Pain when love is near

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Abstract: The aim of the study is to investigate brain responses to acute laser pain when a loved one is nearby. Laser pain stimuli at individual pain threshold were delivered using Th:YAG laser to 17 female participants. The participants were categorised into two groups, \textit{Love Hurts} or \textit{Love Heals}, according to their responses to pain stimulation during the presence of their loved ones. fMRI brain activation was obtained using 3 T Philips Achieva MRI scanner utilising blocked design paradigm comprising 15 blocks of stimulation phase and 15 blocks of no stimulation. fMRI images were analysed using statistical parametric mapping (SPM) focusing on random effects (RFX) analysis. We found that both groups activated pain-related areas such as the thalamus, secondary somatosensory cortex, insula and cingulate cortex. However, \textit{Love Hurts} showed more activity in thalamus, parahippocampal gyrus and hippocampus; while \textit{Love Heals} showed more activity in the entire part of cingulate cortex during the presence of their loved ones. In conclusion, there may be specific brain regions responsible for modulation of pain due to the presence of a loved one thus manifesting as \textit{Love Hurts} or \textit{Love Heals}.

1. Introduction

Pain has diverse dimensions that renders its perception subjective. A similar type of pain may be interpreted and perceived differently by different individuals depending on many modulatory factors including cognition, psychological factors such as emotions and stress, and the threat value of the pain itself [1, 2, 3]. Previous neuroimaging studies have discovered several areas that are consistently activated during pain, the pain-related brain regions, such as secondary somatosensory cortex, insula, anterior cingulate cortex, thalamus, amygdala, ventrolateral prefrontal cortex and orbitofrontal cortex [4, 5, 6].

Pain can be psychologically influenced by the presence of partner [7], friends [8] or any significant other [9]. A common example is the different pain behaviour showed by children in the presence or absence of their parents during medical checkup or treatment. Presence of a parent seems to increase or decrease their pain behavior [10]. In adults, this modulation of pain by loved ones is seen in a study on participants who were shown pictures of their romantic partner while receiving pain [11]. The pain perceived were felt less strongly when compared to the pain felt when pictures of acquaintance were shown.

To our knowledge, no imaging study has been done to see the effect of the presence of a loved one nearby on pain threshold and brain activations. Using youths as the target group, our work aims to investigate neuronal activation due to pain when a loved one is nearby. The study utilised fMRI to capture brain activity and laser pulse as the acute pain stimulation.

2. Method

2.1. Participants

Seventeen (17) right handed female participants with age ranging between 18 and 25 years old (mean age 20.59; SD 2.85 years) participated in this study. They were all MRI compliant, healthy with no history of brain injuries, mental disorders or any serious illnesses, and gave informed consent. During
the study, the participant needed to bring her loved one who could be a parent/family member, partner or best friend. This study was approved by the Human Research Ethics Committee of Universiti Sains Malaysia (USM) (Approval No.: USM KK/PPP/JEPeM [257.4.(3.16)]) allowing all volunteers, their loved ones and the researcher who was delivering the pain stimulation to stay in the scan room.

2.2. Study design
This is a within-subjects study involving two conditions known as Alone condition and Support condition. Alone condition describes the situation where the participant was alone while receiving pain stimulation, while the Support condition represents the situation where the participant was accompanied by a loved one. Based on the difference in pain threshold between the two conditions, the participants were divided into two groups named as Love Hurts, or feeling more pain when a loved one was nearby, and Love Heals, feeling less pain when a loved one was nearby.

2.3. Pain Stimulation
The determination of pain threshold for each participant was done outside the scanner. The Th:YAG laser was used to deliver the pain stimuli, generated from THEMIS laser device available in the Department of Neurosciences, Hospital Universiti Sains Malaysia (HUSM). The laser with a wavelength of 1.96 μm, working at a fixed distance of 12.7 cm, produced 5mm diameter spot on the skin. This narrow laser beam results in a pinprick pain sensation on the dorsum of the hand. The dorsum of hand was selected as target area due to its easy access for pain delivery by a laser applicator which was connected to a controller device via a fiber optic cable. Several points were drawn on the dorsum of hand to mark the location of stimulation (Figure 1). Every time after the stimulation was given, the laser beam was slightly moved to a different point to avoid sensitisation and habituation effect.

![Figure 1. The area to receive laser heat stimulus drawn on the dorsum of the participant’s right hand.](image)

2.4. Thresholding procedure
Laser energies were delivered in an ascending and descending manner and the participants were instructed to respond verbally when they started to feel pain. The laser stimuli was started at the lowest energy level, 200 mJ and increased by 20 mJ increment until pain was reported. This process was repeated 15 times to achieve consistency. The descending series was started at the energy where pain threshold was reported. The energy was then decreased by 20 mJ until the participant reported that there was no pain felt. Similar to ascending, this process was performed 15 times before calculating the mean value of the pain. The value of laser energy when the participant started to feel pain was recorded as pain threshold.

