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NEURAL CORRELATES OF EMOTIONAL EVALUATION AND EMOTIONAL EPISODIC MEMORY: ELECTROPHYSIOLOGICAL AND HEMODYNAMIC EVIDENCE

by

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To Alex and Sanda

Abstract

Despite recent unprecedented progress in the cognitive neuroscience of emotion, a number of unsolved issues still remain. Among them, the temporal and spatial correlates of two types of emotional processing captured my attention: (1) the perception and categorization of emotional stimuli (*emotional evaluation*), and (2) the memory-enhancing effect of emotion (*emotional memory*). Two fundamental affective dimensions are of particular interest in the study of emotion: emotional *arousal* and emotional *valence. Arousal* refers to a continuum that varies from calm to excitement, whereas *valence* refers to a continuum that varies from positive to negative with neutral in the middle. In the present research, issues concerning the effect of arousal and valence on the neural correlates underlying emotional evaluation and emotional episodic memory were addressed using functional neuroimaging tools that allow both temporal (event-related potentials: ERPs) and spatial (functional magnetic resonance imaging: fMRI) measurements. The present dissertation covers the results of three studies. The first two studies (one ERP and one fMRI) focused on encoding processes to identify the effect of arousal and valence on the neural correlates of emotional evaluation and successful emotional encoding. The third study used fMRI and focused on retrieval processes to identify the effect of emotion on the neural mechanisms involved during successful retrieval of consolidated emotional memories. The main findings of these studies were that, while the neural correlates of emotional evaluation were sensitive to both arousal and valence, the neural mechanisms of emotional memory (during both encoding and retrieval) were mainly sensitive to arousal. The encoding studies also found clear evidence concerning the timing (faster emotional encoding), and location (e.g., medial-temporal lobe: MTL) of the mechanisms underlying the memory-enhancing effect of

emotion. The retrieval study revealed that similar MTL mechanisms were also involved during retrieval, and that activity in specific MTL subregions was sensitive to the degree of recollection associated with successful retrieval of remote emotional memories. Taken together, the present research brings novel evidence concerning the effect of emotion on the neural mechanisms underlying various aspects of emotional processing, from initial perception and evaluation to successful encoding and, later, successful retrieval of emotional memories.

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CHAPTER 1

INTRODUCTION

Among the multitude of stimuli comprising our environment, at any moment there are some stimuli that are more relevant to us than others. Consequently, those stimuli will more easily engage our processing resources. What is it, though, that makes some stimuli more important than others? To some extent, stimuli with virtually identical properties may still be preferentially processed because they better serve our current activities and goals. However, there are some stimuli that tend to "capture" our attention regardless of their relevance with respect to a given present activity. This latter category comprises emotional stimuli, which as a result of evolution and ontogenesis gained relevance that transcends that of present activities.

What are, though, the neural mechanisms that allow for such privileged access to processing resources that can make us both emotionally resonate and behave accordingly by approaching something that is desirable, or avoiding something that is potentially harmful? Also, what are the mechanisms that make possible the transition from the activity-specific to the more general relevance of these stimuli? Specifically, what are the mechanisms underlying our ability to encode, store, and retrieve information about our experiences, which ultimately allow us to distinguish what may be approached from what should be avoided? Finally, what alterations in these mechanisms are responsible for clinical conditions such as apathy, anxiety, depression, or post-traumatic stress disorders, and thus make us either diminish or enhance the significance of emotional situations?

These are only a few questions that people have tried to answer for centuries, and neuroscientists have fervidly engaged in answering, particularly during the last decades. Consequently, it is not surprising that the domain of *cognitive neuroscience of emotion* has grown dramatically during the last 15-20 years. Different approaches ranging from neuropsychological and pharmacological to functional neuroimaging have attempted to define the neural mechanisms underlying the operations associated with different aspects of emotional processing in both humans and animals (reviewed in Damasio, 1994; Davidson & Irwin, 1999; Davis & Whalen, 2001; Lane & Nadel, 2000; LeDoux, 2000; McGaugh, 2004; Phan, Wager, Taylor, & Liberzon, 2002; Phelps, 2004; Zald, 2003). As a result of this growth, important progress has been made in identifying the nature of

emotional phenomena and their relationship with other psychological processes, their most important characteristics, as well as their neural correlates.

Among the various psychological phenomena involving emotional processing in humans, two categories have received more attention in the literature on humans, namely *emotional evaluation* and *emotional memory*. *Emotional evaluation* refers to processing associated with the perception and categorization of emotional stimuli, and typically involves explicit rating of pleasantness for various stimuli (e.g., pictures or words). *Emotional memory* refers to processing associated with the modulatory effect of emotion on different stages of memory (e.g., encoding and/or retrieval), and typically involves episodic memory, which refers to explicit memory for personal events (Tulving, 1983).

As concerning the main features defining emotional phenomena, a critical distinction in the emotion literature is the one between two orthogonal affective dimensions: *arousal* and *valence* (Lang, Greenwald, Bradley, & Hamm, 1993; Russell, 1980). *Arousal* refers to a continuum that varies from calm to excitement, whereas *valence* refers to a continuum that varies from pleasant to unpleasant with neutral as an intermediate value (for methods to assess these dimensions, see Bradley & Lang, 1994). The importance of identifying and understanding these two dimensions comes into play when related to the behavioral consequences associated with them. Thus, translated into behavioral coordinates, emotional arousal gives the intensity of the emotional response, whereas emotional valence gives the direction of the response – positive valence is typically associated with approach, whereas negative valence is typically associated with withdrawal.

Important progress has also been made regarding the neural mechanisms underlying the operations associated with various aspects of emotional processing. From the early definition of the Papez circuit and limbic system (MacLean, 1955; Papez, 1937), a growing number of brain regions have been added to the neural networks associated with emotional processing. Among the brain regions most typically associated with emotional processing, the amygdala and the prefrontal cortices have received more attention, although the role of other regions, such as the ventral striatal, diencephalic, posterior parietal, and insula regions have also been explored (e.g., Damasio, 1994;

Davidson & Irwin, 1999; Davis & Whalen, 2001; Lane & Nadel, 2000; LeDoux, 1996; Phan et al., 2002). The amygdala has been associated with a variety of processing, from initial perception/identification of emotional cues and the production of emotional responses to emotional memory-related processing. Additionally, evidence suggests that the amygdala is particularly involved with processing of negative emotions, such as fear (Davis & Whalen, 2001; LeDoux, 1996; McGaugh, 2000; Phelps, 2004; Zald, 2003). The prefrontal cortical regions have been associated with processing that varies from aspects related to the rewarding nature of stimuli to those involved in emotional working memory operations and decision making processes, as well as with aspects concerning personality-related individual differences (Bechara, Damasio, & Damasio, 2000; Damasio, 1994; Davidson, 1995; Rolls, 2000).

A significant contribution to this progress has been made as a result of including functional neuroimaging methods among the techniques used to explore the neural correlates of emotional processing. Particularly important are non-invasive techniques, such as those involving electrophysiological (e.g., event-related potentials: ERP) or hemodynamic measurements (e.g., functional magnetic resonance imaging: fMRI). Non-invasive electrophysiological techniques, such as ERP, typically involve recording of electrical potentials thorough electrodes placed on the scalp. The most important quality of the ERP technique is that it offers excellent temporal resolution (at the level of milliseconds). Functional MRI typically involves measurements of blood flow, and is characterized by excellent spatial resolution (at the level of millimeters). It is important to note that both of these techniques involve measurements that are assumed to be associated with neural activity.

Despite this unprecedented progress in the field of cognitive neuroscience of emotion, a number of unsolved issues still remain. Among the less explored issues are aspects related to the effect of *arousal* and *valence* on the temporal and spatial correlates of *emotional evaluation* and *emotional memory* in neurologically intact human participants. The present research investigated a number of unsolved issues concerning the neural correlates of evaluation and emotional memory, using two complementary functional neuroimaging techniques: ERP and fMRI. The rationale for using these two

techniques is justified by the excellent temporal resolution provided by ERPs and the excellent spatial resolution provided by fMRI. Thus, by using these techniques it is possible to address both timing- and location-related issues concerning the effect of arousal and valence on the neural mechanisms underlying emotional evaluation and emotional memory. In the following paragraphs, I will introduce these techniques, provide details about the experimental paradigms involved, and then introduce the main issues identified and addressed in the present research.

Functional Neuroimaging and Behavioral Methods Employed

In the following paragraphs, I will provide an overview of the ERP and fMRI methods, by emphasizing their most important features. This will prove critical to the understanding of their importance in the study of cognitive processes, in general, and in the study of emotional phenomena, in particular. Then, I will provide details about the behavioral paradigm employed by the present research, and describe several key notions that will be helpful in understanding the usefulness of the methods used in the present approach. For more methodological details, readers are encouraged to see the methods sections accompanying each chapter.

