Comparison between Subjects with Long- and Short-Allele Carriers in the BOLD Signal within Amygdala during Emotional Tasks

Shamil Hadi¹, Mohammad-Reza Siadat¹, Abbas Babajani-Feremi²

¹Department of Computer Science and Engineering, Oakland University, Rochester, MI, USA
²Department of Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, MO, USA

¹Corresponding author (Email: smhadi@oakland.edu)

Abstract

Emotional tasks may result in a strong blood oxygen level-dependent (BOLD) signal in the amygdala in 5-HTTLRP short-allele. Reduced anterior cingulate cortex (ACC)-amygdala connectivity in short-allele provides a potential mechanistic account for the observed increase in amygdala activity. In our study, fearful and threatening facial expressions were presented to two groups of 12 subjects with long- and short-allele carriers. The BOLD signals of the left amygdala of each group were averaged to increase the signal-to-noise ratio. A Bayesian approach was used to estimate the model parameters to elucidate the underlying hemodynamic mechanism. Our results showed a positive BOLD signal in the left amygdala for short-allele individuals, and a negative BOLD signal in the same region for long-allele individuals. This is due to the fact that short-allele is associated with lower availability of serotonin transporter (5-HTT) and this leads to an increase of serotonin (5-HT) concentration in the cACC-amygdala synapse.

1. Introduction

The anterior cingulate cortex (ACC) is a crucial area in the processing of cognitive-emotional stimuli. It is known to be part of the default-mode network which is active in the resting-state [3, 4]. The amygdala is also involved in emotional processing [1]. Several studies have provided an increasingly detailed account of neuronal systems, particularly the amygdala, in response to viewing pictures of fearful and threatening faces [2, 9, 10]. Perturbing the neuronal system by an extrinsic emotional input leads to increased neuronal activity in amygdala, which in turn produces an increased blood oxygen level-dependent (BOLD) signal in that region [2]. A functional connectivity analysis shows that the perigenual anterior cingulate cortex (pACC), which has two distinct regions (the cACC and rACC), and the amygdala are highly connected. Neuronal activity in the rACC is positively correlated with that of amygdala, while neuronal activity in cACC is negatively correlated with the amygdala [2]. In addition, it has been shown that the amygdala has an elevated response to threatening visual stimuli in short-allele [2], which in turn sends a neuronal signal to the rACC and hence back to amygdala through the cACC [5].

The serotonin (5-HT) neurotransmitter is an inhibitory chemical message that is related to perceptual processing. The concentration of 5-HT is important in neuronal systems during cognitive-emotional tasks. Researchers have noticed that 5-HT plays an important role in developing neuronal connections during perceptual processing which leads to an increase in anxiety during adulthood [6].
Our study has mainly focused on the cACC-amygdala interaction and how 5-HT modulates this coupling. The aim of this study is to illustrate the underlying mechanism which produces a negative BOLD response in amygdala during the processing of emotional stimuli. Then, one can make a comparison between the two groups with short- and long-allele individuals. A study has shown an increase in coupling during emotional tasks in short-allele versus long-allele between a region of ventral medial prefrontal cortex and the amygdala [7].

The following sections are organized as follows: The Method Section briefly illustrates two types of subjects with short- and long-allele carriers. It focuses on amygdala-ACC interaction and how the left amygdala produces a negative BOLD signal in long-allele. Then we analyze the observed BOLD signal using a Bayesian approach. We discuss the results in the Discussion Section. And finally, we conclude our thoughts based on the results.

2. Method

The dataset used in this study is described in [9]—a summary of the paradigm and data acquisition used to collect this data is noted below.

2.1. Subjects

Twenty four Caucasians were selected from a large population after testing to make sure that they were free of neurological sickness in their life, including drug or alcohol abuse [8]. All participants in this study gave a written informed consent based on guidelines of the National Institution of Mental health Institution Reviewed Board [2]. The subjects have been classified into two groups; a group of subjects with short-allele carriers and a group of subjects with long-allele carriers [2]. More details were explained in [9].

2.2. Imaging

A gradient echo EPI sequence on a GE 3-T Signa scanner with 24 axial slices (1-mm gap and 4-mm thick) was used to acquire the BOLD functional images with the following parameters: TR/TE = 2000/28 msec, FOV = 24 cm, and matrix size = 64x64. More imaging details were presented in [9].

2.3. fMRI paradigm and task

The fMRI paradigm that is illustrated in Fig. 1 consists of two types of stimuli blocks. The light gray block represents the sensorimotor block (Match Shape) and the dark gray block represents the emotional block (Match Face). Four blocks of emotional tasks were interleaved with five blocks of sensorimotor control tasks [9, 10]. During the processing of cognitive-emotional stimuli, a trio of faces (expressing either fear or anger in Fig. 2B) was presented, and subjects were instructed to select one of two faces (bottom) that was identical to the target face (top). Each block of emotional task consisted of six different images that presented sequentially for 5 seconds. During the sensorimotor control task, a trio of geometric shapes (horizontal and vertical ellipses illustrated in Fig. 2A) was presented; subjects were instructed to select one of two shapes (bottom) that was identical to the target shape (top). Each sensorimotor block had six different images that were presented sequentially for 5 seconds. A brief description preceded all blocks for two seconds, this description stated ”Match Faces” or “Match Shape”).
Fig. 1. Two type blocks in the fMRI paradigm, emotional block (MF, the dark gray box) and sensorimotor block (MS, light gray block). Four blocks of emotional tasks were interleaved with five blocks of sensorimotor control tasks.