2.5. Study procedure
Participant was placed comfortably in the MRI gantry. Prior to scanning, the participants, loved ones and researcher were ensured that they were eligible to be in MRI room. They were cautioned on MR hazards and the precautions to take. Before entering the room, any ferrous materials on their body or in pocket were removed as well as make up and jewelleries. All of them were given blanket, earplugs and MR compatible electrostatic headphone to protect their hearing. In the Alone condition, the
participant was alone in MRI gantry, while in the Support condition, the participant was accompanied by the loved one, who stayed next to the MRI gantry. In Support condition, the participant was aware of the presence of the loved one. However, they were not allowed to talk or touch each other to prevent unnecessary brain activation.

The movement made from the participant’s reaction may result in movement artefacts. Participants were instructed not to move during the scanning. Head motion was also restricted using head restraint. The participants had already been introduced with the painful stimuli during thresholding process, hence the stimulation during scanning was not totally unexpected and not likely to produce much motion.

2.6. Functional MRI Scanning

All participants underwent the standard procedure of fMRI scanning. An fMRI paradigm utilising a block design which consisted of 30 blocks with 15 blocks of stimulation and 15 blocks of no stimulation was arranged alternately (Figure 2). One block lasted 18 seconds in duration. In the stimulation phase, the random energy including the mean pain threshold of participant were given in pseudorandom order to prevent the participant from predicting what energy they will receive. In each block of stimulation, participant received two laser pulses also given at random time, so that the participant could not predict when they would receive the stimuli.

The brain images were obtained from 3 T scanner (Philips Achieva) equipped with a 32-channel SENSE head coil for pulse transmission and signal reception. The echo-planar imaging (EPI) utilised the following parameters: TR/TE/slice/flip angle/FOV = 2000 ms/35 ms/4 mm slices/90°/220×220 mm [13] for functional images. This produced 9 scans in each block of activity and rest, thus resulting in a total measurement of 270 scans throughout a whole run. T1-weighted scan was performed with the following parameters: TR/TE/slice/FOV = 9 ms/4 ms/4 mm slices/240×240 mm [13] for high resolution anatomical image. Total time for functional and structural scan was about 11 minutes for each participant.

![Figure 2](image)

**Figure 2.** The experimental paradigm that consisted of 15 blocks of stimulation and 15 blocks of rest with 18s duration for each block. Two laser stimulations were given in each stimulation block at pseudorandom times. M is the mean pain threshold of participant; H1 and H2 are two random higher energy than the mean value; and; L1 and L2 are two random lower energy than the mean value. The first block is discarded to prevent the sequence error.
2.7. Data Analysis

Functional data sets were analysed using SPM8 (Wellcome Department of Imaging Neurosciences, Institute of Neurology, University College of London, UK) and implemented in MATLAB 7.4 R2007a (Mathworks Inc., MA, USA). The pre-processing steps involved realignment, normalisation and smoothing to reduce artefacts from movement, improve the signal-to-noise ratio (SNR) and corrected into standard stereotaxic space of the Montreal Neurological Institute (MNI) template [14,15]. The smoothing used an 8-mm full-width-at-half-maximum (FWHM) Gaussian kernel [16]. Activated voxels were identified using the general linear model (GLM) with hemodynamic response function for both conditions (Alone and Support).

The analysis was focused on second-level random-effect analysis (RFX). Two-sample t-tests including all participants in each divided groups for each contrast of interest were calculated, providing a statistical parametric map of the T-statistic. The inferences were corrected (at $\alpha_{FWE}=0.05$) and an extent threshold of $k > 10$ voxels were used to identify significant activity changes for pain across participants in each condition. The full factorial of 2 by 2 ANOVA was not suitable to use since the sample is small that it would produce no significant voxels at extent threshold of $k > 10$ voxels.

3. Results

3.1 Pain thresholding

Pain thresholding revealed responses of resulting higher pain threshold and lower pain threshold in the Alone and Support conditions. The variation in the responses then led to the division of the participants into two groups; participants who had lower pain threshold in the presence of the loved one (referred to as Love Hurts, $n=10$), and those with higher pain threshold (referred to as Love Hurts; $n=7$) in the same condition i.e. Support condition.

3.2. Effect of Interest

The pattern of activation due to acute laser pain for each participant was unique and different from each other. Pain stimulation activated pain-related areas across all 17 participants as shown in Figure 3. In Alone condition, activations were in anterior cingulate cortex (ACC), hippocampus and ventrolateral prefrontal cortex (VLPFC), while in Support condition, the secondary somatosensory cortex (SII), insula and VLPFC were activated.

