence, the brain possesses an essential filtering mechanism for survival [6].

The authors of a comprehensive systematic review and meta-analysis [7] of pain neuroimaging studies that used different techniques described multiple brain regions that are involved in the pain experience and are modulated by interactions between ascending and descending pathways. Peripheral and spinal cord structures and brain areas form a network, where cortical regions and the limbic system also play an important role in pain processing. Indeed, brain networks for acute pain perception in healthy subjects are somewhat distinct from those seen in chronic clinical pain conditions. Chronic pain involves brain regions that are critical for cognitive and emotional aspects, the components of which may comprise different characteristics in chronic and acute pain [7].

Anatomically, the brain is divided into the right and left hemispheres, and the structures on each side may present morphological and physiological differences. Cerebral asymmetries are observed from the gestational period and childhood developmental stages; they lead to differences in lateralization of anatomic structures with regard to dendritic cell branching, metabolism, and brain functional activation [8, 9]. The right cerebral hemisphere processes visual information, facial recognition, tactile perception of complex structures, musical ability, nonverbal thoughts, memory, and emotional processing, whereas the left hemisphere is more analytical, synthetic, and related to cognitive processing [10, 11].

There are anatomic differences in the proportion of cerebral neuronal fibers between women and men: Women have greater interhemispheric connectivity between the right and left hemispheres than do men [12]. Another study used a sample of 949 young people (428 men and 521 women between 8 and 22 years old) and evaluated the structural connectome by diffusion tensor images; the authors observed unique sex differences in brain connectivity during development. Specifically, there was a high proportion of intrahemispheric myelinated fibers in the male brain, whereas interhemispheric connections and participation between modules predominated in women, with greater flexibility and higher interhemispheric communication. Overall, the results suggested that male brains are structured to facilitate connectivity between perception and coordinated action, whereas female brains are designed to facilitate communication between analytical and intuitive processing modes [13].

Several works have been done in the direction of characterizing the relationship between pain and emotions, trying to understand how different brain regions behave in this context. However, no work has been done in the direction of characterizing the dynamic relationship between these brain regions and how pain and emotions influence the synchronization between them. To understand how pain affective modulation changes the brain functional networks and the brain's intra- and interhemispheric relations, we built dynamic brain functional networks (BFNs) of healthy volunteers as they viewed affective images under painful thermal induction .

## Methods

### Participants
This investigation encompassed a sample of 40 healthy volunteers, 20 men (mean age of 20.20 years, standard deviation 1.70, range 18–24 years) and 20 women (mean age of 19.75 years, standard deviation 2.27, range 18–28 years); all were students from the University of Granada, Granada, Spain. This research was approved by the Ethics Committee of the School of Medicine of the University of Granada (number 201302400001677) and was conducted in accordance with the Declaration of Helsinki. All participants signed informed consent forms to participate in this study. To assess the dominant hand of each participant, participants were asked about which hand they use most frequently . The results of the Edinburgh Handedness Inventory showed that of the 40 participants, 39 were right-handed. We used the following as non-inclusion criteria : cardiovascular problems, chronic pain, use of illicit substances, being under medical or psychological treatment, or suffering from a mental disorder.

### Affect Induction
Participants were presented with three blocks of images, selected from the International Affective Picture System (IAPS) [14, 15]. This pictographic instrument has been used successfully in several behavioral and psychophysiological studies around the world [3, 16–19].

Each block contained 20 pleasant images (PLE), 20 unpleasant images (UNP), 20 neutral images (NEU), and a black screen (BS). We selected PLE and UNP images with similar arousal ratings—to control the arousal effect—but with different valence ratings. We chose NEU images with low arousal and intermediate valence. The PLE image set included erotic scenes and extreme sports images; the UNP image set encompassed photos of mutilation and attacks on humans and animals; and the NEU image set contained mushrooms and household objects. After task completion, the participants evaluated the emotional dimensions (valence and arousal) of each picture, through assessment of the emotional dimension, using the Self-Assessment Manikin (SAM) scale. The chosen IAPS numbers and more information are described in Appendix 1.

### Thermal Pain Induction
#### Pain Threshold Calculation for Each Participant
We used a computer-controlled temperature stimulator for pain induction (TE Technology TC 36–25 RS232), shaped by an engineer in Granada, Spain, and coupled to a 4 cm × 2 cm Peltier thermal plate. The painful thermal sensation for each participant was collected on a visual

analog scale, which was presented to the patient after a thermal plate had been placed on the left index finger. After 5 s, starting at 37°C, we asked the participants to remove their fingers and assign a value on a 0 to 10 scale, where 0 was the temperature with no discomfort, 5 was the temperature where it began to be unpleasant, and 10 was when the temperature was unbearably unpleasant. The temperature went up 1 degree at a time, and the assessment ended when the visual analog scale rating reached 10. This procedure was repeated three times, and finally, 60% of this average was used as a pain and temperature threshold: $0.6 \times$ (*tolerated warm temperature* – 37°C) + 37°C. Pain was kept continuous over time to approximate natural pain.

### Data Acquisition

After the average temperature had been measured for each participant, the electroencephalography (EEG) equipment was assembled with 64 electrodes (Phillips Electrical Geodesic, Inc., USA). The computer-controlled thermode of temperature ($4 \times 4$ cm Peltier) was used. Brain activity data were collected at a sampling rate of 1,000 Hz, with a reference electrode positioned at Cz, and the impedance was kept below 50 kΩ.

