

fMRI of pain studies using laser-induced heat on skin with and without the loved one near the subject – a pilot study on ‘love hurts’

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Abstract. The aims of this study are to image and investigate the areas of brain response to laser-induced heat pain, to analyse for any difference in the brain response when a subject is alone and when her loved one is present next to the MRI gantry. Pain stimuli was delivered using Th-YAG laser to four female subjects. Blood-Oxygenation-Level-Dependent (BOLD) fMRI experiment was performed using blocked design paradigm with five blocks of painful (P) stimuli and five blocks of non-painful (NP) stimuli arranged in pseudorandom order with an 18 seconds rest (R) between each stimulation phase. Brain images were obtained from 3T Philips Achieva MRI scanner using 32-channel SENSE head coil. A T1-weighted image (TR/TE/slice/FOV = 9ms/4ms/4mm slices/240×240mm) was obtained for verification of brain anatomical structures. An echo-planar-imaging sequence were used for the functional scans (TR/TE/slice/flip/FOV=2000ms/35ms/4mm slices/90°/220×220mm). fMRI data sets were analysed using SPM 8.0 involving preprocessing steps followed by t-contrast analysis for individuals and FFX analysis. In both with and without-loved-one conditions, neuronal responses were seen in the somatosensory gyrus, supramarginal gyrus, thalamus and insula regions, consistent with pain-related areas. FFX analysis showed that the presence of loved one produced more activation in the frontal and supramarginal gyrus during painful and non-painful stimulations compared to absence of a loved one. Brain response to pain is modulated by the presence of a loved one, causing more activation in the cognitive/emotional area i.e. ‘love hurts’.

1. Introduction

Pain is multidimensional and usually is very subjective with respect to individuals. Based on available literatures, pain is defined as the sensory and emotional experience of discomfort.¹ Pain may also be defined as the feeling or perception of irritating, miserable, or unbearable sensation arising from a part of the body.² Basically, all types of pain may result in the activations in common pain-related regions. More specifically, pain from experimental laser heat stimuli activates the areas of primary somatosensory,³⁻⁵ secondary somatosensory,³ insular cortex,³⁻⁷ thalamus,^{3,5} amygdala and anterior cingulate cortex.^{3,4}

While there are many fMRI studies of pain, few have investigated the correlation between pain and the influence of love to pain response. Cheng et al, (2010) requested the subjects to imagine the loved one or an unfamiliar individual being in a painful situation. The fMRI data indicated that the perspective of a loved-one showed increased activity in the anterior cingulate cortex and insula.⁸



So far no known studies have investigated the effect of having a loved one physically nearby on brain activities while pain stimulation is being given. Since pain is related to emotion, this study is carried out to look for the influence of type of emotion i.e. love to the pain response. This study utilised the technique of fMRI to show the activation of the neuronal responses associated with pain. The main focus of the study is to analyse the difference in the hemodynamic response when each subject is alone and when her loved one is present next to the MRI gantry.

2. Method

All volunteers underwent standard procedure for fMRI scanning. Prior to scanning session, all the subjects, the loved ones and researcher have already taken the safety step to ensure they were eligible for MRI examination. Subjects and the loved ones have been cautioned on MR hazards and the precautions should they take. All individuals were asked to fill out the pre-screening form before entering the MR environment and room including the researcher. Ferrous materials on their body or in pocket were removed as well as make up and jewellerys. All of them were given earplugs and MR compatible electrostatic headphone to protect their hearing.

