The influence of depression on deactivation and neural correlates during mental arithmetic tasks

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***Abstract*—Patients of depression often have lower performance in perception, planning, and execution in cognition, compared to healthy controls. Depression has been reported to be associated with functional alterations in the resting state connectivity in the brain. This study investigates whether there are differences in neural dynamics measured by mental arithmetic tasks (MAT) between depressed and healthy subjects. To this end, this study employed an ROI-based functional connectivity analysis, within-condition interregional covariance analysis (WICA), to explore the correlates of the brain deactivation regions. Results of this study showed that the corresponding emotional loop is inhibited in healthy subjects and show the control loops of attention and emotion is inhibited in depressed subjects during MAT, and the patients with depression may produce a stronger stress response than the healthy subjects during the MAT. This may be the key reason for that the mathematical abilities of the depression subjects were inferior to that of the healthy subjects.**

***Index Terms*—Functional magnetic resonance imaging (fMRI); Depression ; Mental arithmetic tasks (MAT); Within-condition interregional covariance analysis (WICA)**

I. Introduction

There is growing evidence from patient and neuro-imaging studies that the depressed patients show not only decreased precision but also inferior performance in perception, anticipation, and decision making, compared to healthy controls [1], [2]. It is still under debate whether depressed and healthy subjects show differences in basic cognitive mechanisms. Some recent functional Magnetic Resonance Imaging (fMRI) studies demonstrated the differences in activities of several brain areas including the frontal cortex, anterior and posterior cingulate cortex, striatum, amygdala, and thalamus [3], [4] between the depressed and healthy subjects in cognitive processing. The aberrant function of these areas has been linked to the symptoms of depression such as a bad mood, listlessness, and self-regulated disturbances [5], [6], [7]. Particularly, Christopher and Murat demonstrated the abnormal task-related deactivation and functional connectivity of the subgenual cingulate cortex in patients with a major depression disorder, compared to healthy controls [8]. However, the differences in basic cognitive mechanisms such as elementary mathematical tasks between depressed and healthy subjects remain less clear.

In the research of deactivations, it has been found that certain brain regions such as the dorsomedial frontal cortex, orbital frontal cortex, anterior cingulate gyrus, posterior cingulate gyrus, and angular gyrus etc. [9], [10], routinely exhibit activity decreases. Because the decreases in these regions were not associated with specific cognitive tasks, they were named task-independent deactivations [8], [9]. The network of these regions shows considerable overlap with the hypothesized "default mode network," which was first described by Raichle [11]. Using the functional connectivity method and ICA (interregional covariance analysis), Fransson has found that the default mode network not only exists in the resting state, but also in the task state [12]. At present, the deactivation studies mostly aim at confirming the brain regions that exhibit a decrease of the brain blood flow, but the response mode and space-time relation from an overall and dynamic angle are less touched.

The above-mentioned deactivation may be relevant to depression, in which resting-state alterations in the activity and connectivity of the anterior cingulate cortex (ACC) have been a frequent finding [8], [13], [14]. An ROI-based functional connectivity analysis is a kind of functional modulation model of the brain circuitry through a cross-correlation analysis of BOLD signals or activation index, and with it the relationship between these ROIs has been assessed through comparing different ROIs in the task state with themselves in the resting state [15], [16]. This method could distinctly notify the interactions between different regions in the same task and directly reflects the functional modulation in the brain circuitry [17].

II. Research Methodology

A. Subjects

A total of 16 depressed college students (9 female and 7 male, age at 18-21 years old) and 14 healthy controls (7 female and 7 male, age at 18-21 years old) recruited from the local population of graduates or undergraduates at Dalian Maritime University participated in this study. Informed consent was obtained before participation.

B. Behavioral Tasks

This study adopts a Mental Arithmetic Task (MAT) to study the differences in brain activity during problem soling in patients and normal controls [4]. The participants solve mental arithmetic problems presented on a computer screen, to which they have to respond using a two-button mouse in time. Based on the lessons learned from our previous pilot study [4], this study does not provide any feedback to the participants after each trial during MAT. Under the experimental condition, each trial starts with two Arabic numbers and a basic arithmetic operation, "+" or "–", 0.5 second later, a third number appeared on the screen (see Fig. 1). The subjects need to decide whether or not the third number was larger than the results of the first arithmetic operation in 1.5 second. Under the control condition, white circles or triangulates were presented as visual stimuli in triplet presented without feedbacks after each trial. The sequence of events under the Control task was the same as that under the mental arithmetic task. The task was to decide whether or not the third graphic in the triplet had the same shape as the pair of graphics presented first. Under the resting condition, the user interface is displayed with a small white attention dot and subjects did not need to perform any task.