### Experimental Tasks

Participants sat in a comfortable chair, EEG electrodes were mounted on the scalp, and the room light was minimized. The tasks had five blocks, as shown in Figure 1A: (I) baseline, (II) UNP image block (2 min), (III) PLE image block (2 min), (IV) NEU image block (2 min), and (V) BS (2 min). Each sequence always began with 3 min of baseline (adaptation), which involved looking at a BS. Then, a sequence of four image blocks (2 min each) and pain induction were started, randomly, counterbalanced through the use of a Latin square design [20]. For example, if in the first presentation of the PLE image block, the thermal stimulation was not performed, in the second presentation of this block, the stimulation was performed. A BS was presented between the blocks of images at random time intervals between 6 and 24 s. When the experiment tasks ended, the participants completed the SAM scale.

### Data Processing

The EEG was recorded with Cz reference electrode and was re-referenced to the average of electrodes. The AFz, FCz, Fz, Cz, POz, Pz, and Oz electrodes, the mastoid bone electrode, and the facial electrodes were removed after collection. Hence, there were 52 electrodes:

Right hemisphere—AF4, FP2, F10, F6, F4, F8, F2, C6, C4, C2, FC4, FC2, FC6, TP8, T8, T10, FT8, P2, CP2, P4, P10, P8, P6, CP6, PO4, and O2.

Left hemisphere—FP1, AF3, F3, F5, F7, F9, FC1, F1, FC5, FC3, C1, C3, C5, FT7, T9, T7, TP7, CP1, CP5, P5, P3, P7, P1, P9, PO3, and O1.

Data were filtered with a band pass filter between 0.1 and 70 Hz through the EEGLAB (Arnaud Delorme and Scott Makeig, San Diego, California, USA) toolbox from MATLAB (Cleve Moler, New Mexico, USA). We applied a baseline correction of 0–10 ms. For data collection, the 50-Hz notch filter was performed. Then, we segmented the EEG data into 100-ms epochs; we obtained a total of 1,200 epochs for each experimental condition (PLE, UNP, NEU, and BS). Epoch amplitudes ±70 μV were considered artifacts and were automatically eliminated. In addition, we performed a visual inspection and removed the epochs with remaining artifacts. After artifact removal, the file size ranged from 601 to 935 epochs. We selected 601 epochs randomly, equivalent to 1 min, to estimate BFNs.

### Construction of BFNs and Time-Varying Graphs

To construct BFNs, we considered the regions where the electrodes were positioned on the scalp (following the international 10–20 system) as nodes and the synchronization of activity across brain regions as edges. BFNs were built through the use of time-varying graphs and the motif synchronization method, as proposed by Rosário et al. [21]. The BFNs were constructed with the following parameters: motif lag 1, TVG step 1, and tau maximum 30.

The motif synchronization method evaluates up and down patterns of the EEG tracing, allowing researchers to observe the synchronicity among electrode channels that are pairwise-compared in each defined time window. This window was 100 ms and ran along the EEG tracing; a graph was built for each window, with all significant connections between the similarity patterns—namely, the motifs [21]. The evaluation of significant connections occurs through the paired comparison between the electrode channels in the considered window. A threshold, corresponding to 95% certainty, is defined in a surrogate dataset; if the evaluated synchronization exceeds the threshold, then a connection is considered. At the end of the entire EEG tracing, there is one graph that represents a network for each instant of the brain record in time—namely, the time-varying graph. The overlap of all graphs obtained from the time-varying graph is shown as an aggregate static network (Figure 1B). The aggregate static network is a weighted graph in which the weight of the edges represents the total time that the pair of electrodes remained connected throughout the measurement.

