



## Is the contribution of the amygdala to the sex- and enhancement-related effects of emotional memory time-dependent?

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### ABSTRACT

A new focus in the field of emotional memory is the study of sex-related differences. Whether the sex-related lateralization of amygdala function (i.e., the female-left/male-right effect) in the emotional enhancement of memory (EEM) is time-dependent remains unclear. To evaluate this phenomenon, we conducted a two time-point study (20 min vs. 24 h) using fMRI and behavioral paradigms. We found that the right amygdala predicted 20-min EEM, while the left amygdala predicted 24-h EEM. The sex-related lateralization of amygdala function was not detected in either the 20-min or the 24-h EEM. Our results further confirm and extend the idea that the amygdala exhibits a lateralized and time-dependent dissociation, occurring even in the 24-h EEM relative to the 20-min EEM. The present and previous studies indicate that sex-related lateralization of amygdala function occurs in the 2- to 3-week EEM, but it does not occur in the 1-week, 24-h, or less than 30-min EEM, suggesting that this effect on emotional memory may also be time-dependent.

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### 1. Introduction

It is easier to remember emotionally arousing events than it is to recall those that are neutral (Bradley, Greenwald, Petry, & Lang, 1992). This phenomenon is known as the emotional enhancement of memory (EEM) (Sommer, Gläscher, & Moritz, 2008; Talmi, Anderson, Riggs, Caplan, & Moscovitch, 2008). Sex-related differences have become a new focus in the study of emotional memory (Cahill, 2006). An important finding from imaging studies is that successful encoding of emotional memory activates the left amygdala in women but the right amygdala in men (Cahill, Uncapher, Kilpatrick, Alkire, & Turner, 2004; Cahill et al., 2001; Canli, Desmond, Zhao, & Gabrieli, 2002; Mackiewicz, Sarinopoulos, Cleven, & Nitschke, 2006). This female-left/male-right effect of amygdala activity was coined the “sex-related lateralization of amygdala function” (Cahill, 2003), or the “sex-related difference” in the present study. Other recent studies, however, have failed to find this effect (Kensinger & Schacter, 2006, 2008; Talmi et al., 2008), although the reason for this inconsistency remains to be elucidated.

McGaugh (2000) defined second-to-hour delayed memory as short-term memory (STM) and hour-to-month delayed memory as long-term memory (LTM). The processes of STM and LTM are

dissociated or time-dependent. Previous studies have shown that EEM occurs over both short (several minutes) (Kensinger & Corkin, 2004; Sergerie, Lepage, & Armony, 2006) and long (one day to weeks) time periods (Adolphs, Tranel, & Denburg, 2000; Cahill et al., 2004; Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000), corresponding to short-term EEM and long-term EEM, respectively. Neuroimaging studies have demonstrated that the involvement of the amygdala is time-dependent and dissociated between short-term EEM and long-term EEM (Hamann, Ely, Grafton, & Kilts, 1999; Mackiewicz et al., 2006; Ritchey, Dolcos, & Cabeza, 2008). Thus, a key factor underlying the inconsistent results observed in the sex-related differences could be the differences in delay time. To date, few studies have explored this discrepancy. It is therefore necessary to systematically investigate whether the sex-related differences are time-dependent.

Previous imaging studies on emotional memory, particularly those investigating sex-related differences, have often been designed using a single time-point model (Cahill et al., 2001, 2004; Canli et al., 2002; Dolcos, LaBar, & Cabeza, 2004; Kensinger, Garoff-Eaton, & Schacter, 2007) that only focused on one stage of EEM (Hamann, 2001; LaBar & Cabeza, 2006). To further evaluate the time-dependence of sex-related differences in EEM, multiple time-point experiments investigating the neural correlates of the different stages of EEM are needed. To our knowledge, only a limited number of imaging studies have adopted the two

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time-point model for EEM (Hamann et al., 1999), and even fewer have accounted for sex-related differences (Mackiewicz et al., 2006; Ritchey et al., 2008). These studies all adopted a relatively longer delay (1–4 weeks) for the long-term EEM, while behavioral experiments have indicated that EEM can also be observed in 24-h delayed memory (Sharot & Phelps, 2004; Sharot & Yonelinas, 2008). Moreover, neurological studies have suggested that lesions of the amygdala can impair 24-h long-term EEM (Adolphs et al., 2000; Buchanan, Denburg, Tranel, & Adolphs, 2001). To date, however, few imaging studies have adopted a delay time of 24 h. The primary goal of this study was to confirm whether the involvement of the amygdala is dissociated between the 20-min and the 24-h EEM and further explore whether the sex-related lateralization of amygdala function is time-dependent in EEM.

## 2. Subjects

Twenty right-handed volunteers (10 women and 10 men, age  $21.7 \pm 0.28$  years) participated in this study. All subjects were recruited from an undergraduate pool and were compensated for their time. None of the subjects reported a history of medical or neurological illness. After a complete description of the study to the subjects, written informed consent was obtained for their involvement in this study in accordance with the review board of the University of Science and Technology of China.

