Modelling brain activations and connectivity of pain modulated by having a loved one nearby

Cite as: AIP Conference Proceedings **1972**, 030008 (2018); https://doi.org/10.1063/1.5041229
Published Online: 05 June 2018

Sofina Tamam, Asma Hayati Ahmad, and Wan Ahmad Kamil

Modelling Brain Activations And Connectivity of Pain Modulated By Having A Loved One Nearby

Sofina Tamam[1,a)], Asma Hayati Ahmad[2,b)] and Wan Ahmad Kamil[2,c)]

[1]*Faculty of Science and Technology, Universiti Sains Islam Malaysia, Bandar Baru Nilai, 71800 Nilai, Negeri Sembilan, Malaysia*
[2]*Department of Physiology, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan*

[a)]Corresponding author: sofinatamam@usim.edu.my
[b)]asmakck@usm.my
[c)]wkamil@usm.my

Abstract. This study is to model the connectivity between activated areas in the brain associated with pain responses in the presence and absence of a loved one. We used Th:YAG laser targeted onto the dorsum of the right hand of 17 Malay-female participants (mean age 20.59; SD 2.85 years) in two conditions: (1) in the absence of a loved one in the functional magnetic resonance imaging (fMRI) room (Alone condition), and (2) in the presence of a loved one (Support condition). The laser-induced pain stimuli were delivered according to an fMRI paradigm utilising blocked design comprising 15 blocks of activity and 15 blocks of rest. Brain activations and connectivity were analysed using statistical parametric mapping (SPM), dynamic causal modelling (DCM) and Bayesian model selection (BMS) analyses. Individual responses to pain were found to be divided into two categories: (1) Love Hurts (participants who reported more pain in the presence of a loved one) involved activations in thalamus (THA), parahippocampal gyrus (PHG) and hippocampus (HIP); and (2) Love Heals (participants who reported less pain in the presence of a loved one) involved activations in all parts of cingulate cortex. BMS showed that Love Heals could be represented by a cortical network involving the area of anterior cingulate cortex (ACC), middle cingulate cortex (MCC) and posterior cingulate cortex (PCC) in the intrinsic connectivity of ACC → PCC → MCC and ACC → MCC. There was no optimal model to explain the increase in pain threshold when accompanied by the loved one in Love Hurts. The present study reveals a new possible cortical network for the reduction of pain by having a loved one nearby

INTRODUCTION

Imaging studies reveal that pain involves the activation of multiple disseminated brain regions, representatives of its multidimensionality. The various factors that modulate pain give rise to distinct networks of brain regions that process different types of pain [1,2,3], as well as the emotions and thoughts associated with the pain experience [4,5].

We previously reported brain activations due to painful laser stimulation in women in the absence and presence of a loved one [6]. Results from this study showed that participants who received pain stimulation while accompanied by a loved one, demonstrated varying responses to laser heat pain depending on the type of attachment to her loved one. Some participants had lower pain threshold in the presence of the loved one (assigned to the group 'Love Hurts'), while others demonstrated higher pain threshold when their loved ones were nearby (assigned to 'Love heals'). Decreased pain threshold in the presence of a loved one was associated with activations in thalamus, parahippocampal gyrus and hippocampus, while increased pain threshold when a loved one was nearby, was accompanied by activations in all parts of cingulate cortex.

Although the brain regions associated with decreased and increased pain threshold in the absence and presence of a loved one have been mapped out, the knowledge of the influence of love to pain perception and its corticol

Recent Advancement on Applied Physics, Industrial Chemistry and Chemical Technology
AIP Conf. Proc. 1972, 030008-1–030008-9; https://doi.org/10.1063/1.5041229
Published by AIP Publishing. 978-0-7354-1679-6/$30.00

network remains incomplete. As an extension to our previous findings, the current study explores the possible connectivity of the response to pain modulated by the presence of a loved one nearby using dynamic causal modelling analysis.

EXPERIMENTAL

This is an extended analysis of our previous study on brain activation related to pain threshold with having a loved one present or absent as a pain modulator [6].