C. Functional Imaging Data Acquisition and Analysis

Subjects performed two runs of the experiments implemented in a block design, while their brains were scanned with a 3.0 T Siemens Magnetom Vision Scanner. Within each run, three 30-sec experimental or control blocks were alternating with 20-sec rest blocks ([18]. Reader may consult Figure 1) for more details.

All fMRI data were analyzed by using SPM8 software packages (Wellcome Department of Cognitive Neurology, Institute of Neurology, London).Images were first spatially realigned, normalized, and smoothed ($8mm$ full width at half-maximum). Statistical analysis used a random effect model, with individual activation maps being generated using a general linear model. The voxel-wise threshold for activation was set at $P < 0.05$, corrected for the number of resolution elements in each of the ROIs by using the SPM small volume correction (SVC) procedure together with brain masks defined by the automated anatomical labeling toolbox (www.fil.ion.ucl.ac.uk_spm_ext_#AAL). The brain masks defined the brain regions over each of which the SVC was performed.

Regions of interest were based on the statistical results of SPM8, and then within-condition interregional covariance analysis (WICA) method was used to calculate functional connectivity of different regions of interest. We denoted I_0 as the mean MRI signal intensity at the baseline condition, which was the average of all images acquired during the three blocks of the baseline. The relative MRI signal intensity, $S_{img}(n)$ during each block was defined as:

$$S_{img}(0) = \frac{I_{img}(n) - I_0}{I_0} \qquad (n = 0, 1, 2, \cdots, 10) \qquad (1)$$

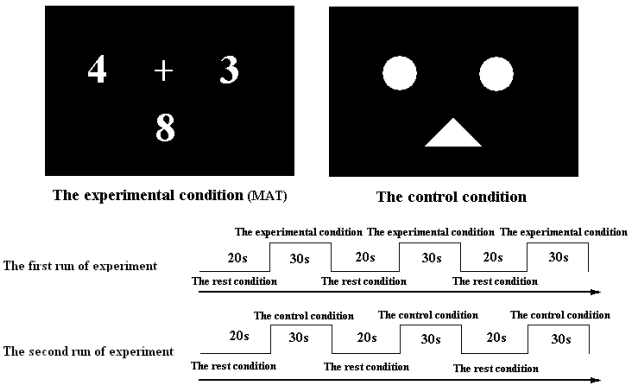

Fig. 1. Exemplars of the stimuli used for the tasks and experimental design. A block design was used. Each task condition lasted for 30s, each rest condition lasted for $20s$.

where $I_{img}(n)$ is the MRI signal intensity of the nth image in a block (baseline, MAT, or Control). And then

$$DS_{MAT}(n) = S_{MAT}(n) - S_{baseline}(n) \qquad (2a)$$

$$DS_{Control}(n) = S_{Control}(n) - S_{baseline}(n) \qquad (2b)$$

We used $DS_{MAT}(n)$, $DS_{Control}(n)$ as time series to calculate correlations between different regions of interest.

III. Experimental Results

A. Behavioral Results of MAT

Table I shows the behavioral results of MAT by depressed and healthy subjects. There is no significant difference in task accuracy and reaction time between two groups during the control condition, but the depressed patients had much lower ($P \leq 0.01$) task accuracy and longer ($P \leq 0.05$) reaction time than that of the healthy controls performing MAT.

B. Results of deactivation imaging

Fig. 2 shows the deactivation maps during MAT performance using xjView toolbox[1], threshold at uncorrected $P \leq 0.05$. The healthy subjects (THS) showed the inhibition of amygdale and ventral cingulate gyrus (BA24) during MAT, while the depressed subjects (TDS) showed the inhibition of left and right prefrontal cortex (BA6/8/9), dorsal anterior cingulate gyrus (BA32) and hippocampus during MAT.