I. The Event-Related Potential Technique

Event-related potential (ERP) recording is among the non-invasive techniques used to evaluate the activity of the human brain. ERPs are small fluctuations in the spontaneous electrical activity of the brain, usually recorded through electrodes placed on the scalp. One important feature of the ERP technique is that the recording of ERPs is time-locked to "events" that occur either in the external environment (e.g., the onset of a stimulus) or in the participants' minds (Picton, Lins, & Scherg, 1995; Rugg, 1995). For this reason and for others, which I will describe below, the ERP technique is very useful for the study of cognitive processes.

Among the most important reasons for the use of ERPs in the study of cognitive processes, three are critical for our understanding of the usefulness of this technique (Allan, Edward, & Rugg, 1998; Rugg, 1995). First, as already highlighted, neural activity associated with the processing of different classes of stimuli can be measured with a temporal resolution, which is sufficient to detect the neural correlates of cognitive

processes that may be active for only tens of milliseconds. This level of temporal resolution is not accessible to other functional neuroimaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Second, also in contrast to blocked PET and fMRI, ERP waveforms can be formed off-line after the experimental trials have been sorted into different conditions based on subjects' behavior (e.g., performance in a memory task). Third, ERPs can be used to investigate whether different experimental conditions engage functionally dissociable cognitive processes. For instance, comparing the ERPs associated with different categories of stimuli (e.g., emotional vs. neutral) can provide insight into the neural mechanisms underlying the cognitive operations involved in their processing.

There also are limitations to this technique. The most evident limitation is related to the possibility of establishing with precision the neural sources of the ERPs. More specifically, it is difficult to clearly identify the brain regions generating the potentials associated with different experimental conditions. Other limitations arise because ERP waveforms can only be used to study processes that are time-locked to some detectable event. For example, activities such as rehearsal of free recall cannot be studied with the current ERP techniques (Rugg, 1995).

To understand the usefulness of ERPs in the study of cognitive processes, it is also important to understand (1) the assumptions that are at the basis of using this technique in cognitive studies, and (2) to know how ERP data are typically analyzed and interpreted. As concerning the first issue, the use of ERPs is based on the following three assumptions (Rugg, 1995): (i) it is assumed that there is a relationship between the latency and the amplitude of ERP waves, and the timing and the strength of activity in the neural populations generating it; (ii) it is assumed that ERP effects with qualitatively different scalp distributions reflect different patterns of neural activity in the brain; (iii) finally, it is also assumed that different patterns of neural activity are most probably identifiable with functionally dissociable cognitive processes.

As concerning the second issue, an important preliminary step in understanding ERP data analysis and interpretation is knowing the ERP nomenclature. The most common ERP nomenclature is based on the identification of various ERP components,

which are most typically described in terms of their polarity and peak-latency (Picton et al., 1995). For example, P300 is a positive component occurring with a latency of 300 ms (i.e., at 300 m after the onset of an event). Data analysis typically involves selective averaging of the ERPs associated with the conditions of interest (e.g., emotional vs. neutral, remembered vs. forgotten, etc.), performed individually, and statistical tests (e.g., *t* tests and/or analyses of variance: ANOVAs) performed across individual data.

Finally, the interpretation of the results typically considers the following six assumptions when inferences are made with respect to the neural mechanisms reflected in ERP differences (Ganis, Kutas, & Sereno, 1996). (1) If the ERP components associated with various experimental conditions (i.e., stimulus categories) are identical in their onset and/or peak-latency, amplitude, and distribution, there is strong evidence that they involve common brain mechanisms. (2) If the ERP components differ only in terms of latency, it is assumed that, although the stimulus conditions involve common processes, the stimulus class showing shorter latencies has privileged access to processing resources. (3) If the ERP components differ only in amplitude, there is also evidence for the involvement of a common neural system. However, the stimulus class showing larger amplitudes may require more processing resources. (4) If an ERP component is absent from the ERPs associated with one class of stimuli, there is weak evidence that the stimuli engage functionally dissociable cognitive processes. (5) If ERPs are similar in morphology but differ in their topographical distribution, it is assumed that both stimuli are processed in similar ways by different brain areas. (6) Finally, if the ERP effects differ in both morphology and distribution, there is strong evidence for functionally dissociable cognitive operations underlying the processing of the conditions compared.

II. The Event-Related Functional Magnetic Resonance Imaging Technique

Functional magnetic resonance imaging (fMRI) is the most advanced technique available to image the functioning brain. It involves recording of fluctuations in the fMR signal, assumed to reflect changes in neural activity associated with various tasks. The most advanced features of the fMRI technique include the possibility of recording the fMR signal on a trial-by-trial basis, in an event-related fashion (i.e., event-related fMRI: ER-fRMI). Thus, similar to ERP recordings, fluctuations in fMR signal can be time-

locked to events/stimuli, and the fMRI data can be selectively analyzed off-line according to the categories of stimuli involved (e.g., emotional vs. neutral), or based on the subjects' performance (e.g., memory performance: remembered vs. forgotten). The ultimate goal of the fMRI recordings is the construction of functional maps of the brain in action ("activation maps"), which can be used to identify the neural correlates of the operations associated with various psychological phenomena. Different from ERP, though, fMRI provides excellent spatial resolution (millimeters), and thus it can be used to investigate more precisely whether different experimental conditions engage functionally dissociable cognitive processes (for a through review of fMRI-related issues, see Huettel, Song, & McCarhty, 2004).

For a better understanding of the fMRI technique, it is important to know the basic principles of the MR recordings, as well as the difference between the *anatomical* and the *functional* MRI. Below, I will briefly describe the basic principles of MRI, then highlight the difference between anatomical and functional MRI. MR recordings rely on the magnetic properties of protons, which are abundantly present in biological tissues. Normally, protons have a random orientation in the tissue, but when exposed to a powerful magnetic field they tend to become aligned to the orientation of the magnetic field. If a second magnetic field (usually a radio frequency pulse) is applied perpendicular to the main magnetic field, the protons start wobbling around their axes. As a result of the wobbling, a rotating magnetic field is produced, and associated with it an electrical current is generated. In short, it is ultimately the fluctuations of this current that are measured by MRI.

Both anatomical and functional MR recordings rely on the same fundamental principles, as summarized above, but the protocols used in anatomical and functional imaging are slightly different. Anatomical MRI relies on differences in the magnetic properties of the protons that vary depending on the nature of the tissue incorporating them (e.g., neural tissue vs. fat). Since differences in magnetic properties are reflected in the properties of the associated electrical currents and ultimately in the MR signal, different tissues will produce distinguishable contrasts in reconstructed MR images. The most popular functional MRI method, on the other hand, is based on measuring the so-

called BOLD (Blood-Oxygenation-Level Dependent) signal, and depends on the magnetic properties of specific chemical constituents of the blood (i.e., hemoglobin) perfusing the tissues. The critical difference in the fMRI contrasts involving BOLD signal is given by the opposite magnetic properties of the oxygenated and deoxygenated hemoglobin: oxyhemoglobin has magnetic properties (it is diamagnetic), whereas deoxyhemoglobin lacks them (it is paramagnetic). Consequently, the two forms of hemoglobin affect differently the magnetic properties of the surrounding tissue, and ultimately the fMR signal (which depends on the ratio between them) - more oxyhemoglobin is associated with greater fMR signal.

The next step in understanding the usefulness of the fMRI technique as an important cognitive neuroscience tool is answering the following two questions. (1) Is there a direct relationship between the fMR signal and neural activity? (2) What is the relationship between the oxy-/deoxyhemoglobin ratio and neural activity? Answering these questions will help understand what is actually measured with fMRI, and which are the most important assumptions that we need to consider when interpreting fMRI data. A short answer to the first question is no. Different intensities in the fMRI signal do not reflect direct changes in neural activity, but as noted above they reflect changes in the ratio between oxyhemoglobin and dexyhemoglobin - greater fMR signal is associated with the presence of more oxyhemoglobin. An important assumption here concerning the relationship between the oxy-/deoxyhemoglobin ratio and neural activity is that more intense neural activity is associated with increased delivery of oxygenated blood to the active regions. Consequently, greater concentration of oxyhemoglobin is available to the active neurons. However, the rate of oxygenation surpasses the rate of oxygen-consumption, and thus leads to increased oxy-/deoxyhemoglobin ratio, which in turn produces increased MR signal. In sum, it is this assumed indirect relationship between the neural activity and the intensity of the fMR signal that substantiate the use of fMRI to study the neural correlates of psychological processes.