The present analysis focused on the development of brain connectivity model for the related areas either for Love Hurts or Love Heals. Analysis of our previous study using Statistical Parametric mapping (SPM) analysis software showed that ‘feeling more pain’ when a loved one was present (or Love Hurts) activated the thalamus, parahippocampal gyrus, while the reaction ‘feeling less pain’ when a loved one was present (Love Heals) activated the anterior, middle and posterior cingulate. Our current analysis used Dynamic Causal Modelling (DCM) to investigate any relationship between the regions activated. The selection of optimum model was based on the probability method applied in SPM i.e. the Bayesian Model Selection (BMS).

Volunteers

Seventeen healthy female volunteers (mean age = 20.59; SD 2.85) were recruited for this study. All of them gave informed consent prior to the experiment to ensure them to be magnetic resonance imaging (MRI) compliant and fulfilled the requirement of the Human Research Ethics Committee of Universiti Sains Malaysia (USM) allowing all volunteers, their loved ones and the researcher who was delivering the pain stimulation to stay in the scan room.

Laser pain stimulations were delivered on the dorsum of hand while the volunteer was either alone or accompanied by their loved one in the MRI room. They were classified as Love Hurts and Love Heals based on their difference in pain threshold between the two conditions.

fMRI Paradigm

The volunteers underwent general procedure for functional magnetic resonance imaging (fMRI) scanning. Details and study design were described in Tamam et al (2017). Briefly, fMRI scan was performed using a block-design paradigm consisting of 30 blocks of 18 seconds duration per block. A run comprises 15 blocks of activity and 15 blocks of no activity arranged alternately. For activity, five random energies including the mean pain threshold of volunteer were given in pseudorandom order. In each block of activity, the volunteer received two laser pulses at random time, so they could not predict when they would receive the stimuli.

Image Acquisition

fMRI scans were conducted using a 3Tesla MRI scanner (Philips Achieva) equipped with with a 32-channel SENSE head coil for pulse transmission and signal reception. Echo Planar Imaging (EPI) pulse sequence with the following parameters were applied: Repetition Time (TR) = 2 s, Echo Time (TE) = 35 ms, Field of View (FOV) = 220 × 220 mm, flip angle = 90° and slice thickness = 4 mm [7].

High resolution anatomical images to image the entire brain structure were obtained using a strongly T1-weighted spin echo pulse sequence with the following parameters: TR = 9 ms, TE = 4 ms, FOV = 240 × 240 mm and slice thickness = 4 mm [7].

fMRI Images Preprocessing Analysis

Images were analysed using MATLAB R2014b (Mathworks Inc., Natick, MA, USA) and SPM software (SPM8, Functional Imaging Laboratory, Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College of London) involved preprocessing and statistical analyses to map the brain activation due to acute laser pain. The preprocessing step involves firstly realigning all images from 6 spatial transformations which were translation (in x, y and z direction) and rotation (yaw, pitch and roll). Secondly, the images were normalised onto a standard space defined by some ideal model or template. A mean image obtained from the realignment process was mapped onto a standard EPI template. Then, images were smoothed using an isotropic 8mm full-width-half-maximum (FWHM) Gaussian kernel. Lastly, a conventional analysis based on the General Linear Model (GLM) was used to generate individual brain activation in the regions of interest using the T-statistic for each voxel. Statistical inferences were then obtained on the basis of random effects analysis (RFX). The inferences were made using the T-statistic at significant level (α) = 0.05, family wise error (FWE) corrected for groups comparisons [8].

Regions of Interest (ROI)

Two groups were considered for RFX analysis, named Love Hurts and Love Heals. The cortical brain regions which were found to be significantly activated during receiving pain for volunteers in the two groups, were defined using the wfupickatlast toolbox at α = 0.05 with FWE correction. Comparison was made between activations for Love Hurts and Love Heals by two-sample statistical method. From their differences, the regions for further analysis were selected from only the left hemisphere. Since stimulations were given on the dorsum of the right hand, the regions of interest was expected to be mainly in the left hemisphere; hence the selection for use in developing the connectivity.

Dynamic Causal Modelling (DCM) Analysis

Dynamic Causal Modelling (DCM) analysis was used in evaluating the connections between relevant regions associated with laser pain, focusing on the left hemisphere. In this study, we selected three pain-related regions for each group (Love Hurts and Love Heals) to analyse their connections to arrive at the most probable connectivity model. The Bayesian model selection (BMS), a statistical probability method was used to estimate the most optimal connectivity model due to the pain response in the context of this study.

Several models were created by considering three probable regions which might be connected with each other and play important functions in pain processing.