C. Results from the WICA

To investigate the interaction of the brain regions that show deactivation during MAT in two groups, this study used an fMRI connectivity analysis method (WICA) [15], [16], [17]. Fig. 3 shows distinct functional pathways in the depressed subjects and the healthy controls during MAT. The activity in the right insular (BA13) was strongly correlated with the activity in right hippocampus for both groups; the activity in the anterior cingulate cortex (BA32) was strongly correlated with that in frontal cortex (BA9), right insular (BA13) and right hippocampus only in the depressed subjects during MAT.

[1]http://www.alivelearn.net/xjview

TABLE I
BEHAVIORAL RESULTS OF MAT IN DEPRESSED AND HEALTHY SUBJECTS (MEAN±S.E.).

Indexs	Tasks	THS	TDS	F value	P value
Judgment Accuracy (%)	The control condition	95.87±0.95	97.50±1.03	1.344	0.257
	The experimental condition (MAT)	90.67±0.94	80.50±5.67	4.817	0.038*
Reaction Time (ms)	The control condition	703.3±36.12	760.8±41.64	1.096	0.305
	The experimental condition (MAT)	726.0±46.47	974.2±68.91	9.500	0.005**

* $P < 0.05$;
** $P < 0.01$.

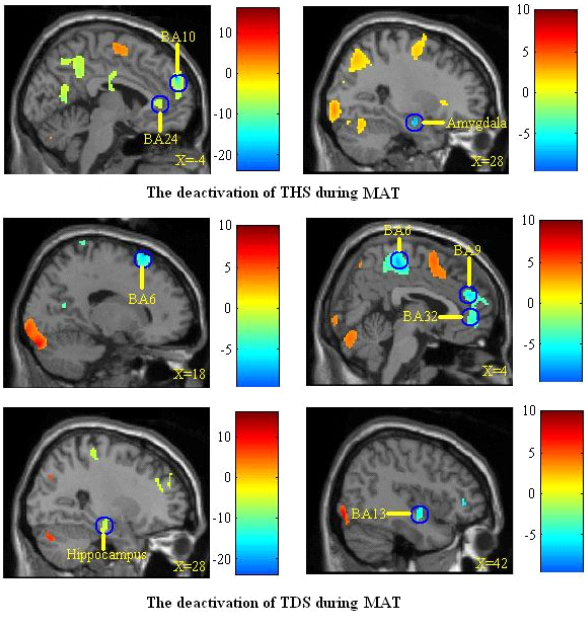

Fig. 2. Comparison of deactivation maps between the depressed subjects (TDS) and the healthy subjects (THS) during MAT, The results are visualized using xjView toolbox, threshold at uncorrected $P < 0.05$.

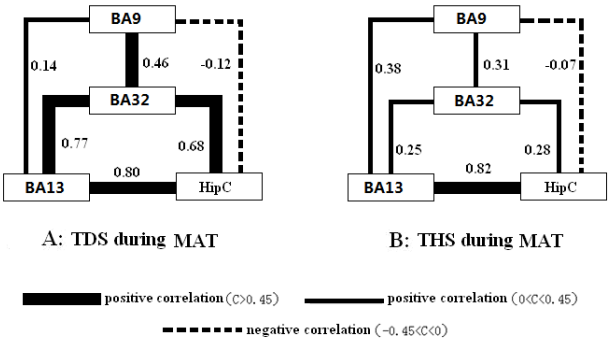

Fig. 3. The functional connectivity between ROIs of deactivation cortex between the depression subjects (TDS) and the healthy subjects (THS) during MAT. The strength of functional connectivity between ROIs was labeled by a number and weighted by lines. HipC: hippocampus.

IV. DISCUSSIONS

Table I shows no significant differences in the task accuracy and reaction time between two subject groups during the control condition. In contrast, during the MAT, the depressed patients had much lower ($P \leq 0.01$) task accuracy and longer ($P \leq 0.05$) reaction time than that of the healthy controls, which may be attributed to the fact that the MAT involved the quantity calculation and comparison of numbers. Depressed subjects seem to have significantly worse performance in the quantity calculation and comparison than that of the healthy subjects, and the ability of mathematics may be influenced by depression.