Analysis of fMRI data, particularly if it involves event-related designs, is similar to analysis of ERP data. By comparing the fMRI signal associated with various tasks, one can make assumptions about the underlying neural mechanisms, and obtain insight

concerning the operations associated with them. For instance, by comparing brain activity associated with a more complex task to brain activity associated with a simpler task (used as control), one can make inferences concerning the neural correlates of the operations that distinguish the more complex task from the simpler task. And, as more complex tasks are assumed to be the result of adding operations associated with simpler tasks, the method of subtraction is the most commonly used in the fMRI studies (for more details, see Huettel et al., 2004). Statistical analysis of fMRI data typically involves individual and group analyses aimed at identifying statistically significant differences in brain activity associated with the conditions of interest (e.g., emotional vs. neutral, remembered vs. forgotten). Finally, statistical analyses can be done at the level of the whole brain, or can be focused on specific regions of interest (ROIs). Below, I will describe the experimental methods employed in our studies and highlight their most important features, which are critical to understand the present research.

III. The Subsequent Memory Paradigm

As mentioned above, an important feature of event-related designs is that they can measure brain activity associated with stimuli/events on a trial-by-trial basis. This flexibility in the way ERP and ER-fMRI data can be analyzed has led to substantial improvement in experimental designs. Among the best examples is the so-called *subsequent memory paradigm*. This paradigm has been initially used in ERP studies (e.g., Paller, Kutas, & Mayes, 1987), but recently it has also been extensively used in ER-fMRI studies (Paller & Wagner, 2002). The critical feature of this paradigm is that brain activity recorded using ERP or ER-fMRI can be selectively averaged based on memory performance. For instance, one can compare activity for items that are remembered vs. forgotten in a memory test, and thus can make inferences about brain activity that is associated with memory performance.

Comparison of activity for remembered vs. forgotten items can involve brain activity recorded during encoding and/or during retrieval. The subsequent memory paradigm has been initially used during encoding to measure the so-called *subsequent memory effect*. This effect represents the difference during encoding between brain activity for items that are subsequently remembered and brain activity for items that are

subsequently forgotten. In such an experimental design, participants are presented with a series of items (e.g., pictures, words), while their brain activity is measured using ERP or ER-fMRI. The subjects are either instructed to voluntarily memorize the list of items (intentional learning), or not given any memory-related instructions (incidental learning). Following the encoding phase, subjects' memory for the presented items is tested, and memory performance is used to separate the ERP/ER-fMRI data according to whether the items were subsequently remembered or forgotten. ERP/ER-fMRI data for remembered and forgotten items are then compared to each other. The difference in activity between these two categories of items is assumed to reflect a difference in memory (Dm), and, if measured during encoding, it is called the *subsequent memory effect*. Typically, brain regions in which activity during encoding is greater for subsequently remembered than for subsequently forgotten items are associated with *encoding success*. If, on the other hand, the difference in activity for remembered and forgotten items is measured not during the initial encoding stage but during the actual retrieval, brain regions showing memory-related differences (i.e., remembered > forgotten) are associated with *retrieval success*.

Emotion Effect / Memory effect / Modulatory Effect of Emotion on Memory

An important feature of the subsequent memory paradigm, particularly in studies of emotion, is that, in addition to comparing brain activity for remembered vs. forgotten items, it also allows simpler comparisons that do not take into account memory performance. For instance, one can look at differences in brain activity for emotional vs. non-emotional items regardless of whether the items are remembered or forgotten in a subsequent memory test. Using this simpler comparison, electrophysiological (e.g., ERP) and hemodynamic (e.g., fMRI) studies identified the so-called *emotion effect*. In ERP studies, the emotion effect is expressed as a difference in amplitude between the ERPs for emotional stimuli (pleasant and/or unpleasant) vs. neutral stimuli (e.g., Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Johnston, Miller, & Burleson, 1986; Naumann, Maier, Diedrich, Becker, & Bartussek, 1997). Similarly, in fMRI studies, the emotion effect is expressed as greater activity for emotional vs. neutral stimuli in the brain regions involved in emotional processing (e.g., Phan et al., 2002; Wager, Phan, Liberzon, &

Taylor, 2003). Activity in these regions can, for instance, be found in tasks involving evaluation of emotional content of various stimuli (e.g., rating stimuli for pleasantness).

The emotion effect identified in the electrophysiological and hemodynamic studies is assumed to have similar neural generators. Since the spatial resolution of ERPs does not allow precise identification of the neural generators of the ERP emotion effect, it is defined in terms of ERP components (e.g., timing, amplitude), and roughly in terms of their scalp location (e.g., anterior-frontal vs. posterior-parietal/occipital, etc). For instance, explained in terms of ERP nomenclature, the ERP emotion effect is most consistently evident after 300 ms following stimulus onset and is maximal over the frontal and parietal scalp locations. The neural generators of the ERP emotion effect are not known, but it is reasonable to assume that it reflects interactions between the amygdala and the cortical regions (e.g. lateral and medial prefrontal, and parieto-occipital areas) that are typically associated with emotional processing in the animal and human literature (for reviews, see Davidson & Irwin, 1999; Lane et al., 1997; LeDoux, 2000; McGaugh, 2004; Phan et al., 2002; Wager et al., 2003; Zald, 2003).

Turning to the *memory effect*, as mentioned above, memory-related differences in brain activity can be assessed during both encoding and retrieval. The brain regions most typically associated with episodic memory function are the prefrontal cortical (PFC) and the medial-temporal lobe (MTL) regions (e.g., Eichenbaum, 2000; Moscovitch, 1992; Squire & Knowlton, 2000). Consistent with the involvement of these regions in episodic memory operations, numerous functional neuroimaging studies have identified *subsequent memory effects* (i.e., greater activity during encoding for remembered vs. forgotten items) in PFC and MTL regions (e.g., Cabeza & Nyberg, 2000; Paller & Wagner, 2002; Rugg, Otten, & Henson, 2002). Thus, these brain regions have been associated with *encoding success*. However, the comparison between activity for remembered vs. forgotten items has rarely been employed during retrieval, to identify the brain regions associated with *retrieval success* (but see Prince, Daselaar, & Cabeza, submitted; Weis, Klaver, Reul, Elger, & Fernandez, 2004). Furthermore, successful encoding and/or retrieval activity has rarely been compared for emotional vs. neutral items.

Comparison of successful encoding/retrieval activity for emotional and neutral items allows identification of the brain regions underlying the *modulatory effect of emotion on memory*, and thus can possibly explain the neural mechanisms underlying the memory-enhancing effect of emotion. For instance, during encoding one can look at successful encoding activity (remembered stimuli – forgotten stimuli = Dm) separately for emotional and neutral stimuli, to measure an emotional Dm (remembered emotional stimuli - forgotten emotional stimuli) and a neutral Dm (remembered neutral stimuli – forgotten neutral stimuli). Most critically, however, to assess the modulatory effect of emotion on memory-related brain activity during encoding, it is crucial to directly compare the emotional and the neutral Dms and thus identify the brain regions where successful encoding activity is greater for emotional than for the neutral stimuli. Similarly, during retrieval, one can identify the brain regions where successful retrieval activity is greater for emotional than for the neutral stimuli.

The present research employed the subsequent memory paradigm to investigate issues concerning the *emotion effect*, the *memory effect*, as well as the *modulatory effect of emotion on memory* during both encoding and retrieval of episodic memories in neurologically intact human subjects. More specifically, the effect of emotional *arousal* and *valence* on the neural mechanisms associated with the aforementioned phenomena was examined using ERP and ER-fMRI measurements. Three studies were conducted. The first two studies (one ERP and one ER-fMRI) focused on encoding, and the third (also ER-fMRI) focused on retrieval. In the following paragraphs, I will provide more details concerning the unsolved issues identified and addressed in these studies.

Unsolved Issues

Study I. Effect of emotion on brain activity associated with emotional evaluation and emotional memory encoding – ERP evidence

I.1. Effect of arousal and valence on ERP correlates of emotional evaluation. Among the unclear issues concerning the ERP emotion effect associated with emotional evaluation, two were identified as being critical for our understanding of the ERP correlates of emotional evaluation. First, it is unclear whether the emotion effect is only

sensitive to arousal (emotional vs. neutral) or to both arousal and valence (pleasant vs. unpleasant). Whereas most studies have only found differences due to arousal (for a brief review, see Diedrich, Naumann, Maier, & Becker, 1997), a few recent studies have also reported differences that could be attributed to emotional valence (Cuthbert et al., 2000; Diedrich et al., 1997). Second, if the emotion effect is sensitive to both arousal and valence, it is unclear if these two dimensions can be dissociated in their topographical and/or temporal characteristics. There is some evidence that valence-related differences tend to be larger in anterior electrodes (Cuthbert et al., 2000; Diedrich et al., 1997), but such topographical dissociation has not been clearly demonstrated by previous ERP studies.