Each subject was provided with a response button and was instructed to focus and give full attention to response. A researcher stayed with the subject in the scanner room to hold the laser with its beam moving to make several spots on the dorsum of the subject's hand. The experiment was repeated twice but in different situation; (1) subject was alone in the MRI gantry (this situation is referred to as 'without-loved-one condition'); (2) subject with the loved one was present next to the gantry (this is referred to as 'with-loved-one condition'). Note that the 'without-loved-one condition' meant that the loved one was many miles away from the experiment setting. The loved one could be one of these candidates; mother, father, partner or best friend which was determined through the Experiences in Close Relationships - Relationship Structure questionnaire.⁹

2.1. Subject

Four right handed female participants (mean age 27.25; SD 0.5 years) involved in this study were MRI compliant and have signed informed consent form in compliance with the regulations of the Universiti Sains Malaysia. This research was approved by the Human Research Ethics Committee of USM in 2012. Ethical approval was obtained for all volunteers, their loved ones who accompany them in the scan room, and the researcher delivering the pain stimulation in the scan room. Participants were all healthy volunteers. Only females were selected to reduce confounding emotional effects and to minimise gender variability. This was based on the study that men and women are different in the type of pain experience and reactions to pain.¹⁰ In addition, women are more sensitive to many sensory tests compared to men.¹¹

2.2. Experimental Paradigm

An fMRI experiment was performed using a block design paradigm. Firstly, the paradigm was developed in E-Prime System so as to synchronise the timing with the MRI scanner. The experiment consisted of 2x5 stimulation blocks of 18 seconds. There were five blocks of painful stimuli (P) and five blocks of non-painful stimuli (NP) arranged in pseudorandom order. Each stimulation phase was followed by an 18 seconds rest (R) of no activity.

The subject needed to focus her attention on the stimuli without any specific discrimination task and to give response to each block of stimuli by pressing the response button. In order to avoid nociceptor fatigue or sensitisation, the laser beam spot was slightly moved after each stimulus.¹² On the second part of the experiment, the loved one that sat next to the MRI gantry was not allowed to touch or talk to the subject to avoid any sensory or audio stimulation which may initiate unnecessary responses.

2.3. Pain Stimuli

The pain stimuli was delivered using Th:Y AG laser from THEMIS laser device available in Hospital Universiti Sains Malaysia (HUSM). The laser with a wavelength of $2\mu\text{m}$ and a diameter of 5mm was targeted to skin via an MRI compatible applicator. In this research context, the painful stimuli means the laser beam with high energy enough to cause pain on the subject's skin while the non-painful stimuli means the laser beam with lower (control) energy that results in warm sensation but not yet reaching pain threshold.

2.4. MR Image Acquisition.

This study utilised the 3.0T Philips Achieva MRI scanner¹³ available in the Department of Radiology, Hospital Universiti Sains Malaysia (HUSM) with a 32-channel SENSE head coil for pulse transmission and signal reception. For each subject, a T1-weighted, high resolution structural image (TR/TE/slice/FOV = 9ms/4ms/4mm slices/240×240mm)¹³ was obtained for verification of brain anatomical regions. An echo-planar imaging (EPI) sequence with the following parameter (TR/TE/slice/flip angle/FOV = 2000ms/35ms/4mm slices/90°/220×220mm)¹³ was used for functional scans. Both scans corresponded to a total scan time of approximately 11 minutes per subject.

2.5. Data Analysis

The data collected was sets of fMRI images in a time series. The researcher also observed the subject's response while she was in the MRI gantry. Image analysis was performed using the MATLAB 7.4 – R2007a (Mathworks Inc., MA, USA) and Statistical Parametric Mapping (SPM 8.0) (Wellcome Department of Imaging Neurosciences, Institute of Neurology, University College of London, UK) software packages. The pre-processing steps were applied to all fMRI data set to remove any data artefacts and to improve the signal-to-noise ratio (SNR) in the time series data acquired. The steps involved were realignment, normalisation and smoothing. The t-contrast comparison was carried out for individuals and group. Since there were only four subjects, the fixed-effect analysis (FFX) was used to see the difference between signals or within subject variability and not to represent a population. The coordinates of activations were matched with MNI coordinate system using wfupickatlas in SPM.