Fig. 2. Illustration of the two fMRI stimuli. (A) During the sensorimotor stimuli, the subjects viewed a trio of geometric shapes; they were instructed to select one of two shapes (bottom) that matched the target shape (top). (B) During the emotional stimuli, the subjects viewed a trio of faces (expression either anger or fear); they were asked to select one of two faces (bottom) that matched the target face (top). The actual figure can be found in [17].

2.4. Identifying the models

To apply a Bayesian model-inversion approach, the model must be predefined. There are four brain areas in our model: right amygdala (R_amy), left amygdala (L_amy), rostral subgenual portion of the ACC (rACC), and caudal supragenual portion of the ACC (cACC). Our focus was to investigate the circuitry feedback from the left amygdala to the cACC and to explain why the left amygdala produces a negative BOLD response during the perceptual processing of emotional tasks. Fig. 3 shows the four brain areas as represented in the Bayesian model. The input enters the system through L_amy; this input induces a neuronal signal that generates a BOLD signal in L_amy.
Fig. 3. The schematic illustration of the model components. There are four brain areas in the model; right amygdala (R_amy), left amygdala (L_amy), caudal supragenual portion of the ACC (cACC) and rostral subgenual portion of the ACC (rACC). The $y_1$, $y_2$, $y_3$, and $y_4$ represent the generated BOLD signals. The model is disturbed via the extrinsic input ($u_t$) and induces responses in the regions that compose the model.

### 2.5. Analysis of regional effects

In this paper we are interested in investigating how emotional stimuli induce negative neuronal feedback to the left amygdala which in turn produces a negative BOLD response within the same brain region in long-allele. Several studies have found that the rACC and amygdala were strongly connected and correlated [2, 5], suggesting that they represented a functional circuitry modulated by the serotonergic system [2]. Amygdala-rACC connectivity is reduced in short-allele carriers which provides the underlying mechanism account for the observed increase in amygdala activity because reduced coupling would cause reduced feedback circuitry of amygdala activity through cACC [9, 10]. Therefore, the BOLD signal produced by L_amy in short-allele is stronger compared to long-allele carriers.

Fig. 4 shows the induced signal in L_amy in both short- and long-allele. The dashed dotted line is the induced signal of short-allele and the solid line is the neuronal response of long-allele. Fig. 5 illustrates the BOLD responses in L_amy from short- and long- allele carriers.

### 2.6. Bayesian Method

Dynamic causal modelling (DCM) is used to investigate the effective connectivity among the involved brain regions in process of fearful and threatening facial expressions [15, 16, 18]. A variational Bayesian estimation approach is used in the DCM to estimate the parameters of the model [15, 18]. The input-output relationship in the DCM is extracted from the state-space representation of the model. Posterior moments (mean and covariance) are subsequently estimated iteratively using the variational Bayesian approach as an expectation–maximization algorithm. A local linear approximation of the input-output relationship around the current conditional expectation is employed in the DCM. In the expectation step, the posterior moments are updated in the DCM using the Gauss–Newton method. In the maximization step, the hyperparameters of the observation noise covariance matrix are updated in the DCM.
Fig. 4. Average of twelve subjects’ neuronal responses in the left amygdala for long and short-allele carriers. The dashed dotted line represents the neuronal activity for short-allele carriers and the solid line is for long-allele carriers.

Fig. 5. Average of twelve subjects’ BOLD responses in the left amygdala for long and short-allele carriers. The dashed dotted line represents the BOLD responses in short-allele carriers and the solid line is the BOLD responses in long-allele carriers.

3. Discussion

We studied the cACC-amygdala interaction using fMRI data of twenty four healthy subjects which was collected during the neuronal processing of fearful and threatening stimuli. We identified an effect of synaptic serotonin concentration on the interaction between amygdala and cACC. The amygdala-cACC has been functionally connected [2], and the pattern of this connectivity shows that, in the studies of primate brains, the amygdala sends a strong signal to rACC and back to the amygdala through cACC, suggesting that this pattern represents the interaction which inhibits the amygdala activity [11-13]. Recent study using magnetic
resonance spectroscopy showed a negative BOLD response in the ACC [14]. It has shown that the negative BOLD responses in the ACC are associated with GABA-concentration [14].

Decreased coupling in cACC-amygdala feedback circuitry leads to reduced feedback regulation of amygdala activity. The causal mechanism behind this feedback circuitry is that short-allele is associated with less 5-HTT availability, which leads to increased serotonin concentration in the cACC-amygdala synapses and causes down regulation of serotonin response. In other words, short-allele individuals have lower reuptake of 5-HT, meaning more serotonin signaling, and they respond as if they were hyposerotonergic. While in long-allele, subjects have higher availability of 5-HTT compared to short-allele, and more reuptake of 5-HT from the synapse.

4. Conclusion

We have observed a positive BOLD signal in the amygdala during emotional stimuli for short-allele individual and a negative BOLD signal in long-allele in the same brain region. This may be due to the fact that short-allele is associated with less availability of 5-HTT and causes a reduced reuptake of synaptic serotonin and hence more serotonin signaling. In other words, elevation of amygdala response in short-allele may be caused by a lifetime excessive serotonin signaling in cACC-amygdala synapses, which leads to down regulation of serotonin response.

Acknowledgment

We would like to thank Daniel Weinberger, Lukas Pezawas, Venkata Mattay, Ahmad Hariri, and Yunxia Tong for providing us with the data and help in processing the data.

Software note

SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) was used for pre-processing and applying the DCM to our fMRI data. SPM8 was implemented by members & collaborators of the Well Trust Center for Neuroimaging and was released in 2009. It is open and free software.

5. References


