Original Article

# Using rDCM Method in the Mixed Model in order to Inference Effective Connectivity in Emotions

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## Abstract

**Purpose:** Recently, data from functional magnetic resonance imaging in the field of neuroscience have been strongly considered for the modeling of cognitive activities. Therefore, the use of a suitable method is important for evaluating functional magnetic resonance imaging data. Regression dynamic causal modeling is introduced as a new version of dynamic causal modeling in order to extract and derive effective connectivity in functional magnetic resonance imaging data. We used this method to investigate the distinction between effective connectivity and the pair of emotional states.

**Materials and Methods:** In this article, the effective connectivity between regions and activity of brain regions of interest during the application of a particular type of stimulation, which simulates the emotions created during human life, is examined in the form of an audio-movie. To do this, we applied the regression dynamic causal modeling method to a network consisting of 18 regions of interest that named the mixed model.

**Results:** In the mixed model, the distinction between happiness-anger, happiness-fear, and happiness-love was more intense. Finally, significant effective connectivities were observed in the auditory regions and regions related to emotion processing.

**Conclusion:** Ultimately, we could represent the distinction between emotions by applying the regression dynamic causal modeling to the mixed model.

## 1. Introduction

Our brain is a complex network of functional and structural areas. Functional Magnetic Resonance Imaging (fMRI) is a non-invasive powerful tool in the study of brain function and can provide a high-quality visualization of the activity location in the brain caused by emotional stimulation or cognitive function [1]. This allows the study of how a healthy brain operates in rest and when applying a particular task or stimulation. While early neurophysiological studies focus on simple cognitive processes with specific brain regions, contemporary studies usually relate to complex cognitive processes and functional integration of these areas, which require the analysis of brain connections. Therefore, the study of brain connections during the expression of emotions as a complex cognitive process is very important.

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To investigate emotions in fMRI data, Poli *et al.* [2] studied the effect of images with various emotional capacities on the brain areas. They collected the articles by searching terms of *happy faces, sad faces, fearful faces, angry faces, disgusted faces,* and *neutral faces.* They extracted spatial coordinates and inserted them in an electronic database. They performed activation likelihood estimation analysis for voxel-based meta-analyses. Processing of emotional faces was associated with increased activation in a number of visual, limbic, temporoparietal and prefrontal areas; the putamen; and the cerebellum. Happy, fearful and sad faces specifically activated the amygdala, whereas angry or disgusted faces had no effect on this brain region. Furthermore, amygdala sensitivity was greater for fearful than for happy or sad faces. Insular activation was selectively reported during processing of disgusted and angry faces. However, insular sensitivity was greater for disgusted than for angry faces. Conversely, neural response in the visual cortex and cerebellum was observable across all emotional conditions. By using analyses of fMRI data, Morawetz *et al.* [3] examined changes in inter-regional connectivity between the amygdala and Inferior Frontal Gyrus (IFG) with other brain regions during reappraisal of emotional responses and used emotion regulation success as an explicit regressor. During down-regulation of emotion, reappraisal success correlated with effective connectivity between IFG with dorsolateral, dorsomedial and ventromedial Prefrontal Cortex (PFC). During up-regulation of emotion, effective coupling between IFG with anterior cingulate cortex, dorsomedial and ventromedial PFC as well as the amygdala correlated with reappraisal success. Activity in the amygdala covaried with activity in lateral and medial prefrontal regions during the up-regulation of emotion and correlated with reappraisal success. Their results suggested that successful reappraisal was linked to changes in effective connectivity between two systems, prefrontal cognitive control regions and regions crucially involved in emotional evaluation.

While most studies in the modalities of neuroimaging in related to emotions have been done using visual stimuli, other studies have been done to examine emotions using various auditory stimuli which its results are reported by Purves *et al*. [4]. According to the results of these studies, the limbic system plays an important role in the processing of emotions. By using DCM and correlation methods, Nguyen *et al.* [5] examined the role of physiological and external factors in insula cortex activity. They used data with natural complex stimulus [6] (used data in this article). Finally, they discovered that cardiac activity would cause posterior insula cortex activity.