For this analysis, we selected the weighted degree (Kp) index and the E-I index, both of which were estimated for the aggregate static network. The E-I index represents intrahemispheric connections (homophily) and interhemispheric connections (heterophily). This functional analysis over time can reveal brain aspects under a new
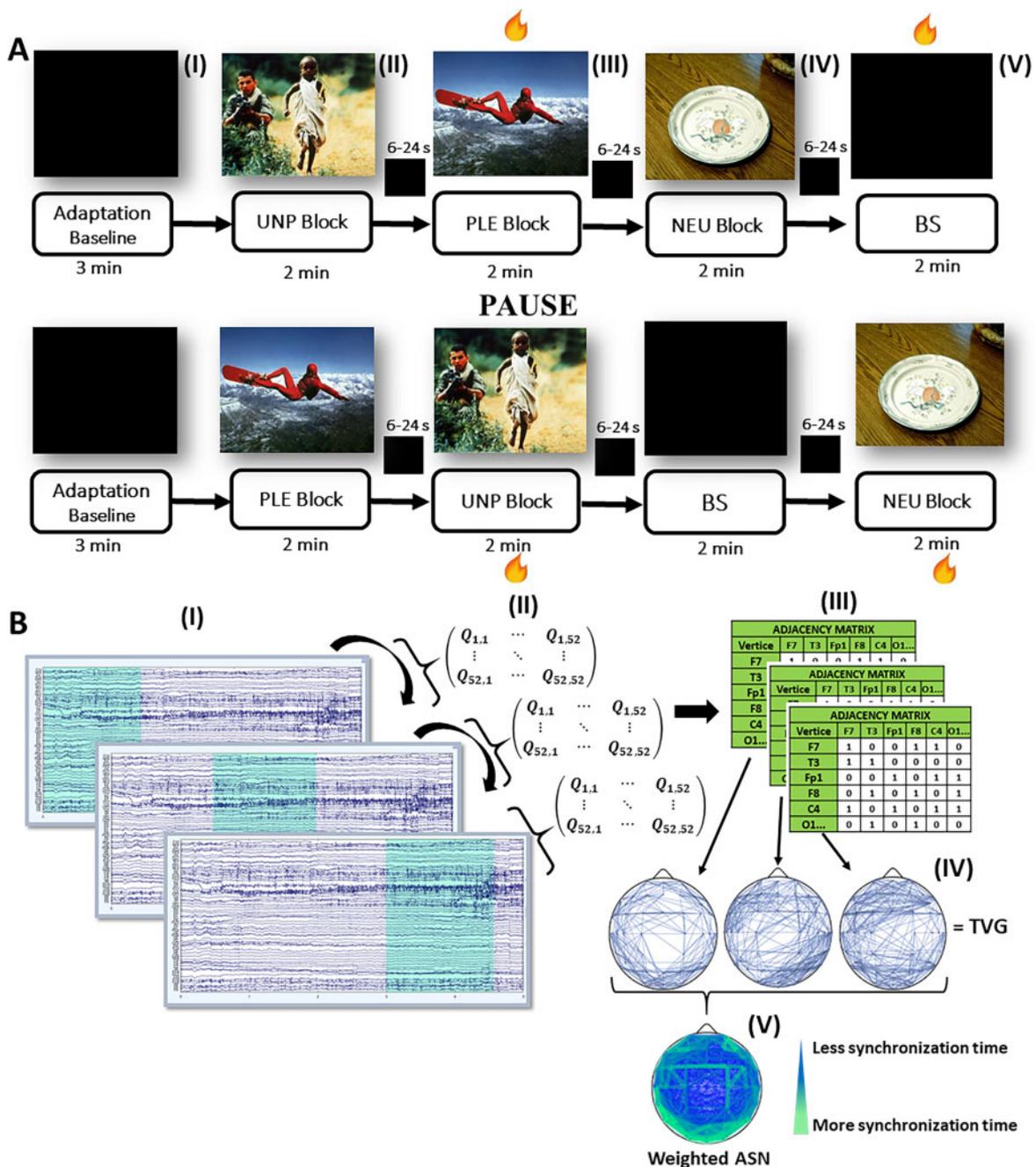
**Figure 1.** (A) The data collection protocol: (I) adaptation with a BS at baseline for 3 min; (II) blocks with UNP, (III) PLE, (IV) NEU images, and (V) a BS. In each block (2 min), there was an interval of 6 to 24 s. The presentation order of each block was defined by Latin square randomization for each participant. The pain induction was randomized. **(B)** Representation of brain functional networks (BFN) construction. (I) Depiction of the delimited window in the EEG tracing that slips over time. In the correlation matrix (II) and in the adjacency matrix (III), the synchronization between the channels (constructed through motifs) are shown. (IV) The created graphs show the connections (synchronies) that occurred at that window. (V) The weighted aggregate static network (ASN) is the sum of the graphs generated for each time window in the EEG tracing. The illustration was based on pleasant without pain condition.

spectrum and thus broaden the ways to evaluate and understand the brain dynamics.

### Connectivity Evaluation Within Hemispheres: Weighted Degree

We defined the index weighted degree, $K_i$, as the total number of times in which an edge connects a node $i$ of the network with another (in this case, two brain regions ):

$$K_i = \sum_{t=1}^{T} \sum_{j=1}^{N} A_{i,j,t}, \qquad (I)$$

where $N$ is the total number of electrodes, $T$ is the total time evaluated, and $A_{i,j,t}$ is the element of the adjacent

tensor indicating the presence (1) or absence (0) of a connection between electrode $i$ and $j$ in time $t$. We defined the mean time connectivity Kp of a subject as the average over all $N$ electrodes. The values of this index do not represent the strength of synchronization as they are used in conventional methods; instead, they represent the persistence of synchronization over time. A weak but persistent synchronization over time will lead to indexes with high values, and conversely, punctual strong synchronizations will be practically disregarded in this approach.

## Intra- and Interhemispheric Connections: Homophily and Heterophily

Researchers proposed the E-I index to evaluate the linkage among members of an organization, i.e., the "crisis management model." This index provides the relationship between external and internal links, where external links are connections among members of different subunits, and internal links are connections among members of the same subunit [22]. We used the weighted aggregate static network to calculate the E-I index. The right and left hemispheres represent the subunits; the idea is to estimate the proportional ratio between synchronization that occurred within the same hemisphere and between hemispheres. The E-I index is given by:

$$E - I\ index_i\ =\ \frac{EL_i - IL_i}{EL_i + IL_i}\ ,\qquad\text{(II)}$$

where $EL_i$ represents the number of times node $i$ was synchronized (in connection) with nodes from the opposed hemisphere. The internal synchronization is represented by $IL_i$ and means the number of times node $i$ was connected within the same hemisphere.

The region is interhemispheric or heterophilic (heterophily) when the E-I index is positive; in this case, most of the connections are made to places outside the hemisphere. When the E-I index has a negative value, most of the connections occur within the same hemisphere; in this case, the region is intrahemispheric or homophilic (homophily). When the connections are evenly split, the index is zero. A heterophilic region signifies that more connections happen among its electrodes and the electrodes of the opposite hemisphere. For example, a heterophilic hemisphere is characterized by more (inter-) connections exchanged with the opposite hemisphere compared with the number of intra-connections. This index represents the dominance of homophilic over heterophilic synchronization/connections (and vice versa) [22]. According to Krackhardt and Stern [22], external (heterophilic/interhemispheric) connections are more important for crisis management , but internal (homophilic/intrahemispheric) connections are more likely to occur.