I.2. ERP correlates of the modulatory effect of emotion on memory formation. As concerning the ERP correlates of the modulatory effect of emotion on memory formation, the main goal was to investigate the relationship between the emotion effect and the subsequent memory effect. That is, considering together the memory advantage for emotional stimuli and the ERP positivity associated with both the emotion effect and the subsequent memory effect, one may predict that the beneficial effect of emotion on memory performance would appear as an interaction between the emotion effect and the subsequent memory effect. However, no study reported evidence supporting this idea, and hence it was investigated in the present ERP study. These issues along with the associated findings are discussed in detail in Chapter 2.

Study II. Effect of emotion on brain activity associated with emotional evaluation and emotional memory encoding – fMRI evidence

The interest in identifying the neural correlates of various operations associated with emotional processing is reflected in the large number of neuroimaging studies of emotion (for reviews, see Phan et al., 2002; Wager et al., 2003). Nevertheless, several issues such as the role of subcortical (e.g., the amygdala) and cortical (e.g., PFC) brain regions during emotional evaluation and emotional memory formation remain unclear. The present study addressed several critical issues that are highly debated in the neuroimaging literature. This was possible due to the experimental design used, which, similar to the ERP study, employed both manipulation of the emotional content of the

stimuli and the use of the subsequent memory paradigm. Thus, this design allowed dissociations of the arousal- and valence-related effects on the neural correlates of emotional evaluation and emotional memory formation. The effect of arousal was defined as greater activity for both positive and negative pictures than for neutral pictures, and the effect of valence was defined as differences between activity for positive and negative pictures. Below, I will briefly introduce the issues addressed in the fMRI study of encoding.

II.1. Role of the amygdala during emotional evaluation. Animal, lesion, and neuroimaging evidence (e.g., Adolphs, Tranel, Damasio, & Damasio, 1994; LeDoux, 2000; Phan et al., 2002; Zald, 2003) has strongly associated the amygdala with the processing of unpleasant stimuli, but it is less clear how this region is involved in the processing of pleasant stimuli. To investigate this issue, amygdalar activity recorded during the rating task was directly compared for pleasant vs. unpleasant pictures. The findings related to this issue are discussed in Chapter 3.

II.2. Role of the prefrontal cortex during emotional evaluation. The vast majority of studies have focused on the limbic system and particularly on the amygdala, whereas other components of the emotional processing network, such as PFC regions, have received relatively less attention. To address this imbalance, the present study also investigated the effects of arousal and valence on prefrontal activity associated with emotional evaluation. The findings related to this issue are discussed in Chapter 5.

II.3. Role of the amygdala and the MTL memory regions during emotional memory formation. According to the *modulation hypothesis* (McGaugh, 2000; McGaugh, Cahill, & Roozendaal, 1996; McGaugh, McIntyre, & Power, 2002), emotional events are remembered better than neutral events possibly because the amygdala enhances the function of medial temporal lobe (MTL) memory structures, including the hippocampus and associated parahippocampal regions (Squire & Zola-Morgan, 1991). Although the modulation hypothesis is supported by a considerable amount of evidence from nonhuman animals (Cahill & McGaugh, 1998; McGaugh, 2000, 2002; McGaugh et al., 2002), evidence from humans is scarce and indirect. For instance, from neuropsychological studies of patients with amygdalar lesions (Adolphs, Cahill, Schul, &

Babinsky, 1997; Adolphs, Tranel, & Denburg, 2000; Cahill, Babinsky, Markowitsch, & McGaugh, 1995; LaBar & Phelps, 1998; Phelps et al., 1998), it is unclear whether the deficits in memory performance for emotional items reflect a lack of amygdalar modulation or the damage of neighboring MTL regions. Also, despite the better spatial resolution provided by functional neuroimaging studies, they have not yet provided complete evidence for the modulation hypothesis. Thus, the main goal was to test the hypothesis that better memory for emotional events than for neutral events is due to an effect of the amygdala on the MTL memory system during encoding (*modulation hypothesis*).

The employment of the subsequent memory paradigm (Paller et al., 1987; Paller & Wagner, 2002) was critical in this pursuit because it allows the identification of subsequent memory (Dm) effects for both emotional (emotional Dm) and neutral (neutral Dm) items, which then can be compared to each other (emotional Dm versus neutral Dm) to identify the brain regions responsible for the modulatory effect of emotion on memory formation. That is, the effects of emotion on successful encoding activity can be revealed by identifying regions where the emotional Dm is greater than the neutral Dm. As described in Chapter 2, the ERP study (Dolcos & Cabeza, 2002) identified significant differences between emotional and neutral Dms, but the ERP method did not provide a precise localization of the neural generators of the observed differences. Thus, in the present study encoding-related activity from MTL regions was obtained using event-related fMRI. Also, to obtain greater spatial resolution in recording activity from these neighboring regions, activity in the amygdala and the MTL memory regions was identified using manually-traced anatomical regions-of-interest (ROIs). The findings related to this issue are discussed in Chapters 3 & 4.

II.4. Role of the PFC regions during emotional memory formation. Although the findings concerning the modulation hypothesis (see Chapters 3 & 4) strongly link the memory-enhancing effect of emotion to an MTL mechanism, it does not exclude the possibility that other brain regions, such as PFC, also play a major role. In fact, in functional neuroimaging studies, PFC regions are as strongly associated with successful encoding operations as MTL regions (e.g., Brewer, Zhao, Desmond, Glover, & Gabrieli,

1998; Paller & Wagner, 2002; Wagner et al., 1998). Thus, it is quite likely that the enhancing effect of emotion on encoding is mediated not only by MTL but also by PFC. Yet, very little is known about the role of PFC on emotional memory formation (see however Canli, Desmond, Zhao, & Gabrieli, 2002). For example, it is uncertain if the Dm effect in PFC is enhanced by emotion, similar to what was found in MTL (see Chapters 3 & 4). It is also unclear whether this putative effect is due to arousal or valence, and which specific PFC regions are involved. Thus, the role of PFC in emotional memory formation was also investigated. The findings related to this issue are discussed in Chapter 5.

Study III. ***Effect of emotion on brain activity associated with emotional memory retrieval – fMRI evidence***

III.1. Role of the amygdala and the MTL memory regions during retrieval of remote emotional memory. Despite abundant neuroimaging evidence now available to support the existence of MTL-mediated mechanisms responsible for the memory-enhancing effect of emotion during encoding (Canli et al., 2002; Dolcos, Graham, LaBar, & Cabeza, 2003; Dolcos, LaBar, & Cabeza, 2004; Hamann, Ely, Grafton, & Kilts, 1999; Kensinger & Corkin, 2004; Kilpatrick & Cahill, 2003; Richardson, Strange, & Dolan, 2004), it is not clear whether the same mechanisms are also engaged during retrieval. The animal literature suggests that the amygdala is involved in both emotional memory encoding (McGaugh, 2004) and retrieval (LeDoux, 2000), but the exact nature of its involvement during retrieval is a matter of current debate (Nadel, 2000; Nader, 2003). The situation in the functional neuroimaging literature is very similar. Although there are a few neuroimaging studies of emotional memory retrieval (Dolan, Lane, Chua, & Fletcher, 2000; Fossati et al., 2004; Kosslyn et al., 1996; Maratos, Dolan, Morris, Henson, & Rugg, 2001; Smith, Henson, Dolan, & Rugg, 2004; Taylor et al., 1998), evidence supporting the involvement of the amygdala and MTL memory regions during successful retrieval of remote emotional memories is inconclusive. Thus, the first goal of the fMRI study of retrieval was to measure activity in the amygdala and the MTL memory regions during retrieval of remote emotional memories.

III.2. Effect of emotion on retrieval activity associated with recollection and familiarity. In addition to the general issue concerning the effect of emotion on the neural

correlates underlying memory retrieval, another issue concerns the more specific effect of emotion on the neural mechanisms associated with different types of memory retrieval processes. One such distinction refers to differences between the neural mechanisms associated with recollection- vs. familiarity-based retrieval operations. That is, memories for personal events are not always equally retrieved. Some of them can be fully recollected – we can *remember* rich details about the time and place the events took place. Others are only familiar to us - we just *know* of their occurrence, but cannot retrieve specific details.

The theoretical models proposing such dissociations are not new in the memory literature, but have only recently received support from neuroimaging studies (for a review, see Yonelinas, 2002). Although several studies have reported results supporting the existence of different neural mechanisms underlying these two types of memory retrieval (Dobbins, Rice, Wagner, & Schacter, 2003; Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Henson, Rugg, Shallice, Josephs, & Dolan, 1999), it is not clear how emotion modulates activity in the brain regions involved in the distinction between what we *remember* or just *know*. This issue is particularly interesting since it is known from behavioral studies that emotion tends to enhance the degree of recollection (e.g., Ochsner, 2000; Talarico, LaBar, & Rubin, in press). Thus, it is possible that emotional arousal enhances activity in the brain regions underlying the ability to successfully recollect details of the study episodes. However, to date no neuroimaging study has investigated this idea. Therefore, the second goal of the retrieval study was to examine the effect of emotion on the neural mechanisms subserving retrieval activity based on recollection vs. familiarity. These issues and the accompanying results are discussed in Chapter 6.