The purpose of the analysis of fMRI data is that, in a robust and reliable way, we can reveal the parts of the brain that during different brain experiences, the intensity of activity in those regions and the relationship between them changes [7]. Also, by applying a particular method, we can examine the strength and direction of the flow of information and activity within a brain network, and show networks that reflect the effect of a neuron on another neuron [8]. Among the available approaches, modeling-based methods are one of the most common methods for the estimation of effective connectivity [9].

In the last decade, there has been an extensive interest and activity in developing methods for obtaining strengths of directed connectivity from fMRI data. Here, we use a new version of DCM called regression Dynamic Causal Modeling (rDCM) for fMRI data which has promising capabilities in great neural networks. For the first time, this method was introduced by Frässle *et al.* [10] upon applying to a simulated dataset, including 66 regions and an experimental dataset (face perception), including 6 regions.

In this article, the aforesaid method is used to estimate the effective connectivity during applying to a special type of stimulation which is the simulation of the emotions that created in a form of an audio-movie during the life of a human being. The reason for choosing this method is the high speed of the method compared to the DCM method in the number of high regions. This method applied to a mixed model consists of 18 Regions Of Interest (ROIs) and in five types of emotions in order to distinguish between the emotions.

In the following, first we will explain materials (data and extracting of time series), the method and steps of applying this method, then we will describe the findings of the research, discussion, and limitations of the study.

## 2. Materials and Methods

After pre-processing the given data, to perform analyses, two approaches of voxel-based and ROI-based can be used. Voxel-based studies increase the dimension of the analysis, so in this research, we use the ROI-based approach. For this purpose, first, we have to extract the mask of the regions of interest from the labeled Atlas. We chose the Harvard-Oxford Atlas and the areas were selected according to the Harvard-Oxford Atlas. Eventually, the time series of each region was extracted by the averaging method. Then, in order to examine each emotion separately, we create stimulation for each emotion. After that, we defined the model. We used the rDCM method to estimate the effective connectivity. Finally, we applied the non-parametric permutation method for performing statistical analyses.

## 2.1.Empirical Data

In this research, we used the recorded data by Hanke *et al.* [6]. Data were recorded from 20 right-handed healthy people (8 females and 12 males, between 21 and 38 years old, average age 26.6) during long-term stimulation with "Forrest Gump" audio-movie [6]. After participants volunteered for the study, each filled out a questionnaire on basic demographic information, musical preference, proficiency and education, as well as familiarity with the "Forrest Gump" movie. The story of the movie is explained by the narrator, so the additional voice of sound explanation can primarily focus on explaining visual scenes and facial expressions without creating disorder in the storyline. Functional images with gradient-echo, 2 s repetition time 22 ms echo time, 0.78 ms echo spacing, were acquired during stimulation using a whole-body 7-Tesla Siemens MAGNETOM magnetic resonance scanner equipped with a local circularly polarized head transmit and a 32-channel brain receive. 36 axial slices with a 10% inter-slice gap were recorded in ascending order. Data were recorded in 8 segments. Each segment of audio-movie is a combination of different emotions.

Our aim is to investigate each emotion individually. Therefore, we considered time points of consecutive volumes of each segment of BOLD data in which the label of only one emotion exists, as specific stimulation of that emotion. Consequently, the analysis was done on the extracted time series (by using FSL and SPM12 software and MarsBar Toolbox) from four segments (3, 6, 7 and 8) which contained the specific stimulation of five emotions. The length of each emotion is different from the other emotion. These five emotions include emotions of happiness (126 s), sadness (208 s), anger (128 s), fear (68 s) and love (84 s).