We also estimated the E-I index for different brain regions—namely, frontal (FT: right and left), central (CT: right and left), parietal (PA: right and left), temporal (TE: right and left), and occipital (OCC: right and left).

In this case, a region is homophilic when most connections occur from this region to any other region within the same hemisphere and heterophilic when most connections are to regions on the opposite hemisphere.

## Statistical Analysis

We used the Kolmogorov–Smirnov test to conform that our data were normally distributed. For statistical comparisons, we evaluated the BFN indexes (Kp and E-I index) and the SAM scale (valence and arousal) by using repeated-measures analysis of variance (ANOVA, general linear model [GLM]) in the SPSS software (IBM Corp, Armonk, NY, USA). To evaluate the visual analog scale scale, we applied paired $t$ tests. For all comparisons, we performed Bonferroni adjustment with 5% significance.

To evaluate connectivity over time within the hemispheres, we computed the Kp separately for each hemisphere, for each subject, and for each experimental condition (combination of each emotion with and without thermal pain stimulation). To estimate and describe whether cortical connections occurred more within or outside the hemisphere, we used the averaged E-I index, by region and by hemisphere, for each participant and each emotion, with and without pain induction. For all statistical variables, the Levene test indicated that there was no significant difference in variances between groups.

To analyze the SAM scores, we applied a one-way repeated-measures ANOVA (we tagged this test as ANOVA1, to be used as a reference in the *Results* section), using the within-subject factor ($3 \times 3$): valence (PLE vs UNP vs NEU) and arousal (PLE vs UNP vs NEU).

To evaluate cortical connectivity in the brain hemispheres, we performed a three-way repeated-measures ANOVA (tagged as ANOVA2), using intra-subject comparison ($4 \times 2 \times 2$): emotion (PLE vs UNP vs NEU vs BS), pain (pain vs no pain), and hemisphere (right vs left). The reported $P$ values passed Mauchly's sphericity test.

To evaluate the interaction between intra- and interhemispheric brain connections (homophilic and heterophilic) in women and men, we undertook a two-way repeated-measures ANOVA (tagged as ANOVA3) using intra-subject comparison ($4 \times 2$): emotion (PLE vs UNP vs NEU vs BS) and pain (pain vs no pain) and with the between-subject factor, sex. The presented $P$ values are based on Greenhouse-Geisser correction because the data did not pass Mauchly's sphericity test.

To evaluate which brain hemisphere had more homophily, we performed a three-way repeated-measures ANOVA (tagged as ANOVA4) for intra-subject comparison ($4 \times 2 \times 2$): emotion (PLE vs UNP vs NEU vs BS), hemisphere (right vs left), and pain (pain vs no pain). The presented $P$ values passed Mauchly's sphericity test only for emotion vs hemisphere vs pain comparison.

To assess which of the brain regions within each hemisphere had the most intra- or interhemispheric (homophilic or heterophilic) interactions, we averaged the E-I index for each brain region separately by emotion, with and without pain for each participant. Ten brain regions were divided: right frontal (R FT)—FP2, AF4, F10, F8, F6, and F4; left frontal (L FT)—FP1, AF3, F9, F7, F5, and F3; right central (R CT)—FC6, FC4, FC2, F2, C6, C4, and C2; left central (L CT)—FC5, FC3, FC1, F1, C5, C3, and C1; right temporal (R TE)—TP8, FT8, T10, and T8; left temporal (L TE)—TP7, FT7, T9, and T7; right parietal (R PA)—CP6, CP2, P10, P8, P6, P4, and P2; left parietal (L PA)—CP5; CP1; P9, P7, P5, P3, and P1; right occipital (R OCC)—PO4 and O2; and left occipital (L OCC)—PO3 and O1. We performed a three-way repeated-measures ANOVA (tagged as ANOVA5) $(10 \times 4 \times 2)$: region (R FT vs L FT vs R CT vs L CT vs R TE vs L TE vs R PA vs L PA vs R OCC vs L OCC), emotion (PLE vs UNP vs NEU vs BS), and pain (pain vs no pain). The data did not pass Mauchly's sphericity test, so the presented $P$ values were subjected to Greenhouse-Geisser correction.

## Results

### Self-Assessment Manikin Scale and Visual Analog Scale

We examined whether there were differences in how the participants rated the arousal and valence of the different image sets (ANOVA1). Both presented a significant difference: emotion $(F(2,57) = 449.43, P < 0.001)$ and dimension $(F(2,57) = 461.92, P < 0.001)$. In post hoc comparisons, the emotions caused by viewing PLE, UNP, or NEU images were different from each other (all presenting $P < 0.001$). With regard to the arousal dimension, we did not find differences between viewing PLE and UNP images $(P = 1.000)$ because we chose the images that would cause the same excitation level. The NEU vs PLE and NEU vs UNP comparisons were all significant $(P < 0.001)$. With regard to the pain comparison by the visual analog scale, we found significative difference between the pain and no pain conditions $(P < 0.001, df = 2)$.

### Cortical Connectivity in the Hemispheres

We observed that the pain condition broke the brain symmetry (ANOVA2: $F(1,39) = 6.250, P = 0.017$), with increased connectivity in the left hemisphere $(P = 0.022,$ Figure 2).