Figure 2 shows the inhibition of amygdale and ventral cingulate gyrus (BA24) in healthy subjects during MAT, while depressed subjects showed the inhibition of prefrontal cortex (BA6/8/9), dorsal anterior cingulate gyrus (BA32), insular (BA13) and hippocampus. Previous neurological studies showed that the corresponding emotional loop is inhibited in healthy subjects and the control loops of attention and emotion is inhibited in the depressed subjects during MAT. Of particular note is that the depressed subjects exhibited deactivation in the hippocampus during MAT. Neuroanatomy shows that the human hippocampus contains high concentrations of adrenal glucocorticoids (mainly cortisol) receptor than other brain regions, so it is particularly sensitive to stress. Studies have shown that the hippocampus is involved in the integration of perception information, explaining the significance of the environmental information and setting the tone for behavioral responses and neuroendocrine responses. The special distribution of glucocorticoid receptor and the memory function shows that the hippocampus is affected by stress [19], [20], [21]. Many studies showed that the hippocampus plays an important regulatory role in the inhibition of activity of PHA-axis which is harmful to body and mind and usually induced by stress [22], [23], [24]. Pruessner and others showed the deactivation volume of the hippocampus had a positive linear correlation to the quantity of cortisol release [25]. Therefore, the hippocampus can inhibit the excessive activation of PHA axis and play a role in maintaining the harmony of circadianrhythm and the calmness of emotion during stress. The deactivation of the hippocampus in the depressed subjects during MAT found in the current study may lead to the over-activity of PHA axis and the excessive secretion of cortisol, which can induce negative emotions negatively affecting the body and mental state. Their fMRI study in MAT also reported deactivations of limbic system, suggesting elevated activation during nonstressful situations [25]. This study reported comparable deactivation of the

brain areas in the depressed subjects during the experimental condition. In consideration of the functions in which these areas participate [25], we speculate that the anterior cingulate cortex, the insula, the hippocampus, and the medial frontal cortex are active areas during the resting state or nonstressful situations and play important roles in self-regulation after stress reaction. Therefore, one conclusion can be drawn is that the depressed subjects may produce a stronger stress response than the healthy subjects during the MAT.

To further demonstrate the above-mentioned conclusion, we employed an ROI-based functional connectivity analysis, WICA, to analyze the interaction of the brain regions that show deactivation during the MAT. The results showed stronger connectivity between the anterior cingulate cortex and other deactivation regions in the depressed subjects than that in the healthy subjects during the MAT (Figure 3). Further, we believe the deactivated regions found in this study play important roles in self-regulation and depression may suppress the operation of a network which involves the anterior cingulate cortex and other limbic system components to disturb the harmony of physical and psychological states during the MAT, and the inhibition of this network may be the key reason for the poor performance of cognitive tasks in the depressed subjects.

V. Conclusions

Three conclusions can be drawn by the above analysis. First, the emotional response loop in the brain is inhibited in the healthy subjects during MAT, which may improve attention and emotional control and make the subjects complete the task relatively easily. In contrast, the control loop of attention and emotions is inhibited in the depressed subjects during MAT, which can produce negative emotions and make difficult it for the depressed subjects to complete the MAT. Second, empirical results suggested the deactivations of the limbic system and anterior frontal cortex in the depressed subjects during MAT which play an important role in the impaired effects of psychosocial stress to body and mind health, so that the depressed subjects may produce a stronger stress response than the healthy subjects during the MAT. Third, the results of this study demonstrated a neural network of deactivation involving the limbic system components and anterior frontal cortex, which was strengthened by depression during MAT, and the inhibition of this network may be the key reason for the poor performance of cognitive tasks in the depressed subjects.

It should be noted that a limitation of the study is inherent in the WICA methodology used. While WICA provides a relatively simple and expedite way of investigating statistical dependencies (or functional connectivity) changes during task performance, it cannot provide information on the causal interactions which can extract networks of causal influences of one neural element over another (or effective connectivity). The results of study could be usefully validated and extended with the use of the techniques for extracting effective connectivity such as covariance structural equation modeling [26] and dynamic causal modeling [27], which would be able to provide more information on what was driving the connectivity changes we have shown. Furthermore, the Future studies should adopt the cognitive tasks with scalar difficulties and include measures of stress perception, as well as a satisfactory assessment of the amounts to the deactivations in brain to investigate the detailed underlying mechanism of the influence of depression on deactivation and neural correlates during MAT.

Acknowledgments

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