## 2.2. rDCM Method

S In recent decades, the use of nonlinear and bilinear DCM methods has increased in order to study effective connectivity. As shown in Equation 1 [11], nonlinear DCM is described that $A$ represents the weight of connections between the regions, and $B^{(i)}$ is the modulation of these connections. Also $u_j$ and $x_j$ are inputs and neuronal states, respectively. $C$ matrix is a representation of the influence of inputs in the model. Finally, $D^{(j)}$ represents the influence of each region on the link between regions.

$$f(x,u) = \frac{\mathrm{dx}}{\mathrm{dt}} = \left(\mathrm{A} + \sum_{\mathrm{i=1}}^{\mathrm{m}} \mathrm{u_j B^{(i)}} + \sum_{\mathrm{j=1}}^{\mathrm{m}} \mathrm{x_j D^{(j)}}\right)\mathrm{x} + \mathrm{Cu} \quad (1)$$

In this research, in order to estimate the effective connectivity, the rDCM approach was used which is based on a few modifications in implementation of the main DCM [12] (according to Equation 1). Therefore, the effects of D and B are not considered. In fact, this method uses the linear DCM and translates this model to the frequency domain. Then, in order to influence the hemodynamic response [13] in the state equation, the convolution of the hemodynamic response function with the state equation is used. Finally, the partial independence assumption is considered between connectivity parameters and also, distribution of gamma prior is used for the precision of the noise that leads to the significant increase in performance of calculation (for more details please study [10]).

## 2.3.Applying rDCM Method

In order to implement rDCM, after extracting the time series of ROIs and also extracting the specific stimulus of each emotion, we defined the mixed model. In this model, 18 cerebral regions (extracted from Harvard-Oxford Atlas) in fMRI images with full connections were considered in the linear model and the input to ten existing auditory regions was entered.

In the mixed model, we considered 18 regions as ROI (see Figure 1A) according to previous studies and the existing regions with regard to auditory, emotional, and visual processes in the brain. Here, the input is entered into all auditory regions and the connections between the regions are defined fully (see Figure 1B). Therefore, the coupling between regions matrix (A) and matrix (C) will be formed. This model will be created for every five inputs. The used regions in this model included 10 auditory regions [14], 5 emotion processing regions [2, 5, 15] (INS, Amy.R, Amy.L, Hip.R and Hip.L) and 3 visual regions (OLi, OF and OP). Each of 5 emotional processing regions is considered regarding the previous studies. The reason for the selection of visual regions in this model is to examine the activity of these regions at the time of recalling the film scenes and visualization of people. Through the 5 emotion processing regions, two regions are related to memory and essentially are considered the aspect of recallin the emotional memories (Hip.R and Hip.L). The purpose of defining this model is to investigate the effective connectivity between auditory regions with emotional and visual regions at the time of applying the types of emotional stimulations through audio-movie. In fact, with the definition of this model, we represented that at the time of the expression of each emotion in the brain, which regions are connected with each other and which of them has the most activity in each emotion.

We used DCM12 in SPM12 to define this model. In order to apply rDCM method, TAPAS toolbox (www.translationalneuromodeling.org/software) was used in the MATLAB software environment. Ultimately, in each emotion, through several stages, an estimation of the parameters for investigating the effective connections was obtained.

### 2.4.Statistical Test

In order to carry out statistical analysis, we used the non-parametric permutation test. In between-group comparison, for expressing the significant of the directed coupling between two emotions and also in the entire connections, 100,000 permutations were created. Test statistic was considered as median difference and mean difference. To determine the significant of the directed coupling between two nodes in a special emotion, 1,000 permutations were created. Test statistic was considered as mean difference and the significant level was selected $p<0.05$.