### Interaction Between Intra- and Interhemispheric Connections (Homophilic and Heterophilic)

With ANOVA3, we assessed whether women and men exhibited differences in brain interaction under emotions and pain. The intra- and interhemispheric brain activity interaction of women and men was different
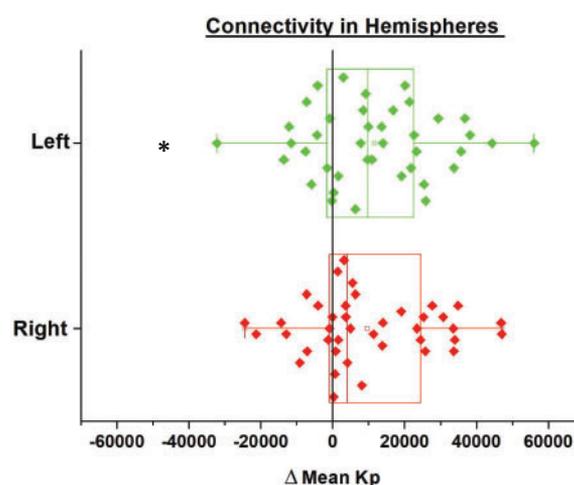


**Figure 2**. The mean difference between the pain and no-pain conditions for the right and left hemispheres. The weighted degree (Kp) increased in the pain condition in the left hemisphere cortex. The points depict the participants who mainly fell on the positive side of the graph; the greatest variation occurred in the left hemisphere. ΔKp indicates the difference between the pain and no-pain condition. *Significant difference between the means $(P = 0.022)$.

$(F(1,38) = 21.055, P < 0.001)$. Both women and men made homophilic connections $(P < 0.001)$, but women had more homophily than men (mean: women $= -0.042$ and men $= -0.025$). These differences indicated that brain connections in women occurred more within each hemisphere than in men (intrahemispherically). Figure 3B depicts the mean and standard deviation (E-I index) for women and men with regard to pain and no pain and viewing the different image sets or a BS. The average variation in women was greater than in men.

To evaluate which hemisphere was more homophilic during pain under emotion induction, we used the mean E-I index for each hemisphere of each subject; viewing PLE, UNP, or NEU images or a BS; and with and without pain (ANOVA4). For emotion, the $P$ value was marginally significant $(F(1,36) = 3.547, P = 0.053)$. For participants, the pain and nonpain conditions were different $(F(1,25) = 12.686, P = 0.002)$, as shown by an increase in homophily under pain, through post hoc pairwise comparison $(P = 0.002)$. The left hemisphere revealed more homophily for the pain condition $(P < 0.001)$, with increased interaction within it $(F(1,25) = 8.839, P = 0.006)$. We expected an increase in homophily and connectivity in the right brain hemisphere because the thermal stimulus was applied to the left index finger.

Brain activity elicited by viewing the images or a BS showed alterations between hemispheres $(F(1,36) = 18.078; P < 0.001)$. When the participants viewed UNP images, the right hemisphere presented more homophily than when they viewed NEU images $(P = 0.004)$. For the left hemisphere, brain activity when the participant was viewing a BS showed significant differences compared with all emotions, and it was more
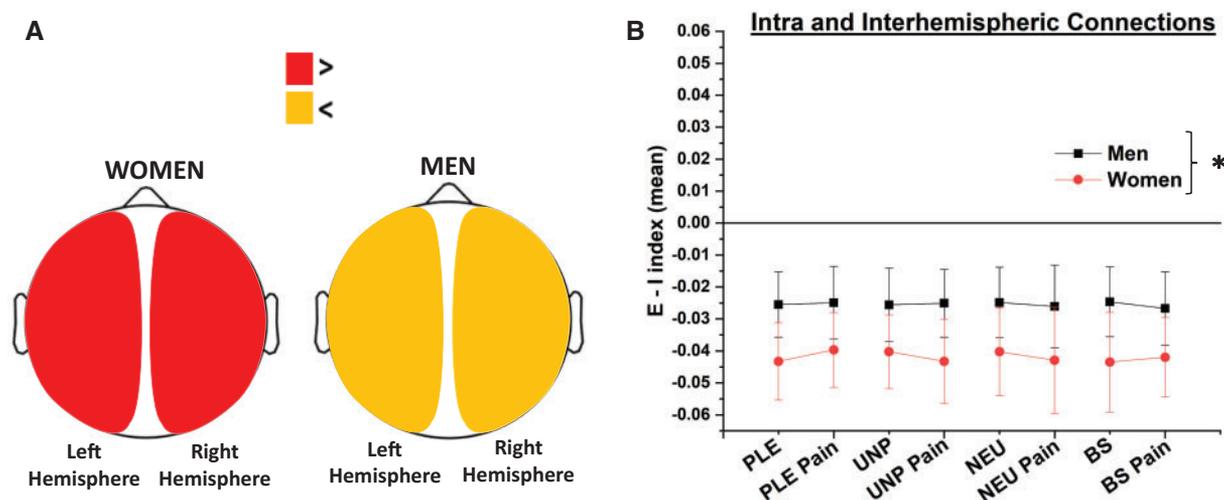
**Figure 3**. (A) Depiction of brain homophily between women and men: Women were more homophilic (>) than men (<) (averages: women = −0.042 and men = −0.025; $P < 0.001$). (B) The homophily and heterophily (E-I) index for the PLE, UNP, NEU, and BS conditions between women and men, with and without pain (there were no significant differences when separated by emotions).

homophilic: PLE ($P = 0.016$), UNP ($P = 0.001$), and NEU ($P = 0.001$). There was decreased right hemisphere connectivity and increased left hemisphere homophily in response to a BS.