2. Result

The height threshold for individual analysis were in the range of $5.24 < T < 5.29$ ($p < 0.05(\text{FWE})$) for without-loved-one condition and $5.12 < T < 5.24$ ($p < 0.05(\text{FWE})$) for with-loved-one condition. While the height threshold for FFX analysis were $T = 5.06$ ($p < 0.05(\text{FWE})$) for without-loved-one condition and $T = 4.93$ ($p < 0.05(\text{FWE})$) for with-loved-one condition.

3.1. Observation

During scanning, subject's responses to stimuli were monitored. In the with-loved-one condition, three out of four subjects pressed the response button for almost all stimuli, including the non-painful stimuli.

3.2. Individual Analysis

Figure 1 showed activations in individual subjects in both conditions during painful (P) stimulation. There were clear activations found in the somatosensory gyrus, insula, supramarginal gyrus and thalamus.

When the loved one was present (Figure 1(b)), neuronal responses appeared in more regions in the brain but with lower intensities in all subjects (A, B, C and D). The activated area that was not found in without-loved-one condition (Figure 1(a)) was the cingulum.

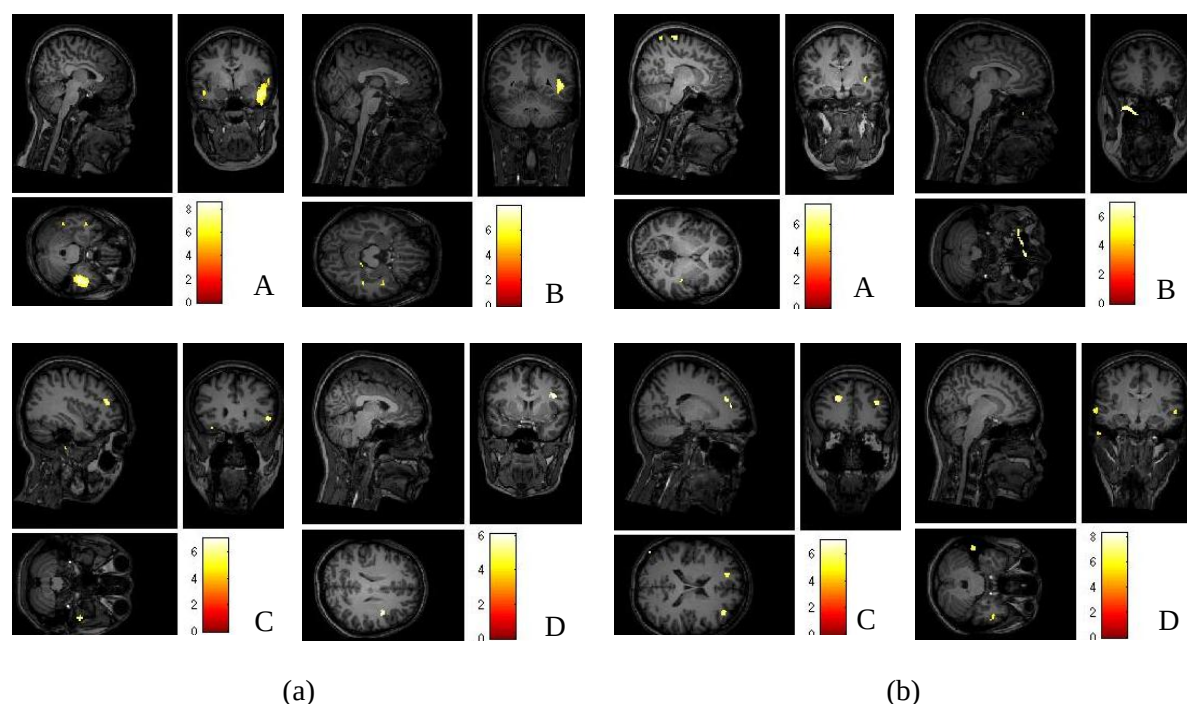


Figure 1. Neuronal responses during painful stimulation in four subjects A, B, C, and D in (a) the without-loved-one condition and (b) the with-loved-one condition.

Table 1. Summary of the areas of activation, coordinates and t-values in two different conditions for all stimulations.