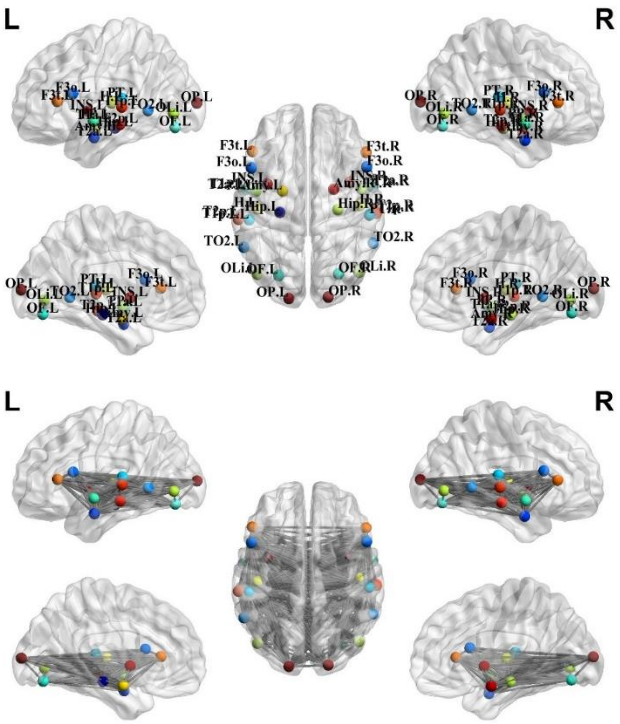



**Figure 1.** Spatial pattern of mixed model. (A) Regions of interest. (B) The connections between the regions are defined fully

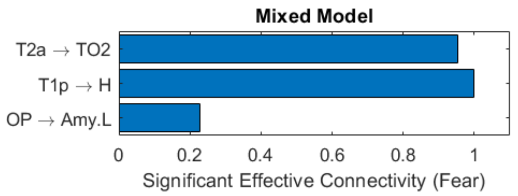
## 3. Results

As previously mentioned, the model was considered fully connected. In this model, according to the research purposes, two types of results will be concluded. First, the most meaningful connectivities between the nodes are extracted in each emotion. In fact, in this analysis, in each emotion, the connections that are the most active are determined. Then in the second analysis, the distinction in connectivity between the nodes among the two emotions is expressed by the mean and median difference test statistic. In the second analysis, it can be concluded that the most distinction is between which emotions and in which connectivity.

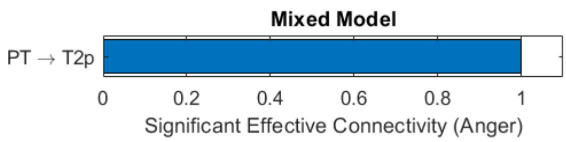
### 3.1. Findings in Five Emotions

In Figures 2A to 2E, in each emotion, the effective connectivity between the regions is expressed by their abbreviation with the highest level of connectivity. Here, connectivity values between zero and one are normalized, and the most negative number is scaled to zero.

As shown in Figure 2A, the most connectivity in anger is related to a connection between the PT and T2p regions, which relate to the auditory areas. In Figure 2B, the most connectivity in the emotion of fear is related to the connectivity between the two H and T1p regions, which relate to the auditory areas. In Figure 2C, the most relationship in the emotion of happiness is the connection between the two areas of F3o and INS, which relates to the relationship between the auditory area and the INS region. In figure 2D, the most connectivity in the emotion of love is the connectivity between the two regions of INS and F3t, which relates to the connection between INS and the auditory region. Finally, in figure 1E, the most connection in the emotion of sad is the connectivity between the PT and INS regions as well as the INS and Hip.L.




A

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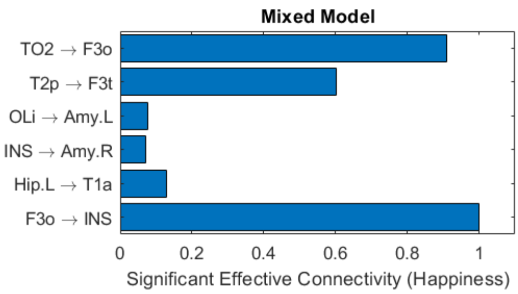
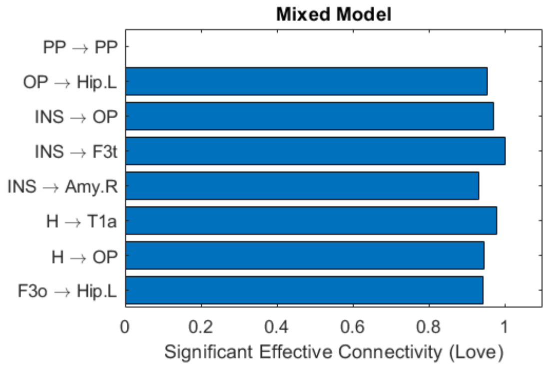
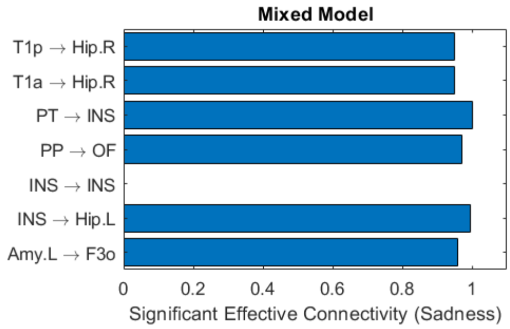