Thesis Overview

The goal of the present research is to investigate unsolved issues concerning the effect of arousal and valence on the neural correlates of emotional evaluation and emotional episodic memory. Three studies were employed to address these uncertainties, involving two complementary functional neuroimaging methods – one offering excellent temporal resolution (i.e., ERP), and the other offering excellent spatial resolution (i.e.,

ER-fMRI). The first two studies (one ERP and one fMRI) focused on aspects related to the initial perceptual processing and episodic memory encoding operations, whereas the third study focused on processing associated with retrieval from episodic memory. The chapter structure of the thesis is as follows. Chapter 2 focuses on the effect of arousal and valence on the ERP correlates of emotional evaluation and successful encoding of emotional memories, with an emphasis on temporal and spatial dissociations. Chapters 3-5 focus on the effect of arousal and valence on the fMRI correlates of emotional evaluation and successful encoding of emotional memories, with an emphasis on MTL and PFC mechanisms. Chapter 6 focuses on the fMRI correlates of successful emotional retrieval, following a lengthy retention interval. This study also emphasizes the dissociable effect of arousal on the MTL mechanisms contributing to recollection vs. familiarity. Finally, Chapter 7 summarizes the key findings of the present research and discusses their significance. All five chapters addressing the issues introduced above are either published (Chapters 2-5) or submitted for publication (Chapter 6). Therefore, to keep the content of the chapters as close to the submitted versions as possible, the manuscripts were only slightly changed when organized as separate chapters.

References

Adolphs, R., Cahill, L., Schul, R., & Babinsky, R. (1997). Impaired declarative memory for emotional material following bilateral amygdala damage in humans. *Learn Mem, 4*(3), 291-300.

Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. (1994). Impaired recognition of emotions in facial expressions following bilateral damage to the human amygdala. *Nature, 372*, 699-672.

Adolphs, R., Tranel, D., & Denburg, N. (2000). Impaired emotional declarative memory following unilateral amygdala damage. *Learn Mem, 7*(3), 180-186.

Allan, K., Edward, L., & Rugg, M. D. (1998). Electrophysiological evidence for dissociable processes contributing to recollection. *Acta Psychologica, 1998*, 231-252.

Bechara, A., Damasio, H., & Damasio, A. R. (2000). Emotion, decision making and the orbitofrontal cortex. *Cereb Cortex, 10*(3), 295-307.

Bradley, M. M., & Lang, P. J. (1994). Measuring emotion: The self-assessment manikin and the semantic differential. *J. Behav. Ther. & Exp.Psychiat., 25*(1), 49-59.

Brewer, J. B., Zhao, Z., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (1998). Making memories: Brain activity that predicts how well visual experience will be remembered. *Science, 281*, 1185-1187.

Cabeza, R., & Nyberg, L. (2000). Imaging cognition II: An empirical review of 275 PET and fMRI studies. *J. Cogn. Neurosci., 12*(1), 1-47.

Cahill, L., Babinsky, R., Markowitsch, H., & McGaugh, J. L. (1995). The amygdala and emotional memory. *Nature, 377*, 295-296.

Cahill, L., & McGaugh, J. L. (1998). Mechanisms of emotional arousal and lasting declarative memory. *Trends Neurosci, 21*(7), 294-299.

Canli, T., Desmond, J. E., Zhao, Z., & Gabrieli, J. D. E. (2002). Sex differences in the neural basis of emotional memories. *Proc Natl Acad Sci U S A, 99*(16), 10789-10794.

Cuthbert, B. N., Schupp, H. T., Bradley, M. M., Birbaumer, N., & Lang, P. J. (2000). Brain potentials in affective picture processing: Covariation with autonomic arousal and affective report. *Biological Psychology, 52*, 95-111.

Damasio, A. R. (1994). *Descartes' Error.* New York, NY: Putnam.

Davidson, R. J. (1995). Cerebral asymmetry, emotion and affective style. In R. J. Davidson & K. Hugdahl (Eds.), *Brain Asymmetry* (pp. 361-387): MIT Press.

Davidson, R. J., & Irwin, W. (1999). The functional neuroanatomy of emotion and affective style. *Trends in Cognitive Sciences, 3*(1), 11-20.

Davis, M., & Whalen, P. J. (2001). The amygdala: Vigilance and emotion. *Mol Psychiatry, 6*(1), 13-34.

Diedrich, O., Naumann, E., Maier, S., & Becker, G. (1997). A frontal positive slow wave in the ERP associated with emotional slides. *Journal of Psychophysiology, 11*(1), 71-84.

Dobbins, I. G., Rice, H. J., Wagner, A. D., & Schacter, D. L. (2003). Memory orientation and success: Separable neurocognitive components underlying episodic recognition. *Neuropsychologia, 41*, 318-333.

Dolan, R. J., Lane, R., Chua, P., & Fletcher, P. (2000). Dissociable temporal lobe activations during emotional episodic memory retrieval. *Neuroimage, 11*(3), 203-209.

Dolcos, F., & Cabeza, R. (2002). Event-related potentials of emotional memory: Encoding pleasant, unpleasant, and neutral Pictures. *Cogn, Affect, & Behav Neurosci, 2*(3), 252-263.

Dolcos, F., Graham, R., LaBar, K., & Cabeza, R. (2003). Coactivation of the amygdala and hippocampus predicts better recall for emotional than for neutral pictures. *Brain and Cognition, 51*, 221-223.

Dolcos, F., LaBar, K. S., & Cabeza, R. (2004). Interaction between the amygdala and the medial temporal lobe memory system predicts better memory for emotional events. *Neuron, 42*, 855-863.

Eichenbaum, H. (2000). A cortical-hippocampal system for declarative memory. *Nat Rev Neurosci, 1*(1), 41-50.

Eldridge, L. L., Knowlton, B. J., Furmanski, C. S., Bookheimer, S. Y., & Engel, S. A. (2000). Remembering episodes: A selective role for the hippocampus during retrieval. *Nature Neuroscience, 3*(11), 1149-1152.

Fossati, P., Hevenor, S. J., Lepage, M., Graham, S. J., Grady, C., Keightley, M. L., Craik, F. I., & Mayberg, H. S. (2004). Distributed self in episodic memory: Neural correlates of successful retrieval of self-encoded positive and negative personality traits. *Neuroimage, 22*, 1596-1604.

Ganis, G., Kutas, M., & Sereno, M. I. (1996). The search for 'common sense': An electrophysiological study of the comprehension of words and pictures in reading. *Journal of Cognitive Neuroscience, 8*(2), 89-106.

Hamann, S. B., Ely, T. D., Grafton, S. T., & Kilts, C. D. (1999). Amygdala activity related to enhanced memory for pleasant and aversive stimuli. *Nat Neurosci, 2*(3), 289-293.

Henson, R. N. A., Rugg, M. D., Shallice, T., Josephs, O., & Dolan, R. J. (1999). Recollection and familiarity in recognition memory: An event-related functional magnetic resonance imaging study. *The Journal of Neuroscience, 19*(10), 3962-3972.

Huettel, S. A., Song, A. W., & McCarhty, G. (2004). *Functional Magnetic Resonance Imaging* (1st ed.). Sunderland, MA: Sinauer Associates.

Johnston, V. S., Miller, D. R., & Burleson, M. H. (1986). Multiple P3s to emotional stimuli and their theoretical significance. *Psychophysiology, 23*(6), 684-694.

Kensinger, E. A., & Corkin, S. (2004). Two routes to emotional memory: Distinct neural processes for valence and arousal. *Proc Natl Acad Sci U S A, 101*(9), 3310-3315.

Kilpatrick, L., & Cahill, L. (2003). Amygdala modulation of parahippocampal and frontal regions during emotionally influenced memory storage. *NeuroImage, 20*(4), 2091-2099.

Kosslyn, S. M., Shin, L. M., Thompson, W. L., McNally, R. J., Rauch, S. L., & Pitman, R. K. (1996). Neural effects of vizualizing and perceiving aversive stimuli: A PET investigation. *Neuroreport, 7*, 1569-1576.

LaBar, K. S., & Phelps, E. A. (1998). Arousal-mediated memory consolidation: Role of the medial temporal lobe in humans. *Psychol Sci, 9*(6), 490-493.