Without-Loved-One Condition					With-Loved-One Condition					
	Areas of activation	Coordinate (x y z) mm			t-values	Areas of activation	Coordinate (x y z) mm			t-values
P	Temporal-Sup	56	6	-2	6.72	Frontal-Mid	36	56	20	6.32
	Supramarginal	-60	-52	26	6.66	Temporal-Mid	68	-48	4	6.12
	Somatosensory	44	-28	34	6.41	Somatosensory	48	-36	62	6.08
	Thalamus	16	-12	16	6.19	Mid-Cingulate	0	16	40	5.92
	Supramarginal	66	-44	28	5.88	SMA	34	-12	66	5.67
	Somatosensory	68	-14	18	5.87	SMA	42	-18	64	5.59
	Insula	68	-36	26	5.79	SMA	-50	12	34	5.58
	Supramarginal	-38	16	-4	5.61	Insula	40	8	4	5.50
NP	Supramarginal	-60	-52	28	7.90	Temporal-Sup	64	2	4	6.94
	Frontal-Inf	48	22	10	7.37	Somatosensory	46	-36	62	6.16
	Parietal-Inf	58	-56	46	6.92	Frontal-Mid	36	56	20	6.00
	SMA	0	16	66	6.73	SMA	-48	4	42	5.73
	Somatosensory	48	-24	32	6.71	Frontal-Sup	22	-12	72	5.68
	Insula	-40	16	-4	6.32	Mid-Cingulate	0	16	40	5.66
R	Supramarginal	-60	-52	26	7.61	Frontal-Sup	-20	60	24	5.60
	Parietal-Inf	58	-56	46	6.57	Frontal-Inf	48	28	-18	5.53
	Frontal-Mid	26	60	22	6.54	Rectus	-8	58	-18	5.52
	Frontal-Inf	46	22	14	6.26	Temporal-Sup	56	14	-16	5.21

P = painful stimulation, NP = non-painful stimulation, R = rest

Temporal-Sup = superior temporal gyrus, Temporal-Mid = middle temporal gyrus, Frontal_Mid = middle frontal gyrus, Frontal-Inf = inferior frontal gyrus, Frontal-Sup = superior frontal gyrus, Parietal-Inf = inferior parietal gyrus, SMA = sensory motor area

3.3.2. Painful vs Rest (P-R). In the without-loved-one condition, the differences were found in SMA, precuneus and cuneus (Figure 2). These were the regions more activated during painful stimuli compared to during rest. In the with-loved-one condition, more differences were found in frontal and temporal areas, sensory motor area and mid-cingulate (mCC).



Figure 2. The brain signal in the painful vs rest comparison for (a) without-loved-one condition and (b) with-loved-one condition.

3.3.3. Non-Painful vs Rest (NP-R). There was no difference found during non-painful stimuli compared to rest in the without-loved-one condition. However, many activations were found in the with-loved-one condition including in the SMA, supramarginal and mid-cingulate (mCC) as shown in Figure 3.



Figure 3. The brain signal in the Non-Painful vs Rest Comparison for (a) Without-Loved-One Condition and (b) With-Loved-One Condition.

3.3.4. Painful vs Non-Painful (P-NP). In the without-loved-one condition, the differences were seen in somatosensory gyrus (SI) and cuneus as shown in Figure 4. (a). However in Figure 4. (b), there was no difference in the brain activation between painful and non-painful stimuli in the with-loved-one condition.