RESULTS AND DISCUSSIONS

Regions of Interest (ROI)

The Love Hurts is the group of volunteers who presented more pain in the presence of the loved one, while in the opposite the Love Heals is the group of volunteers who demonstrated less pain in the same condition. The difference in pain activations between these two groups is presented in Table 1.

TABLE 1. The difference in brain activation contrast between Love Hurts group and Love Heals group when the loved one was nearby at corrected value of FWE, α =0.05.

Contrast comparison	Coordinate	T-value	Activated Area
Love Hurts - 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

Based on the comparison, in the presence of the loved one, Love Hurts group showed more activations in left thalamus, left parahippocampal gyrus, right supplementary motor area (SMA) and left hippocampus. While in Love Heals group, having a loved one nearby activated mainly the left anterior, middle and posterior cingulate cortex, right SII and right supramarginal gyrus.

By considering only the left hemisphere, the main areas activated to be considered for further analysis were the thalamus, parahippocampal gyrus and hippocampus for Love Hurts group, while the entire parts of cingulate cortex for Love Heals group.

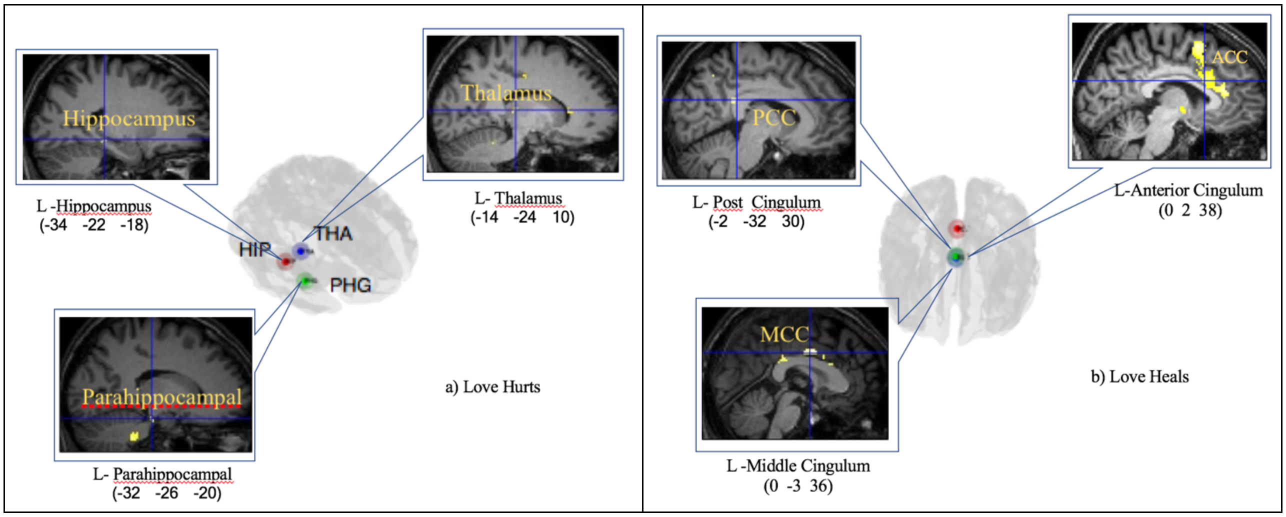
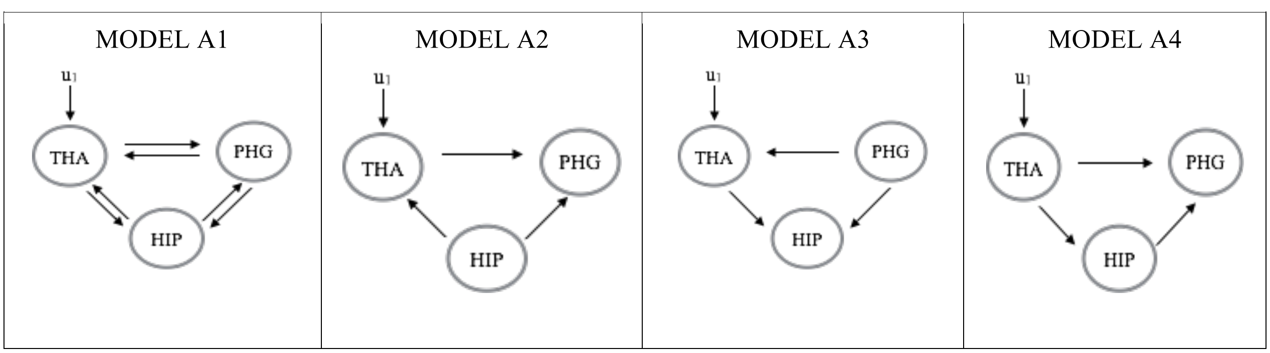