C




D




E

**Figure 2.** Coupling between the regions in five emotions state. (A) The effective connectivity between the regions in anger, (B) in Fear, (C) in happiness, (D) in love and (E) in sadness

## 3.2.Findings in Each Pair of Emotions

In this analysis, the distinction in connectivity between the nodes among the two emotions is examined and expressed by the mean and median difference test statistic. As a result, it can say that the most distinction is between which emotions and in which connectivity.

In Figure 3, the level of distinction of effective connectivity between the regions between the two emotions of anger-love by the abbreviation of each region and the input receiver region with the highest significant level of distinction, using the mean difference test statistic is expressed. These charts are plotted in terms of meaningful values of the distinction of connectivity between regions among the two emotions.

The highest number of significant distinction in the coupling between areas was found using the mean difference test statistic between the happiness-anger, happiness-love, and happiness-fear. Also in the input receiver areas, there was thehighest number of distinction in fear-love, fear-sadness and happiness-sad

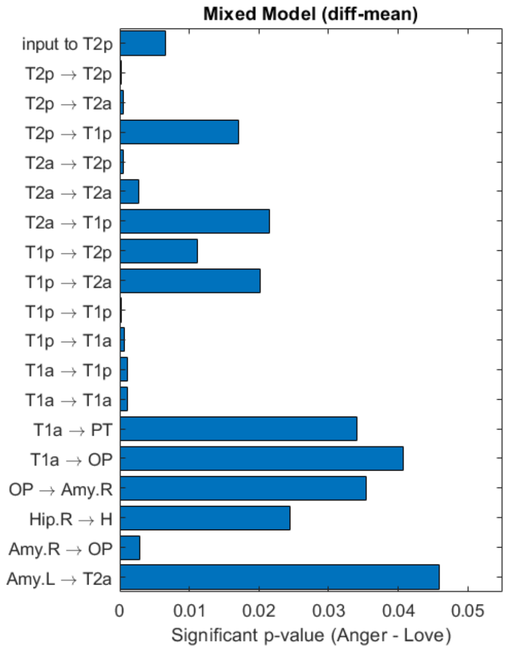



**Figure 3.** The significant distinction of coupling between regions and input connections between emotions of anger and love using mean difference test statistic

As shown in Table 1, the most significant distinction is between happiness-fear and happiness-love in the relationship between areas as well as the most significant distinction in the input recipient area with the mean difference test statistic.

**Table 1.** Significant distinctions in the coupling between the regions in pair-emotions (happiness-fear, happiness-love, and happiness-angry) using mean difference test statistic

| | *h - f* | *h - l* | *h – a* |
|---|---|---|---|
| *A* | INS –> H | OP –> T1a | T1p –> T1a |
| | H –> F3t | F3t –> H | PP –> INS |
| | T1p –> Hip.R | Hip.R –> H | INS –> H |
| *C* | F3t | T1a | H |
| | T1p | - | PT |
| | - | - | T1p |

Also, in Figure 4, between the two emotions of anger-love, the effective connectivity between the regions with the abbreviation of each region and the input recipient areas with the highest significant level of distinction is expressed using the median difference test statistic. These charts are plotted in terms of meaningful values of the distinction of connectivity between regions among each of the two emotions (due to the excessive number of charts, only a few of them are presented).