When we compared emotions and pain to determine the effect of the emotion and pain interactions ($F_{(2,50)} = 22.081$, $P < 0.001$), we found that brain activity evoked by viewing PLE images without pain increased homophily ($P < 0.001$) and viewing UNP and NEU images with pain increased homophily (UNP: $P = 0.002$; NEU: $P < 0.001$). Only the brain activity in response to viewing PLE images during pain exhibited decreased homophily.

The emotion, hemisphere, and pain interaction ($F_{(3,68)} = 8.259$, $P < 0.001$) can be seen in Figure 4. The brain activity of the participants without pain increased homophily when they were viewing PLE images in both hemispheres: right ($P = 0.002$) and left ($P < 0.001$). For brain activity when participants were viewing UNP images, there was no difference in the right hemisphere ($P = 0.671$) with and without pain, but the left hemisphere ($P < 0.001$) showed increased homophily for the pain condition. With regard to brain activity when participants were viewing NEU images, in both hemispheres—right ($P = 0.001$) and left ($P = 0.002$)—pain increased homophily. Finally, when participants were viewing a BS, there was increased homophily in the right hemisphere ($P = 0.013$) without pain and in the left hemisphere ($P = 0.001$) for the pain condition (Figure 4A and B).

We performed ANOVA5 to determine which of the brain regions within each hemisphere had the most intra- or interhemispheric (homophilic or heterophilic) interactions. The activity of the brain regions exhibited differences ($F_{(5,180)} = 112.461$, $P < 0.001$), demonstrating a physiological condition because brain region activities are normally different. Emotions affected the brain

regions ($F_{(7,277)} = 2.208$, $P = 0.033$); the significant differences are presented in Table 1 and Figure 5. There were no significant differences for pain when we introduced the hemisphere factor.

The brain activity in the left frontal region when participants were viewing PLE and UNP images presented less homophily than when participants were viewing a BS. The UNP vs BS comparison also elucidated an increase in homophily for the BS in the left temporal and central regions. The BS condition presented more homophilic brain activity than did PLE and UNP emotions; that is, there were more intrahemispheric interactions in the BS visualization and decreased homophily in PLE and UNP. For more information about these statistical analyses, please see the Supplementary Data.

## Discussion

According to the literature, the left cerebral hemisphere presents analytical characteristics and is related to cognitive processing [10, 11]. In our study, there was increased cerebral connectivity in the left hemisphere under pain, a phenomenon that altered brain symmetry. This change specifies that the brain wave patterns were more synchronic in the left hemisphere in the pain condition. This increase in connectivity suggests that the left hemisphere processed participants' pain regardless of the images they viewed. These findings indicate that the pain condition can functionally modify brain symmetry.

We observed increased homophily for the painful sensation in the left hemisphere. Viewing the UNP or NEU images or a BS increased homophily during pain; however viewing PLE images increased homophily without pain.