FIGURE 1. An fMRI images and related coordinates during laser pain stimulation in the presence of the loved one. (a) The areas and peak coordinates of thalamus, parahippocampal gyrus and hippocampus which appeared in Love Hurts reactions and (b) the anterior cingulate cortex (ACC), middle cingulate cortex (MCC) and posterior cingulate cortex (PCC) which appeared in Love Heals reactions.

Dynamic Causal Modelling (DCM) Analysis

Fifteen linear connectivity models were developed for each group and then analysed using BMS to estimate the optimal ones. Figure 2(a) shows the linear models which may explain the connections between activated regions significant to Love Hurts and Fig. 2(b) Love Heals.



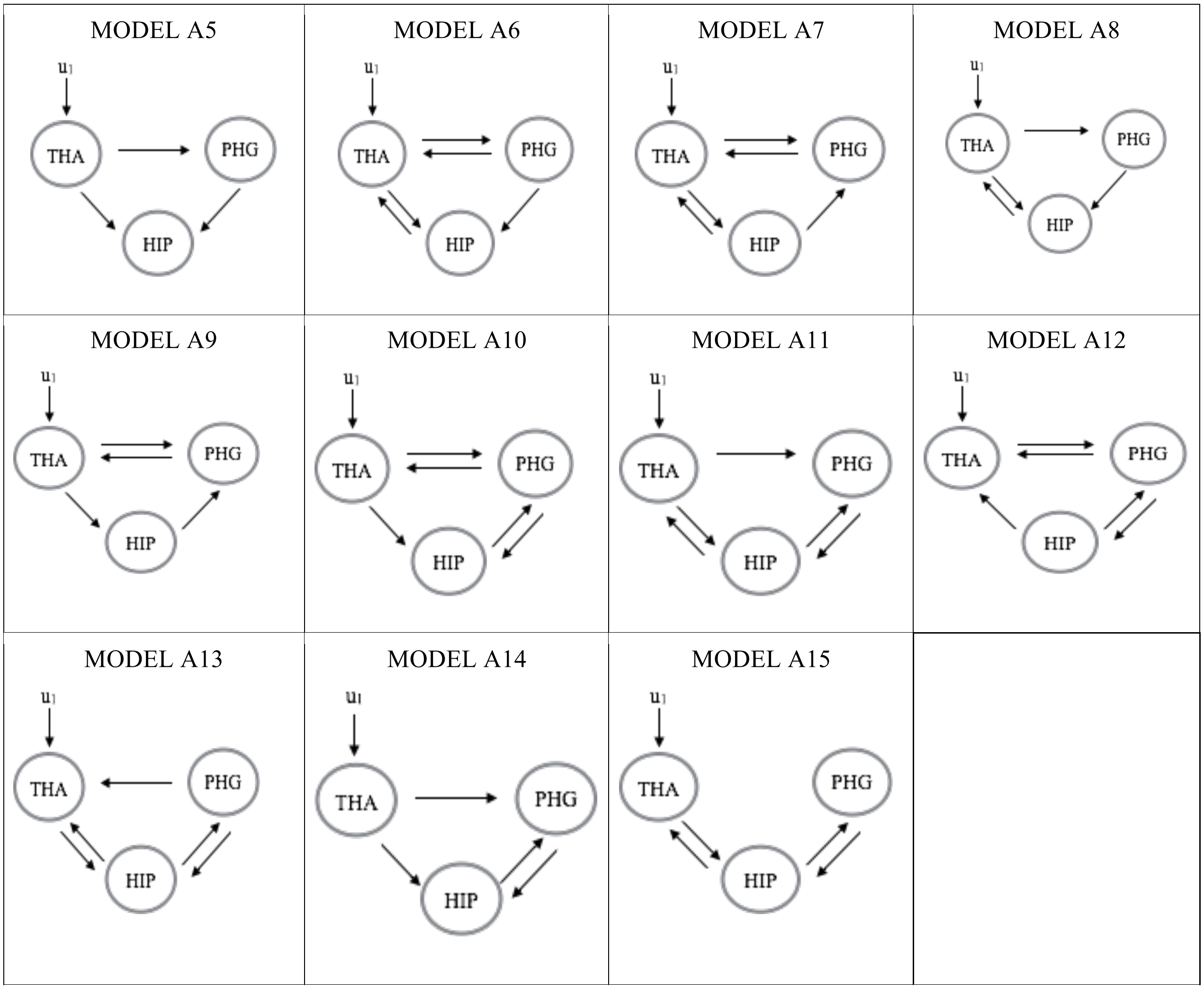
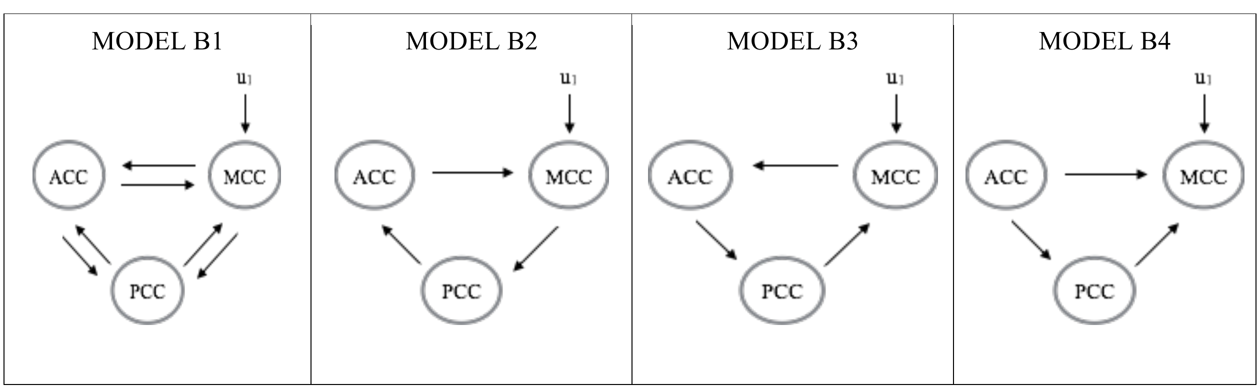