![Figure 3](image-url)

**Figure 3.** Statistical parametric map of random effect analysis (RFX) of 17 participants. In Alone condition, the anterior cingulate cortex (ACC), insula, hippocampus, ventrolateral prefrontal cortex (VLPFC) and amygdala were activated when participant was alone while receiving pain stimuli. While in Support condition, the secondary somatosensory (SII), insula, thalamus, VLPFC and supramarginal gyrus were activated in the presence of the loved one. Images obtained from FWE corrected p-value at significance level $\alpha =0.05$, in sagittal orientation. The crosshair is the location of labelled area.
3.3. RFX Analyses

To compare brain activations between Love Hurts and Love Heals groups, a two-sample t-test was performed in second-level SPM analysis. Table 1 showed the comparison of brain activation between both groups.

In the group Love Hurts, feeling more pain in the presence of a loved one (Support condition) activated the left thalamus, left parahippocampal gyrus and left hippocampus, while the Love Heals group, having a loved one nearby caused less pain and activated mainly the left anterior, middle and posterior cingulate cortex. On the other hand, being alone while receiving pain activated the left insula in the Love Hurts group in accompaniment with less pain. In the Love Heals group, feeling more pain in the absence of a loved one nearby activated the left superior frontal (Table 1 and Figure 4).

| Condition | Contrast comparison | Coordinate | T-value | Activated Area |
|-----------|---------------------|------------|---------|----------------|
| Alone     | Love Hurts - Love Heals | -40 -12 10 | 5.13    | L - Insula     |
|           |                     | -24 -32 -8 | 4.97    | L - Hippocampus|
|           |                     | -6 -46 18  | 3.92    | L - PCC        |
|           |                     | -10 -12 44 | 3.91    | L - MCC        |
|           |                     | 2 -2 46    | 3.78    | R - SMA        |
|           | Love Heals - Love Hurts | -16 -22 -18 | 4.25  | L - Parahippocampal |
|           |                     | -22 56 26 | 4.25    | L - Sup Frontal|
|           |                     | -6 8 64    | 4.03    | L - SMA        |
| Support   | Love Heals - Love Heals | -14 -24 10 | 4.82    | L - Thalamus   |
|           |                     | -32 -26 -20| 4.72    | L - Parahippocampal |
|           |                     | 16 -8 54   | 4.57    | R - SMA        |
|           |                     | -34 -22 -18| 4.43    | L - Hippocampus|
|           | Love Heals - Love Heals | 0 2 38     | 4.97    | L - ACC        |
|           |                     | 58 -24 52  | 4.42    | R - SII        |
|           |                     | 64 -18 44  | 4.24    | R - Supramarginal|
|           |                     | -2 -32 30  | 4.09    | L - PCC        |
|           |                     | 0 -3 36    | 3.86    | L - MCC        |

FWE = family wise error correction, L = left, R = right, SMA = supplementary motor area, ACC = anterior cingulate cortex, MCC = middle cingulate cortex, PCC = posterior cingulate cortex,
4. Discussion

In this study, pain stimulation activated pain-related brain regions consistent with previous pain imaging studies. The brain areas that were activated have significant function in pain processing. For instance, the thalamus acts as a relay station which is the gateway for the transmission of pain signals originating from the peripheries to the cerebral cortex; while SII process the sensory-discriminative aspect of pain where it gives information about the location and intensity of stimulation.

This study shows that feeling more pain in the presence of a loved one, the Love Hurts phenomenon, seems to be related with activations in thalamus, parahippocampal gyrus and hippocampus. On the other hand, reduction of pain when a loved one is nearby, or Love Heals, is accompanied by activations in all parts of cingulate cortex. The relevant functions of thalamus and parahippocampal gyrus in pain processing may contribute to the Love Hurts response while the hippocampus may be involved in ‘tuning’ the sensitivity of brain regions involved in pain processing in a context-dependent manner. In Love Heals, the cingulate cortex play important role in processing cognitive factors such as attention, expectation, and anticipation, therefore is likely to be involved in processing the expectation towards the loved one; as well as in processing positive emotions in relation to the loved one.

The activation produced by Love Hurts in Alone condition and Love Heals in Support condition represented an interaction of pain reduction; while the Love Hurts in Support condition and the Love Heals in alone condition represented the interaction of pain increment. Our results show that MCC and PCC may play a role in pain reduction consistent with their function in processing the affective-cognitive aspect of pain, as well as in emotional and attentional modulation of pain. The parahippocampal gyrus, activated in the interaction of pain increasing, has been shown to be related to expectation of high intensity stimulus.

5. Conclusion

We conclude that there may be specific brain regions responsible for modulation of pain due to the presence of a loved one thus manifesting as Love Hurts or Love Heals.
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