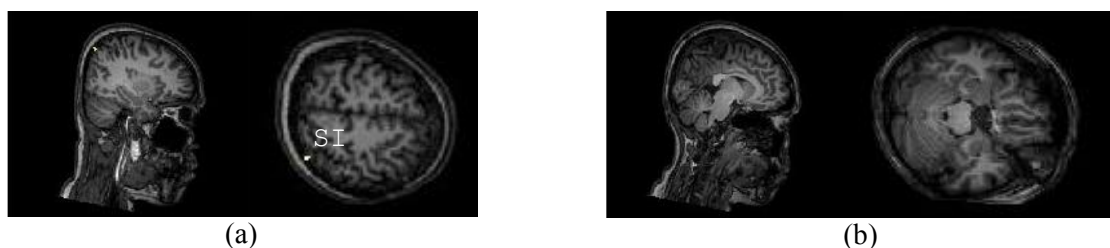


Figure 4. The brain signal in the Painful vs Non-Painful Comparison for (a) Without-Loved-One Condition and (b) With-Loved-One Condition

3.3.5. Non-Painful vs Painful (NP-P). This comparison did not give significant result.

3.3.6. Direct Contrast Comparison. Table 2 shows the comparisons between the with-loved-one and without-loved-one conditions during all stimulations. During painful stimulation, presence of loved one produced more activities in frontal gyrus and right supramarginal gyrus compared to when the loved one was absent. The non-painful stimulation produced activities in right and left supramarginal,

frontal and temporal regions. On the other hand, the contrast with vs without loved one did not produce any significant activations.

Table 2. The direct contrast comparison between painful and non-painful stimulations for both with and without-loved-one conditions.

Pain Stimulation	Contrast Comparisons	Coordinate of activations			Anatomical Area
P-R	(with vs without) loved one	40	54	22	Frontal-Mid
		34	58	14	Frontal-Mid
		60	-36	36	Right Supramarginal
	(without vs with) loved one	-	-	-	-
NP-R	(with vs without) loved one	60	-34	36	Right Supramarginal
		-62	-48	20	Temporal-Sup
		62	-48	28	Left Supramarginal
		-38	50	20	Frontal-Mid
	(without vs with) loved one	-	-	-	-

4. Discussion

The current study demonstrates that pain stimulation in all subjects activated pain-related areas similar to that observed in previous studies. These areas include the somatosensory gyrus, insula cortex and thalamus^{3-8,12}.

From the behavioural observation, three out of four subjects tended to show more pain when the loved one was with them. This reaction maybe compared to a study which found that patient who felt their spouses was solicitous reported more pain when their spouses watched than when the employee (stranger) did.¹⁴ A similar reaction may occur even when the parents or the family members were around. The solicitousness of the loved one may lead to more pain behaviour.¹⁵

The obvious difference in FFX analyses between the conditions, with and without loved one, seems to suggest evidence of 'love hurts'. Non-painful stimuli should not lead to pain experienced by the subject; however, the activation pattern during non-painful stimuli was similar to that of during painful stimuli in with-loved-one condition. With loved-one present, a warm sensation can result in pain to some individuals. In the without-loved-one condition, on the other hand, the results showed that non-painful stimulation i.e. warm sensation gave no pain to subject, just like during rest. In the with-loved-one condition, the love hurts evidence was stronger when the comparison of painful and non-painful stimuli showed no difference. It meant that when the loved one stayed near the subject, warm or pain stimuli was similarly felt. This study only used four subjects. Results should become better when more participants are added.

By comparing contrast areas between the conditions, the with-loved-one condition indicated more activation. With the presence of a loved one, painful as well as non-painful stimulations activated the supramarginal gyrus and frontal gyrus. In contrast, in Cheng's work,⁸ the presence of loved one was associated with stronger neuronal activation in cingulate cortex. Functionally, frontal gyrus is associated with cognition and emotion as well as attention to pain while the supramarginal gyrus appears to play a central role in controlling our empathy towards other people.¹⁶

5. Conclusions

BOLD fMRI technique utilising the experimental paradigm for pain studies developed for this work has been able to map different neuronal activations in different parts of the brain when the subject is with the loved one and when she is not with the loved one near the gantry. Overall, this study indicates that the love hurts phenomena can be the reason for an individual to experience more pain when the loved one was around.

Acknowledgement

The authors would like to thank the Department of Radiology, Hospital Universiti Sains Malaysia (HUSM) for the permission to use the MRI scanner.

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