FIGURE 2(a). Fifteen linear connectivity models analysed separately for the response decreased pain threshold in the presence of a loved one (Love Hurts). THA (thalamus), HIP (hippocampus) and PHG (parahippocampal gyrus) are the regions in the brain which are expected to be involved in the interaction.



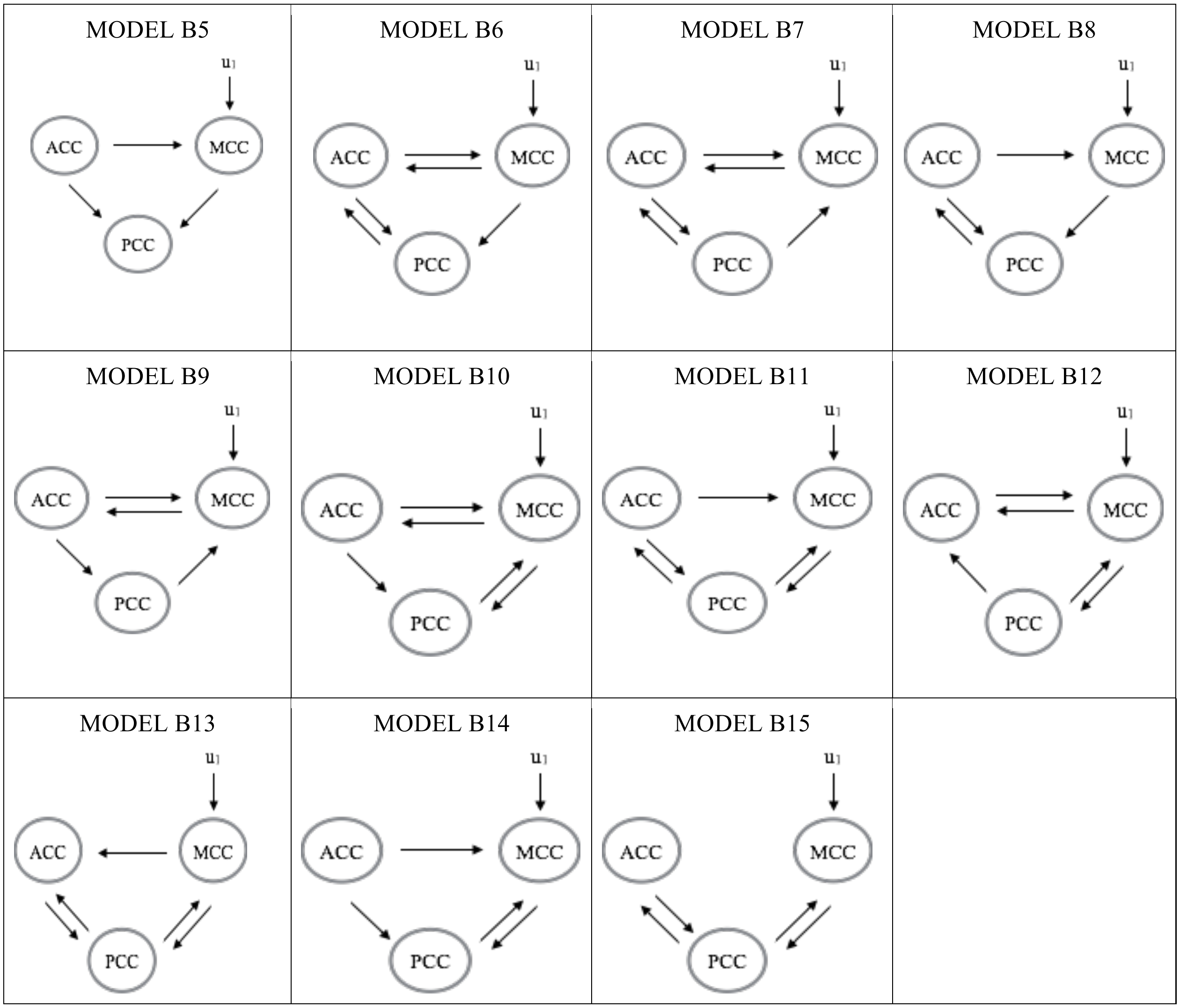


FIGURE 2(b). Fifteen linear connectivity models analysed separately for the response increased pain threshold in the presence of a loved one (Love Heals). ACC (anterior cingulate cortex), MCC (middle cingulate cortex), and PCC (posterior cingulate cortex) are the regions in the brain which are expected to be involved in the interaction.

The BMS revealed a linear model found to be the optimal one to explain the interaction of increased pain threshold in Love Heals. Bayesian model selection (BMS) showed that Love Heals could be represented by a cortical network involving the intrinsic connectivity demonstrated by model B4 (Fig. 3). In this model, the three divisions of cingulate cortex were connected intrinsically by unidirectional connectivity of ACC → PCC → MCC and ACC → MCC. On the other hand, there was no optimal model among the 15 tested models found to explain the interaction of decreased pain threshold in Love Hurts.