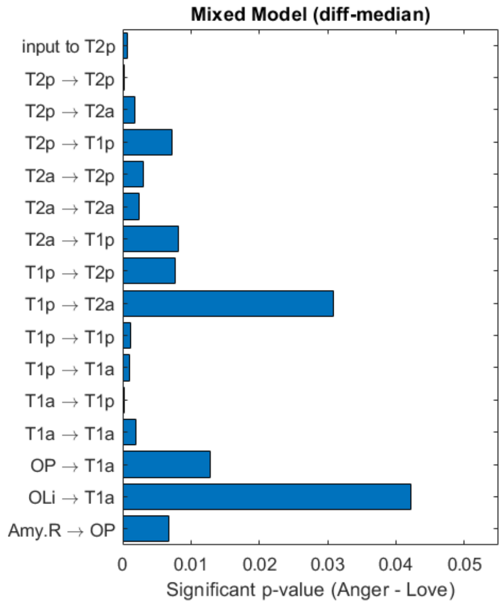



**Figure 4.** The significant distinction of connectivity between regions and input connections between emotions of anger and love using median difference test statistic

The highest number of significant distinction in the coupling between areas was found using the median difference test statistic between the happiness-anger, happiness-fear, and happiness-love. Also in the input recipient areas, the most distinction was found in fear-love, fear-sadness, and happiness-sadness.

Therefore, it seems that the two mean and median difference test statistics for the number of coupling between regions and the distinct connection of input recipient regions between emotions have similar results, although there are differences in the type of related nodes.

As shown in Table 2, the most significant distinction is represented between happiness-fear and happiness-love in the connection between areas and also the most significant distinction in the input recipient region with the median difference test statistic.

**Table 2.** Significant distinctions in the coupling between the regions in pair-emotions (happiness-fear, happiness-love, and happiness-angry) using the median difference test statistic

| | *h - f* | *h - l* | *h - a* |
|---|---|---|---|
| *A* | INS –> H<br>H –> F3t<br>T1p –> Hip.R | OP –> T1a<br>F3t –> H<br>Hip.R –> H | INS –> H<br>PP –> INS<br>T1a –> T2a |
| *C* | F3t<br>T1p<br>- | T1a<br>-<br>- | T1a<br>PT<br>T1p |

## 4. Discussion

In this article, the regression dynamic causal modeling method for fMRI data was used as a new type of DCM that provides a very efficient computational analysis of effective connectivity. This development is based on the linear DCM correction in the time domain as a special case of linear regression in the frequency domain.

Using empirical data, rDCM was applied to a model consisting of 18 regions. In this study, according to the obtained results, we can point to the important role of the INS area in emotions. This result was similar to the results of previous studies. Previous studies indicated that the role of the amygdala in emotions was significant, while in this study it was less important than the insula region. Also, the H region plays an important role in this stimulation as an auditory area.

In this study, the non-parametric permutation test was used to extract significant connection. The significance level was considered as 5%. In group comparison, two mean and median difference test statistics were used. The highest number of significant distinction in the coupling between areas was found using the mean difference test statistic between the happiness-anger, happiness-love, and happiness-fear. Also in the input receiver areas, there was the highest number of distinction in fear-love, fear-sadness, and happiness-sad. The highest number of significant distinction in the coupling between areas was found using the median difference test statistic between the happiness-anger, happiness-fear, and happiness-love. Also in the input recipient areas, the most distinction was found in fear-love, fear-sadness, and happiness-sadness.

Finally, by comparing the results, there was not a lot of significant difference in the number of connections distinction between regions. Although the finding connections were different in terms of type and value of significant.

### 4.1.Limitations and Suggestions for Future Studies

The current implementation of rDCM is the starting point and has three major constraints compared to the original DCM approach. Regarding the constant hemodynamic response function, rDCM currently does not include changes in the BOLD signal in brain regions and subjects. Also, matrix B (available in bilinear DCM) is not considered in the rDCM method.

In future studies, repeated emotional block stimuli can be used. Also, by increasing the number of areas, connections between other areas of the brain can be extracted.

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