Lane, D. R., & Nadel, L. (2000). *Cognitive Neuroscience of Emotion*. New York: Oxford University Press, Inc.

Lane, R. D., Reiman, E. M., Bradley, M. M., Lang, P. J., Ahern, G. L., Davidson, R. J., & Schwartz, G. E. (1997). Neuroanatomical correlates of pleasant and unpleasant emotion. *Neuropsychologia, 35*(11), 1437-1444.

Lang, P. J., Greenwald, M. K., Bradley, M. M., & Hamm, A. O. (1993). Looking at pictures: Affective, facial, visceral, and behavioral reactions. *Psychophysiol, 30*(3), 261-273.

LeDoux, J. E. (1996). *The Emotional Brain*. New York, NY: Simon & Shuster.

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annu. Rev. Neurosci., 23*, 155-184.

MacLean, P. D. (1955). The limbic system ("visceral brain") and emotional brain. *Arch Neurol Psych, 73*, 130-134.

Maratos, E. J., Dolan, R. J., Morris, J. S., Henson, R. N., & Rugg, M. D. (2001). Neural activity associated with episodic memory for emotional context. *Neuropsychologia, 39*(9), 910-920.

McGaugh, J. L. (2000). Memory-a century of consolidation. *Science, 287*(5451), 248-251.

McGaugh, J. L. (2002). Memory consolidation and the amygdala: A systems perspective. *Trends Neurosci, 25*(9), 456-461.

McGaugh, J. L. (2004). The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annu. Rev. Neurosci., 27*, 1-28.

McGaugh, J. L., Cahill, L., & Roozendaal, B. (1996). Involvement of the amygdala in memory storage: Interaction with other brain systems. *Proc Natl Acad Sci U S A, 93*, 13508-13514.

McGaugh, J. L., McIntyre, C. K., & Power, A. E. (2002). Amygdala modulation of memory consolidation: Interaction with other brain systems. *Neurobiology of Learning and Memory, 78*(3), 539-552.

Moscovitch, M. (1992). Memory and working-with-memory: A component process model based on modules and central systems. *Journal of Cognitive Neuroscience, 4*, 257-267.

Nadel, L. (2000). Memory traces revisited. *Nat Rev Neurosci, 1*(209-12).

Nader, K. (2003). Memory traces unbound. *Trend Neurosci, 26*(2), 65-72.

Naumann, E., Maier, S., Diedrich, O., Becker, G., & Bartussek, D. (1997). Structural, semantic, and emotion-focused processing of neutral and negative nouns: Event-related potential correlates. *Journal of Psychophysiology, 11*(2), 158-172.

Ochsner, K. N. (2000). Are affective events richly recollected or simply familiar? The experience and process of recognizing feelings past. *J Exp Psychol Gen, 129*(2), 242-261.

Paller, K. A., Kutas, M., & Mayes, A. R. (1987). Neural correlates of encoding in an incidental learning paradigm. *Electroenc Clin Neuropsychol, 67*, 360-371.

Paller, K. A., & Wagner, A. D. (2002). Observing the transformation of experience into memory. *Trends Cogn Sci, 6*(2), 93-102.

Papez, J. W. (1937). A proposed mechanism of emotion. *Arch Neurol Psych, 38*, 725-743.

Phan, K. L., Wager, T., Taylor, S. F., & Liberzon, I. (2002). Functional neuroanatomy of emotion: A meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage, 16*(2), 331-348.

Phelps, E. A. (2004). Human emotion and memory: Interactions of the amygdala and hippocampal complex. *Curr Opin Neurobiol, 14*, 198-202.

Phelps, E. A., LaBar, K. S., Anderson, A. K., O'Connor, K. J., Fulbright, R. K., & Spencer, D. D. (1998). Specifying the contributions of the human amygdala to emotional memory: A case study. *Neurocase, 4*, 527-540.

Picton, P. W., Lins, O. G., & Scherg, M. (1995). The recording and analysis of event-related potentials. In F. a. G. Boller, J. (Ed.), *Handbook of Neuropsychology* (Vol. 10, pp. 2-75): Elsevier Science B.V.

Prince, S. E., Daselaar, S. M., & Cabeza, R. (submitted). Neural correlates of relational memory: Successful encoding and retrieval of semantic and perceptual associations. *Manuscript submitted for publication.*

Richardson, M. P., Strange, B. A., & Dolan, R. J. (2004). Encoding of emotional memories depends on amygdala and hippocampus and their interaction. *Nat Neurosci, 7*(3), 278-285.

Rolls, E. T. (2000). The orbitofrontal cortex and reward. *Cereb Cortex, 10*(3), 284-294.

Rugg, M. D. (1995). ERP studies of memory. In M. G. H. Coles & M. D. Rugg (Eds.), *Electrophysiology of mind : Event-related brain potentials and cognition* (pp. 132-170). Oxford, New York: Oxford University Press.

Rugg, M. D., Otten, L. J., & Henson, R. N. (2002). The neural basis of episodic memory: Evidence from functional neuroimaging. *Philos Trans R Soc Lond B Biol Sci, 357*(1424), 1097-1110.

Russell, J. (1980). A circumplex model of affect. *Journal of Personality and Social Psychology, 39*, 1161-1178.

Smith, A. P. R., Henson, R. N. A., Dolan, R. J., & Rugg, M. D. (2004). fMRI correlates of episodic retrieval of emotional contexts. *Neuroimage, 22*, 868-878.

Squire, L. R., & Knowlton, B. J. (2000). The Medial Temporal Lobe, the Hippocampus, and the Memory Systems of the Brain. In M. S. Gazzaniga (Ed.), *The New Cognitive Neurosciences* (pp. 765-779). Cambridge, Massachusetts

London, England: The MIT Press.

Squire, L. R., & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science, 253*(5026), 1380-1386.

Talarico, J. T., LaBar, K. S., & Rubin, D. C. (in press). Emotional intensity predicts autobiographical memory experience. *Memory & Cognition.*

Taylor, S. F., Liberzon, I., Fig, L. M., Decker, L. R., Minoshima, S., & Koeppe, R. A. (1998). The effect of emotional content on visual recognition memory: a PET activation study. *Neuroimage, 8*(2), 188-197.

Tulving, E. (1983). *Elements of episodic memory.* Oxford [Oxfordshire]; New York: Clarendon Press; Oxford University Press.

Wager, T. D., Phan, K. L., Liberzon, I., & Taylor, S. F. (2003). Valence, gender, and lateralization of functional brain anatomy in emotion: a meta-analysis of findings from neuroimaging. *Neuroimage, 19*(3), 513-531.

Wagner, A. D., Schacter, D. L., Rotte, M., Koutstaal, W., Maril, A., Dale, A. M., Rosen, B. R., & Buckner, R. L. (1998). Building memories: Remembering and forgetting of verbal experiences as predicted by brain activity. *Science, 281*, 1188-1191.

Weis, S., Klaver, P., Reul, J., Elger, C. E., & Fernandez, G. (2004). Temporal and cerebellar brain regions that suppot both declarative memory formation and retrieval. *Cereb Cortex, 14*, 256-267.

Yonelinas, A. P. (2002). The nature of recollection and familiarity: A review of 30 years of research. *J. Mem. Language, 46*, 441-517.

Zald, D. H. (2003). The human amygdala and the emotional evaluation of sensory stimuli. *Brain Res Brain Res Rev, 41*(1), 88-123.

CHAPTER 2

EFFECT OF EMOTION ON BRAIN ACTIVITY ASSOCIATED WITH EMOTIONAL EVALUATION AND EMOTIONAL MEMORY ENCODING – ERP EVIDENCE

Event-Related Potentials of Emotional Memory: Encoding Pleasant, Unpleasant, and Neutral Pictures

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Emotional events tend to be remembered better than nonemotional events (Bradley, Greenwald, Petry, & Lang, 1992; Christianson, 1992). The neural correlates of this memory-enhancing effect of emotion and their temporal aspects, in particular, are not well understood. Taking advantage of the temporal resolution of event-related potentials (ERPs), the present study investigated the time-course of the electrophysiological correlates of encoding pleasant, unpleasant, and neutral pictures.

During the last decade, the field of cognitive neuroscience of emotion has grown dramatically. Most studies have focused on the perception and evaluation of emotional stimuli (*emotional processing*) and on the effects of emotion on memory formation (*emotional memory*). A critical distinction in this literature is the one between two affective dimensions: emotional *arousal* and emotional *valence*. *Arousal* refers to a continuum that varies from calm to excitement, whereas *valence* refers to a continuum that varies from pleasant to unpleasant with neutral as an intermediate value (see Bradley & Lang, 1994 for methods to assess these two dimensions).