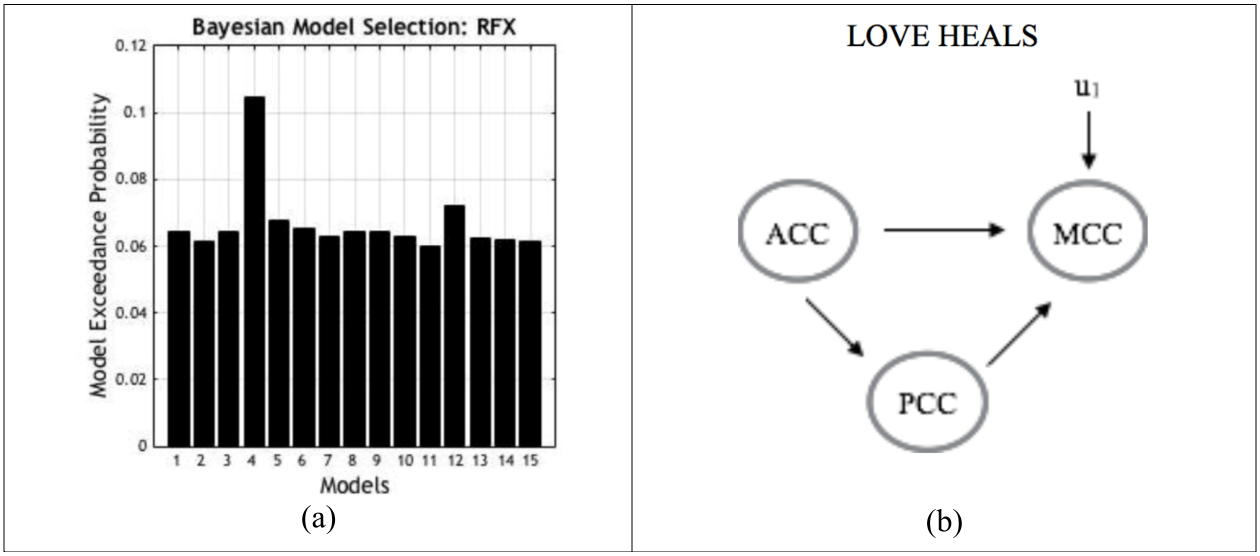


FIGURE 3. (a) Histogram of all linear models based on probability for interaction in Love Heals group. (b) The probable model (B4) for Love Heals involves the three divisions of cingulate cortex (ACC, MCC and PCC). The external input (laser stimulus) as pain stimulation evokes activity in MCC, then allows the other regions to play their function in this interaction. The model shows that these regions are connected intrinsically by a unidirectional connectivity.

DISCUSSION

The Relevance of the Selected Regions

Our previous study found two responses of individuals during receipt of pain stimulation while they were accompanied by their loved ones; decreased (Love Hurts) or increased (Love Heals) pain threshold. The Love Hurts response involved activations in thalamus, parahippocampal gyrus and hippocampus; while the Love Heals involved activations in all parts of cingulate cortex. These regions were then selected for further connectivity analysis based on their functions in pain processing and also by considering only one side of the brain. In order to allow for connectivity, at least two regions are needed to investigate their connection [9]. The difference of activations found between Love Hurts and Love Heals did not provide enough information about the relevant areas in the right hemisphere. That is why the areas were selected only from the left hemisphere which involved regions as stated above.

The thalamus was selected due to its function which act as a relay; allowing the information of pain signals from peripheral nerves to be conducted to the cerebral cortex [10,11]. Thalamus is the area most consistently activated by painful stimuli and is essential in the interpretation of our sensation especially pain [12]. The parahippocampal gyrus is related to the expectation of a high-intensity stimulus. It means that people who are sensitive to anxiety-inducing cues have increased activation in the parahippocampal gyrus [11]. The hippocampus has been shown to be involved in ‘tuning’ the sensitivity of brain regions involved in pain processing in a context-dependent manner [13].

The cingulate cortex is related to the affective-motivational component of pain. In most studies, the ACC and MCC are emphasized due to their roles in mediating affective responses to noxious stimuli [14,15,16,17]. These regions process cognitive factors such as attention, expectation, and anticipation, therefore is likely to be involved in processing the expectation towards the loved one [18], as well as in processing positive emotions in relation to the loved one [5].

Connectivity Model

The connectivity analysis gives us information about the direction of the connections and the strength of the interaction [19]. In Love Hurts, an input u_1 (laser energy stimulus) is expected to evoke activity in thalamus and predicts the activity in parahippocampal gyrus and/or hippocampus. The model was generated in such way in accordance with transmission of information by neurons from the periphery to the spinal cord and relays the signal to the thalamus before terminating in the cerebral cortex [10,20]. Unfortunately, among 15 linear models, there was no optimum model selected by Bayesian Model Selection (BMS) which was based on probability. These probabilities define a characteristic of the models as precisely as it can by presenting the probability of one model being more likely than the other models [19].

The effective connectivity describes the causal influences that neural units exert over another [19]. In this study, the significant connectivity can be seen in the interaction of increased pain threshold shown by the Love Heals group. All parts of cingulate cortex have been shown to play important roles in pain processing [16,17]. Our study adds another dimension in the role of ACC to explain the Love Heals phenomenon. The model chosen involves the connectivity of ACC → PCC → MCC and ACC → MCC. The positive input u_1 (laser stimulus) means that the laser energy stimulation will lead to the occurrence of events in MCC. In this model, an input laser energy M evoked activity in MCC. However, based on the model, any increase of activity in MCC does not directly affect the changes in ACC and PCC since there was no connection directed from MCC to any of the other regions. But, any changes in ACC would result in an increase in activity in PCC and MCC, while changes in PCC would increase activity in MCC.