According to an evaluation of neuronal fibers [13], men have greater intrahemispheric connectivity, whereas
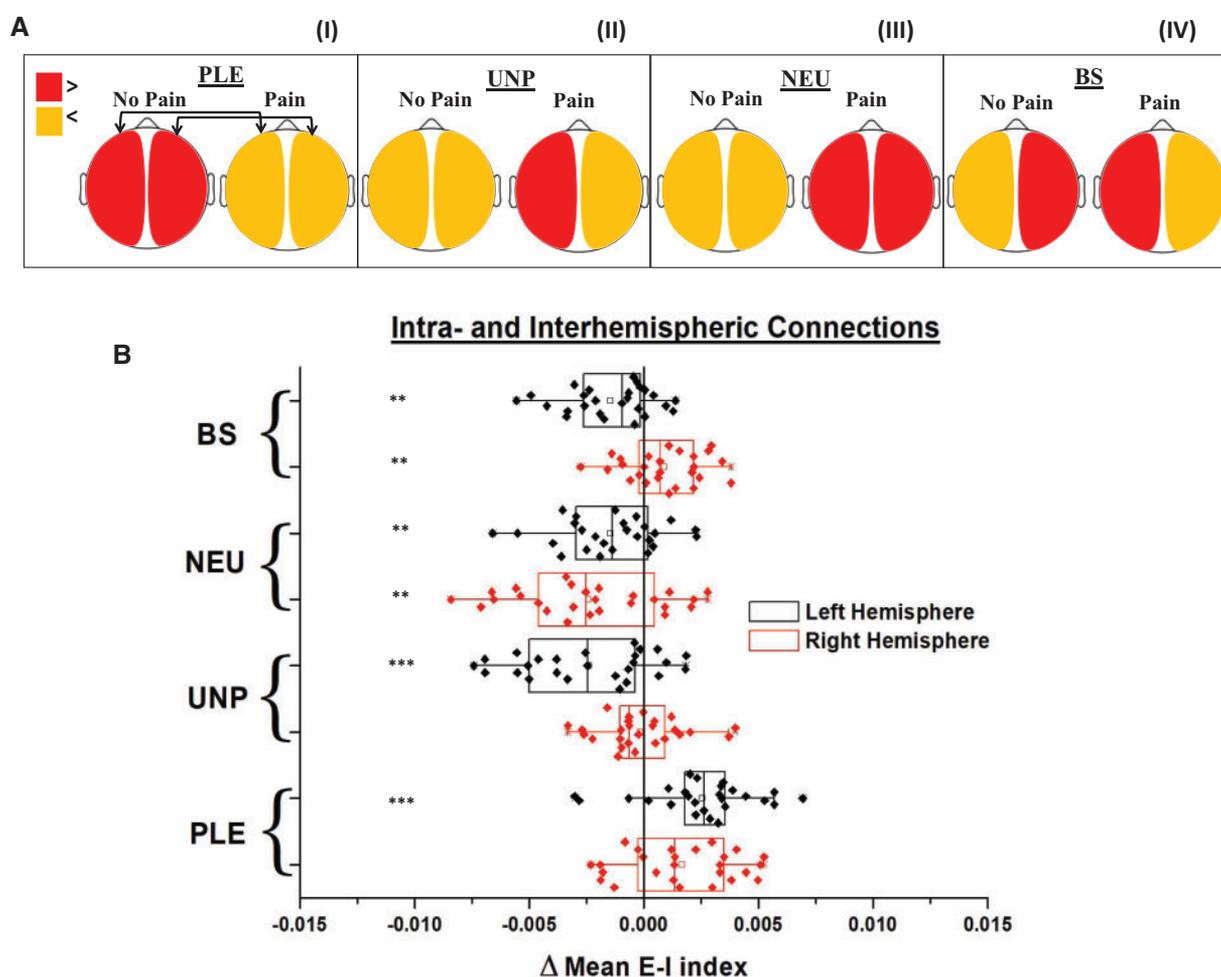
**Figure 4.** (A) Representation of brain homophily increase between hemispheres. (I) Homophily increased when participants were viewing PLE (pleasant) images without pain in the right ($P = 0.002$) and left ($P < 0.001$) hemispheres. The arrows represent the hemisphere pairs compared for pain induction for the PLE, UNP, NEU affective induction and BS conditions. (II) Homophily increased in the left hemisphere ($P < 0.001$) when participants were viewing UNP images with pain. (III) There was increased homophily in the right ($P = 0.001$) and left ($P = 0.002$) hemispheres when participants were viewing NEU images under the pain condition. (IV) Homophily increased when participants were viewing a BS without pain in the right hemisphere ($P = 0.013$) and in the left hemisphere ($P = 0.001$). (B) The graph shows these differences in homophily with and without pain, seen in (A), meaning the E-I index under affective induction. $\Delta$ = E-I index$_{pain}$—E-I index$_{without\ pain}$. The asterisks indicate significant differences: * $<0.05$; ** $<0.01$ and *** $<0.001$.

**Table 1.** Results for region vs emotion comparison

| Regions | Emotions | More Homophilic | Less Homophilic | P Value |
|---------|----------|-----------------|-----------------|---------|
| L FT | PLE vs BS | BS | PLE | $P = 0.009*$ |
|  | UNP vs BS | BS | UNP | $P = 0.004*$ |
| L CT | UNP vs BS | BS | UNP | $P = 0.049*$ |
| L TE | UNP vs BS | BS | UNP | $P = 0.021*$ |
|  | PLE vs BS | BS | PLE | $P = 0.054*$ |

*Significant differences. Bonferroni applied with 5% significance. Post hoc region vs emotion comparison in the left frontal (L FT), left central (L CT), and left temporal (L TE). The post hoc comparison PLE vs BS in the L TE was marginally significant.

women have greater interhemispheric connections. For brain electrical activity, we found that both women and men had intrahemispheric connections, but women had more of them than men. Some investigators have reported that women have interhemispheric connectivity in the upper frontal cortex, as shown by high connectivity, besides hemispheric specialization in brain neuronal fibers, with greater interhemispheric connectivity in the right and left prefrontal cortex [12]. For functional activity considering time, we found that men and women
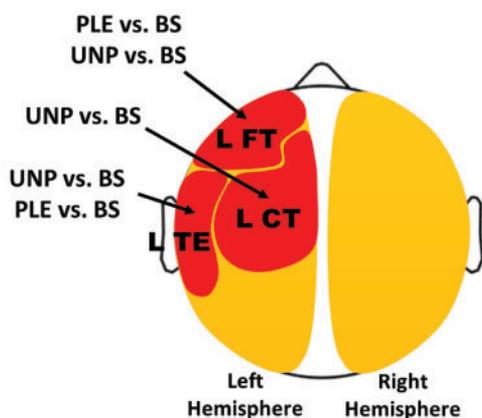
**Figure 5.** Depiction of increased homophily for the region vs emotion comparison. In the left frontal (L FT) region, there was an increase when participants were viewing a BS compared with PLE (pleasant) ($P = 0.009$) and UNP ($P = 0.004$) images. Viewing a BS also increased homophily in the left central (L CT) ($P = 0.049$) and left temporal (L TE) ($P = 0.021$) regions compared with viewing UNP images. The comparision between viewing a BS and PLE images was marginally significant ($P = 0.054$).

showed the same pattern of activity when viewing PLE, UNP, or NEU images or a BS, but women presented more intrahemispheric interactions. Of note, most previous studies used a larger sample size than we used [12, 13]. Therefore, we need to interpret our results with caution. Future studies with a larger sample number, with emotion and pain, should be done to understand these interactions better.