Different approaches ranging from behavioral and pharmacological to electrophysiological and functional neuroimaging have attempted to define the anatomical and functional correlates of *emotional processing* and *emotional memory* (Cahill, 1996; Davidson & Irwin, 1999; Lane & Nadel, 2000; LeDoux, 1993; Phelps & Anderson, 1997). In the following paragraphs studies in these two lines of research are briefly reviewed by presenting both general background information and specific ERP evidence. At the end of each section, the shortcomings of previous ERP studies are highlighted and the rationale of the present approach is stated.

Neural correlates of emotional processing. Lesion (Adolphs, Tranel, Damasio, & Damasio, 1994; Bechara, Damasio, Damasio, & Lee, 1999), electrophysiological (Davidson & Tomarken, 1989; Wheeler, Davidson, & Tomarken, 1993) and functional neuroimaging (Canli, Desmond, Zhao, Glover, & Gabrieli, 1998; Davidson, 1995; Davidson & Irwin, 1999) evidence supports the role of the prefrontal cortex (PFC) and the amygdala in the evaluation of the emotional content of stimuli. The roles of other structures, such as ventral striatum, anterior cingulate, posterior parietal, and insula regions have been also explored (Davidson & Irwin, 1999; Lane & Nadel, 2000).

In the case of PFC, different hypotheses have been proposed concerning the involvement of various PFC subregions in emotional processes. The right-hemisphere hypothesis proposes that the right hemisphere is specialized for the perception, expression, and experience of emotion (e.g., Borod, Koff, & Caron, 1983; see also Borod et al., 1998). The valence hypothesis proposes that the left hemisphere is primarily associated with processing of pleasant emotions, whereas the right hemisphere is primarily associated with processing of unpleasant emotions. This hypothesis is supported by electrophysiological (Davidson & Tomarken, 1989) and functional neuroimaging evidence (Canli et al., 1998; see also Davidson, 1995; Davidson & Irwin, 1999).

As concerning the amygdala, this region has been strongly associated with emotional processing by both lesion (Adolphs et al., 1994) and functional neuroimaging studies (Irwin et al., 1996; Lane et al., 1997; Morris et al., 1996; Schneider et al., 1997). For instance, lesion studies show that patients with bilateral amygdalar damage are impaired in detecting emotional facial expression (Adolphs et al., 1994), and imaging studies on neurologically intact subjects have reported amygdalar activations associated with processing of both pleasant and unpleasant stimuli (Irwin et al., 1996; Lane et al., 1997; Morris et al., 1996; Schneider et al., 1997).

ERP studies of emotion have identified an *emotion effect*: ERPs for emotional stimuli (pleasant or unpleasant) tend to be more positive going than ERPs for neutral stimuli (Carretie, Iglesias, & Garcia, 1997; Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Johnston, Miller, & Burleson, 1986; Naumann, Maier, Diedrich, Becker, & Bartussek, 1997; Vanderploeg, Brown, & Marsh, 1987). The emotion effect has been found in different ERP components, including the P300 component (e.g., Johnston et al., 1986; Naumann, Bartussek, Diedrich, & Laufer, 1992; see also Diedrich, Naumann, Maier, & Becker, 1997), the N300 component (Carretie, Iglesias, & Garcia, 1997; Carretie, Iglesias, Garcia, & Ballesteros, 1997), and the slow wave (SW) component (Cuthbert et al., 2000; Diedrich et al., 1997), but most consistently, the emotion effect is expressed in a P300-SW complex. The P300 component may be more sensitive to emotion under intentional emotional processing (e.g., Johnston et al., 1986; Naumann et al., 1992), while the N300 component appears more sensitive during incidental emotional

processing (Carretie, Iglesias, & Garcia, 1997; Carretie, Iglesias, et al., 1997). However, the evidence is inconclusive (Naumann et al., 1992). The neural generators of the emotion effect are not known, but it is reasonable to assume that it reflects interactions between the amygdala and cortical regions (Amaral, Price, Pitkanen, & Carmichael, 1992; LaBar et al., 1999; Lane et al., 1997).

There are two main unsolved issues concerning the emotion ERP effect. First, it is unclear if the emotion effect is only sensitive to arousal (emotional vs. neutral) or to both arousal and valence (pleasant vs. unpleasant). Whereas most studies have only found differences due to arousal (see Diedrich et al., 1997 for a brief review), a few recent studies have also reported differences that could be attributed to emotional valence (Cuthbert et al., 2000; Diedrich et al., 1997). A possible explanation of why previous studies have not find clear differences due to valence could be the use of word stimuli, which tend to generate smaller emotion effect overall (3-4 μV in amplitude) (e.g., Naumann et al., 1997) compared to more complex visual stimuli, such as pictures (5-6 μV or more) (e.g., Cuthbert et al., 2000). The failure to clearly dissociate the arousal and valence could also be due to the fact that most studies have either compared only unpleasant and neutral items, or have not equated the pleasant and unpleasant stimuli for arousal. Also, many studies have used a relatively small number of stimuli per condition (20 or lower), which may not give enough statistical power for fine dissociations. Second, if the emotion effect is sensitive to both arousal and valence, it is unclear if these two dimensions can be dissociated in their topographical and/or temporal characteristics. There is some evidence that valence-related differences tend to be larger in anterior electrodes (Cuthbert et al., 2000; Diedrich et al., 1997), but most studies have employed too few electrodes (e.g., 9) to allow a clear dissociation in topography.

To explore these issues, the present study investigated the effect of arousal and valence on ERPs recorded from 32 electrodes, while subjects rated the emotional content of 60 pleasant, 60 unpleasant, and 60 neutral pictures. Pictures were selected so that both pleasant and unpleasant pictures differed from neutral pictures in terms of both arousal and valence, whereas pleasant and unpleasant pictures differed from each other only in terms of valence.

The enhancing effect of emotion on memory formation. Behavioral (Bradley et al., 1992), pharmacological (Cahill & McGaugh, 1998; McGaugh, Cahill, & Roozendaal, 1996), lesion (Adolphs, Tranel, & Denburg, 2000; Cahill, Babinsky, Markowitsch, & McGaugh, 1995; LaBar & Phelps, 1998) and neuroimaging (Cahill et al., 1996; Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000; Canli, Zhao, Desmond, Glover, & Gabrieli, 1999; Hamann, Ely, Grafton, & Kilts, 1999) studies suggest that the beneficial effect of emotion on memory is related to both arousal and valence, with arousal being the most critical factor. Pharmacological studies with animals have investigated the role of peripheral adrenergic systems, and their interaction with other neurotransmitter systems (e.g., cholinergic, GABA-ergic, opiod-peptidergic) in the amygdala (Cahill & McGaugh, 1998; McGaugh et al., 1996). The results of these studies suggest that the amygdala exerts its enhancing role on memory for emotionally arousing stimuli through the modulation of hippocampal activity (*modulation hypothesis*, e.g., Cahill & McGaugh, 1998; McGaugh et al., 1996).

Lesion (Adolphs et al., 2000; Cahill et al., 1995; LaBar & Phelps, 1998) and functional neuroimaging (Cahill et al., 1996; Canli et al., 2000; Canli et al., 1999; Hamann et al., 1999) studies on humans support the role of the amygdala in the formation of emotional memory. For instance, lesion studies have shown that patients with bilateral amygdala damage do not remember emotional story segments better than the neutral ones (Cahill et al., 1995), and temporal-lobectomy patients, unlike control subjects, do not exhibit an increase in memory for arousing words over time (LaBar & Phelps, 1998). Also, subjects with left amygdalar damage are impaired in their memory for emotional stimuli, despite entirely normal memory for neutral stimuli (Adolphs et al., 2000). Imaging studies using emotional stimuli have shown that the number of emotional items remembered was correlated with activity in the amygdalar (Cahill et al., 1996; Hamann et al., 1999) and hippocampal regions (Hamann et al., 1999). Also, a more recent event-related fMRI study (Canli et al., 2000) found that left amygdalar activity during encoding predicted memory for unpleasant but not for neutral pictures.

In the ERP literature, there are a considerable number of studies on emotion (for reviews, see Diedrich et al., 1997; Halgren & Marinkovic, 1995) and on memory (for

reviews, see Rugg, 1995; Wagner, Koutstaal, & Schacter, 1999), but very few of them have investigated the *modulatory effect of emotion on memory*. Some of the latter have examined the effect of emotion on memory retrieval (e.g., Maratos, Allan, & Rugg, 2000; Maratos & Rugg, 2001; Windmann & Kutas, 2001), but only a couple of studies focused on emotional encoding. One study (Palomba, Angrilli, & Mini, 1997) measured ERPs during the encoding of emotional and neutral pictures, and found that the amplitude of ERPs recorded from a parietal electrode (i.e., PZ) was positively correlated with the number of subsequently remembered slides. Another study (LaBar et al., 1999) combined event-related potential and blood flow (fMRI) measurements during the encoding of unpleasant and neutral pictures, and identified a neural network (including prefrontal, parietal and occipitotemporal cortices) potentially involved in the encoding of unpleasant pictures.