CONCLUSION

In summary, the current study reveals a new possible cortical network for the increase in pain threshold by having a loved one nearby. The individuals who manifested Love Hurts and those manifesting Love Heals, the presence of a loved one seemed to activate THA, PHG and HIP in the Love Hurts case, while activations in all parts in cingulate cortex comprising the ACC, MCC and PCC were found in the Love Heals case. Activations in these regions are significant due to their roles in pain processing. Although the connectivity model to represent the Love Hurts is failed to obtain, however, the BMS showed that Love Heals can be represented by a cortical network involving the connectivity of ACC → PCC → MCC and ACC → MCC. This interaction currently explained by linear intrinsic connectivity and need some further consideration to be then explain by probably nonlinear model.

ACKNOWLEDGEMENT

USM Research University Individual Grant 1001/PPSP/812130.

REFERENCES

1. A. S. Jaggi and N. Singh, Brain Res. **1381**, 187-201(2011).
2. E. P. Mills, F. Di Pietro, Z. Alshelh, C. C. Peck, G. M. Murray, E. R. Vickers and L. A. Henderson, J. Neurosci. **38**(2), 1647-17 (2017).
3. C. D. Chong, T. J. Schwedt and W. Hougaard, J. Cereb. Blood Flow Metab., 1-20 (2017).
4. S. K. Ng, D. M. Urquhart, P. B. Fitzgerald, F. M. Cicuttini, S. M. Hussain and B. M. Fitzgibbon, Clinical Journal of Pain. **34**(3), 237-261 (2018).
5. B. L. Fredrikcson and M. A. Cohn, “Positive emotions” in *Handbook of Emotion, 3rd Ed*, edited by M. Lewis, J. M. Haviland-Jonesm and L. F. Barrett, (Guilford Press. New York, 2008), pp. 777 – 796.
6. S. Tamam, A. H. Ahmad, M. E. Aziz and W. A. Kamil, Journal of Physics: Conf. Series. **851**(1), 1-7 (2017).
7. M. Noll-Hussong, A. Otti, L. Laeer, A. Wohlschlaeger, C. Zimmer, C. Lahmann, H. Guendel, Journal of Psychosomatic Research, **68**(5), 483–487 (2010).
8. K. J. Friston, J. Ashburner, S. J. Kiebel, T. E. Nicholas and W. D. Penny, *Statistical parametric mapping: The analysis of functional brain images*. (Academic Pres., 2006).
9. K. J. Friston, L. Harrison and W. Penny, Neuroimage, **19**(4), 1273-1302 (2003).
10. C. B. Abd Aziz and A. H. Ahmad, Malaysian Journal of Medical Sciences, **13**(2), 11–18 (2006).
11. B. A. Vogt, Pain processing, cingulate cortex and the medial pain system. Retrieved December 2015, http://www.cingulumneurosciences. org/pain/shtml. (2015).
12. K. Wiech and I. Tracey, Frontiers in Neuroscience. **46**, 1 – 12 (2013).
13. C. M. McMurtry, P. J. McGrath, C. T. Chambers, Journal of Pediatrics **148**(4), 560-561 (2006).

14. M. Valet, T. Sprenger, H. Boecker, F. Willoch, E. Rummeny, B. Conrad, P. Erhard and T. R. Tolle, Pain. **109**, 399 – 408 (2004).
15. B. A. Vogt, Nat. Rev. Neurosci., **6**(7), 538 – 544 (2005).
16. M. H. Opisov, G. D. Dssor and F. Porreca, Journal of Clinical Investigation. **120**(11), 3379 – 3787 (2010).
17. K. Wiech, S. Jhabdi, C. S. Lin, J. Andersson and I. Tracey, Pain. **155**(10), 2047 – 2055 (2014).
18. Y. Cheng, C. Chen, C. P. Lin, K. H. Chou and J. Decety, Neuroimage. **51**, 923 – 929 (2010).
19. K. N. Stephan and K. J. Friston, WireS Cognitive Sciences, **1**, 446 – 459 (2010).
20. A. H. Ahmad and C. B. Abd Aziz, Malaysian Journal of Medical Sciences, **21**(Spec Issue), 46–54 (2014).