## 3. Stimuli

Approximately 80% of the pictures used in this study were selected from the International Affective Picture System (IAPS) picture database (Lang, Bradley, & Cuthbert, 2005). The others (about 20%) were obtained from the Internet. According to Russell's circumplex model (Russell, 1980, 2003), each picture was sorted into one of four emotional categories (fear, sadness, happiness, and neutral) by 20 other volunteers (10 women and 10 men who did not participate in the experiment). The emotional arousal and valence level of each picture was also rated according to the Self-Assessment Manikin (SAM) paradigm (nine-point scales, 1 = sleepy or very unpleasant, 9 = very excited or very pleasant) (Lang et al., 2005). A picture was placed into an emotional category when 18 or more volunteers selected the same category and when the mean of its arousal and valence rating was within a defined range. The emotional categories were fear [F, high arousal (6–9) and negative valence], sadness [S, moderate arousal (3–6) and negative valence], happiness [H, moderate arousal (3–6) and positive valence], and neutral [N, low arousal (1–3) and moderate valence]. Overall, we obtained 640 pictures, with a total of 160 for each emotional category. Pictures in each category were randomly divided into four sets, with each set containing 40 pictures. For each emotional category, two sets of pictures were used both in the encoding and recognition phase, while the other two sets were only used during the recognition phases as novel stimuli, or “foils”. Eighty colorful mosaic pictures created from the emotional pictures were selected as control pictures. Each control picture was composed of a  $6 \times 9$  mosaic of  $102 \times 102$  pixels per mosaic. The other 160 pictures from each of the four emotional categories were used to train the subjects before the experiment.

## 4. Paradigms and procedures

Each subject completed one phase of encoding and two phases of recognition, with one phase with an interval of 20 min for short-term recognition (RS) and another phase with an interval of 24 h for long-term recognition (RL). Functional MR images were only

acquired during the encoding phase, and behavioral data were obtained during the recognition phase.

To simplify the relationship between the subsequent memory effects and epochs, decrease the relative distinctiveness between trials, and control the effects of cognitive factors (Sommer et al., 2008; Talmi, 2007), blocking trials were used for encoding. According to the theory of mood-dependent memory, memory is facilitated when the mood at retrieval is matched to the mood at encoding (Lewis & Critchley, 2003). Blocking trials might induce subjects to have the same sustained mood at retrieval as that at encoding. Therefore, pure block design was applied to retrieval as well. Each functional scanning session lasted for 297 s and consisted of nine blocks (four emotional blocks and five control blocks) presented in an alternating fashion. Each block lasted for 33 s, which included a 3-s instruction at the beginning along with 10 trials with pictures from the same emotional category (emotional blocks) or mosaics (control blocks). In each trial, the picture was presented for 2 s and was followed by a 1-s black screen. In the emotional block, subjects were required to rate the picture on a three-point emotional intensity scale (1 = low, 2 = middle, and 3 = high) by pressing different buttons with the index, middle, and ring fingers of the right hand. They were also instructed to remember the picture. In control blocks, subjects were required to judge the color hue of the mosaic picture (1 = warm, 2 = cold) by pressing different buttons with the index and ring fingers of the right hand (Fig. 1).

For each subject, eight fMRI scanning sessions were acquired, with two sessions for each emotional category. One was defined as the short-term encoding session (ES), the pictures of which were used for short-term (i.e., 20 min) recognition. The other session was defined as the long-term encoding session (EL), the pictures of which were used for long-term (i.e., 24 h) recognition. The fMRI scanning sessions were separated by a 1-min resting period. Each emotional picture was presented only once during the entire fMRI scanning session. The sequences of functional scanning were randomized within each subject and were counterbalanced across subjects.

After the encoding phase, each subject completed a short-term recognition test (RS, 20-min delay) and a long-term recognition test (RL, 24-h delay) outside the scanner. Each phase consisted of four 240-s sessions, with one session for each emotional category. Each session included 80 pictures from one emotional category, 40 of which had been presented during the encoding phase (as target items) and 40 that had never been seen by the subjects (as foils). These pictures were each randomly presented for 3 s, and the subjects were instructed to judge whether each picture was “old” or “new” by pressing a key.

Two hours before the fMRI scanning, all subjects had been trained for the experiment. After the long-term recognition test, each subject was asked to rate the emotional arousal and valence of all emotional pictures on a nine-point scale (Lang et al., 2005).

## 5. Scanning procedures

All imaging data were obtained using a 1.5-T General Electric Medical Systems Signa MRI scanner at the first Affiliated Hospital of Anhui Medical University. A circularly polarized head coil was used with foam padding to restrict head motion. Functional images were acquired with T2\*-weighted echo-planar imaging sequences (TE = 40 ms, TR = 3 s, FOV = 22 cm, Matrix =  $64 \times 64$ ) and 30 axial slices (slice gap = 0.2 mm, voxel size:  $3.44 \times 3.44 \times 4$  mm<sup>3</sup>) encompassing the entire brain. Functional MRI data were acquired with eight sessions of 297 s (99 images per slice). Corresponding high-resolution T1-weighted spin-echo images (for anatomical

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