A study observed increased frontal brain interaction when volunteers viewed NEU compared with negative images. In a functional magnetic resonance imaging (fMRI) study, the negative condition showed increased left premotor connectivity to the left insula [23]. In our EEG study, we observed a change in brain activity to the left frontal, left central, and left temporal areas. There was increased homophily when participants were viewing a BS compared with PLE and UNP images in the left frontal and left temporal connects. To the left central region, viewing a BS increased homophily compared with viewing UNP images. These results showed that pleasant and unpleasant emotions can alter brain interactions, making activity within brain regions less homophilic, compared with viewing a BS, which induced more interactions—namely, increased homophily.

Attention can modulate pain through selectivity [2], and emotions modulate pain through spinal and supraspinatus modulatory mechanisms [3]. It is known that although arousal evoked by negative images increases pain, the effect of attention induced by NEU images reduces pain, causing distraction and analgesia [3]. The modulation mediated by viewing PLE and UNP images may also have been influenced by attentional selection that prioritizes received stimuli and influences the cognitive system. The cognitive system's assessment of which stimuli

should be given priority and for how long shows that the brain has a filtering mechanism that is essential for survival [6].

Some brain regions play an important role in emotion processing. The limbic system makes connections with cerebral regions, such as the amygdala and the prefrontal cortex [24]. An fMRI report indicated that the left amygdala is more active when an individual is viewing sad and happy images [25]. The prefrontal cortex also plays an important role in affective modulation because it can regulate the response time of emotions [24]. According to Davidson [24], the right and left prefrontal cortices have different functions and modulate the emotional response through the extensive connections between the frontal cortex and the amygdala. The left prefrontal cortex can inhibit the amygdala and thus decrease the time course of negative emotions while accentuating positive emotions [24]. Our findings showed that the left frontal region exhibited decreased homophily when PLE and UNP images were presented; there was increased interaction with the right hemisphere. This decrease in homophilic interactions may indicate emotion regulation within the amygdala. Schneider et al. [25] observed through fMRI that in individuals exposed to sad and happy images, the signal intensity in the left amygdala increased with increased oxygenation [25].

The modulation of pain by emotions and its expression in brain synchronization patterns highlight the role of emotions in pain characterization studies or in clinical pain assessments based on brain activity. This approach expands perspectives in the treatment of diseases—for example, the use of emotional induction as an effective nonpharmacological intervention for acute and chronic pain [3].

## Conclusion

We evaluated cortical brain connectivity within the hemispheres and the intra- and interhemispheric (homophilic and heterophilic) connections of healthy participants, upon viewing PLE, UNP, or NEU images or a BS with or without thermal pain induction. We found increased connectivity in the left hemisphere for the pain condition. Overall, the pain condition increased homophily and connectivity in the left hemisphere, indicating that new connections due to pain occurred in that area. This reinforces the importance of the left hemisphere in pain processing.

When participants viewed PLE images, both hemispheres showed lower intrahemispheric interactions without a thermal pain sensation, whereas UNP images led to greater intrahemispheric interaction in the left hemisphere with pain. When NEU images were viewed, both hemispheres increased intrahemispheric interaction in the pain condition. For a BS (with no images), there was a disruption in hemispheric symmetry in pain, with the right hemisphere without pain being more

homophilic (intrahemispheric) and the left hemisphere with pain being more homophilic.

The curious ipsilateral effect of thermal-induced pain in the left hand and alterations in the left brain, mainly for UNP images, is not easy to explain. As a conjecture, we could suggest that the UNP images might potentially generate pain-like networks, as the overall result for the painful condition showed an increase in connectivity and homophily in the left hemisphere. Specifically, most of the UNP images included pictures of mutilation and attacks on humans and animals, all pain related. Further work would probably need to be done focusing on the problem of lateralization to answer this causal relationship.

In the assessment of homophily among brain regions, we found that the left frontal, central, and temporal regions varied between decreasing and increasing homophily, depending on the visual stimulus received. There was less homophily in these regions when participants were viewing emotion-evoking stimuli (PLE and UNP); this finding indicates that the interaction of these regions was greater in the right hemisphere under the display of PLE and UNP images. During the BS condition, homophily increased in these left frontal, central, and temporal regions.

For the most part, the brain presents homophilic characteristics. This condition changes, with increased or decreased homophily, depending on the sex of the individual, emotions, or pain. The left brain hemisphere tends to be related to pain processing.

## Acknowledgments

## Supplementary Data

Supplementary Data may be found online at http://pain-medicine.oxfordjournals.org.

## Appendix 1

Images were selected from International Affective Picture System (IAPS) [15]. PLE images included erotic scenes and sport images, with IAPS numbers: 4652, 4658, 4668, 4669, 4670, 4672, 4676, 4681, 8178, 8185, 8186, 8193, 8251, 8300, 8341, 8370, 8400, 8490, 8496, and 8499. The UNP set included photos of mutilation and human and animal attacks, with IAPS numbers: 1050, 1113, 2811, 3064, 3100, 3170, 3400, 3550, 6212, 6250, 6263, 6313, 6410, 6550, 6560, 6570.1, 9040, 9120, 9187, and 9400. For NEU images, mushrooms and household objects were included, with IAPS numbers: 5530, 5531, 5532, 5533, 5534, 7001, 7002, 7003, 7004, 7006, 7009, 7010, 7012, 7020, 7025, 7030, 7031, 7032, 7035, and 7040. To control for the effect of valence, PLE and UNP images were selected at similar rates, and for contrast, NEU images were chosen with low and intermediate valence.

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