A limitation of these studies is that they did not use what is probably the most powerful method available to investigate the neural correlates of memory encoding: *the subsequent memory paradigm*. In this paradigm, encoding trials are sorted according to whether the item presented in each trial was remembered or forgotten in a subsequent memory test (Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Paller, Kutas, & Mayes, 1987; Wagner et al., 1998). ERPs for items that are subsequently remembered tend to be more positive going than ERPs for items that are subsequently forgotten (e.g., Fabiani, Karis, & Donchin, 1986; Paller et al., 1987; Sanquist, Rohrbaugh, Syndulko, & Lindsley, 1980); for reviews, see also (Rugg, 1995; Wagner et al, 1999). This difference is known as the *subsequent memory effect* (or *Dm effect;* Paller et al., 1987). It can occur over frontal, midline, or parietal locations, and it can onset as early as 300-400 ms and persist beyond 1200 ms (Rugg, 1995).

The main goal of the present study was to investigate the relationship between the *emotion effect* and the *subsequent memory effect*. Considering together the memory advantage for emotional stimuli and the ERP positivity associated with both the emotion effect and the subsequent memory effect, it is reasonable to predict that the beneficial effect of emotion on memory performance will appear as an interaction between the emotion effect and the subsequent memory effect. That is, if emotional stimuli are better

remembered because they are better encoded (as suggested by the aforementioned lesion, pharmacological, and neuroimaging evidence), then the subsequent memory effect should be modulated by the emotional content of the encoded stimuli. Yet, the only ERP study to our knowledge that directly investigated the subsequent memory effect for emotional stimuli (Leiphart, Rosenfeld, & Gabrieli, 1993) failed to find a subsequent memory effect or a modulatory influence of emotion on the subsequent memory effect. This null finding could be related to two aspects of this study. First, as suggested by the authors, it could be related to the use of a shallow encoding task, which contrasts with the use of deep encoding tasks in other subsequent memory studies (e.g., Paller et al., 1987). Second, the null finding could be related to the use of words as stimuli. As mentioned above, words tend to elicit a weaker emotion effect than pictorial stimuli do, thereby reducing the chances of finding a significant emotion-related difference in the subsequent memory effect.

Thus, in the present study the modulatory influence of emotion on the subsequent memory effect was investigated using a deep encoding task (pleasantness rating) and pictures as stimuli. ERPs were recorded while subjects rated random series of pleasant, unpleasant, and neutral pictures on a 5-point pleasantness scale. After the encoding phase, subjects performed a free recall task in which they wrote a description for each picture they could remember. Encoding ERPs were separately averaged for pleasant, unpleasant, and neutral pictures, and, within each category, for subsequently remembered and forgotten items.

Two predictions were made concerning emotional processing (*emotion effect*), and two predictions were made concerning emotional memory (*modulatory effect of emotion on memory formation*). Concerning emotional processing, we expected that emotion effect would be mainly reflected in the modulation of P300-SW complex and would be sensitive to both arousal and valence, and that valence-related differences would have an anterior distribution, possibly leading to clear topographical dissociation from arousal-related differences (Cuthbert et al., 2000; Diedrich et al., 1997). Concerning emotional memory, we predicted that memory for emotional pictures would be better than for neutral pictures (Bradley et al., 1992), and, consistent with this behavioral difference,

the subsequent memory effect would be more pronounced for emotional than for neutral pictures.

Methods

Participants

Fifteen healthy right-handed female university students participated in the experiment in exchange for payment or credits. Female participants were chosen because previous studies using the same kind of stimuli have found that women show more physiological reactivity with valence judgments than men (Lang, Greenwald, Bradley, & Hamm, 1993), and because women are more likely to report intense emotional experiences (Shields, 1991). The experimental data were collected with the understanding and written consent of each subject, and the procedures used for data collection adhere to generally accepted practices for experimental research on human participants.

Materials

Stimuli consisted of a pool of 180 pictures (60 pleasant, 60 unpleasant, and 60 neutral) selected from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 1997a). IAPS pictures are rated on a 9-point scale both in terms of arousal (1= calm and 9=excited) and valence (1=unpleasant, 5=neutral, 9=pleasant) using the Self Assessment Manikin method (Bradley & Lang, 1994). The average arousal and valence scores of the selected pictures were respectively 6.0 and 7.1 for pleasant pictures, 6.2 and 2.3 for unpleasant pictures, and 2.9 and 5.0 for neutral pictures. Pleasant and unpleasant pictures differed from each other in terms of emotional valence, but not in terms of emotional arousal, whereas both pleasant and unpleasant pictures differed from neutral pictures in terms of both arousal and valence. These two facts were confirmed by two ANOVAs. First, an ANOVA on the valence scores of pleasant, unpleasant, and neutral pictures yielded a significant main effect of valence ($F(2,118)=1292.3$, $p < 0.0001$), and post-hoc tests showed significant difference between the valence scores of all three categories ($p < 0.05$). Second, an ANOVA on the arousal scores of pleasant, unpleasant, and neutral pictures yielded a significant main effect of arousal ($F(2,118)=1246.2$, $p < 0.0001$), and post-hoc tests showed significant difference between the arousal scores of

both pleasant and unpleasant pictures and the neutral pictures ($p < 0.05$), but no significant difference between the pleasant and unpleasant pictures ($p > 0.05$). The pictures were formatted so that on the screen they had a height between 10 and 13 cm and a width between 10 and 17 cm. The 180 pictures were divided into six sets of 30 pictures (10 pleasant, 10 unpleasant, and 10 neutral), which were assigned to 6 study-test blocks.

Procedure

The experiment was conducted on a PC using the SuperLab software (Cedrus Inc.). The experimental session consisted of a practice session and 6 study-test blocks. Eight different block orders were employed, and the order of the pictures within each block was randomized for each subject. Encoding trials consisted of 4 events: blank (500ms), cross fixation (500ms), picture (2000ms), and rating screen (until response). Subjects were instructed to experience the feelings or thoughts elicited by each picture and to rate the pictures according to their initial reaction using a 5-point scale (1 = very unpleasant, 2 = slightly unpleasant, 3 = neutral, 4 = slightly pleasant, and 5 = very pleasant). The subjects were also instructed to remember the pictures for a subsequent memory test (intentional learning). After each study phase, subjects were asked to recall as many pictures as possible during 6 minutes. They were provided with response sheets, and instructed to write down a description for each picture using one line per picture. They were asked to provide enough detail so that an outsider could identify each picture (e.g., diver vs. skier) and differentiate it from similar pictures (e.g., platform diver vs. springboard diver). Only pictures whose descriptions were detailed enough to allow both identification and differentiation were classified as remembered.

ERP recording

EEG was recorded from 32 Ag/AgCl electrodes embedded in a cap (Quikcap, Neurosoft Inc., Sterling Virginia), with respect to a linked mastoid reference. Recording sites were based on a variation of the 10/20 international electrode placement system (Jasper, 1958), including the following electrodes: frontopolar (FP1, FP2), frontal (F3, F7, FZ, F4, F8), frontocentral (FC3, FCZ, FC4), central (C3, CZ, C4), centroparietal (CP3, CPZ, CP4), parietal (P3, PZ, P4), frontotemporal (FT7, FT8), temporal (T7, T8), temporoparietal (TP7, TP8), and occipital (O1, OZ, O2). Horizontal eye-movements were monitored with

bipolar electrodes placed symmetrically on the outer canthus of each eye, and vertical movements were monitored with bipolar electrodes situated on the left supraorbital and infraorbital ridges. All channels were amplified with a filter bandwith of 0.03-50 Hz and sampled on-line at an A/D rate of 500 Hz. The recording epoch was 1500 ms, beginning 100 ms prior to picture onset. Trials with values above 100μV or below −100μV, possibly due to eye movement artifacts, were eliminated from the analysis. To ensure an adequate signal to noise ratio in the ERPs, subjects who had less than 16 artifact-free trials per condition were excluded from analysis and replaced (a total of four subjects were excluded and replaced).

Results

Behavioral results

Valence ratings. The average valence scores of the pictures, as rated by the subjects, were 4.11 for pleasant pictures (SD = 0.37), 1.47 for unpleasant pictures (SD = 0.24), and 2.95 for neutral pictures (SD= 0.24) (1 = very unpleasant, 3 = neutral, and 5 = very pleasant). An ANOVA on the valence rating scores of pleasant, unpleasant, and neutral pictures yielded a significant main effect of valence ($F(2, 28) = 312.48$, $p < 0.0001$), and post-hoc tests showed significant differences between the valence scores of all three categories (all $p < 0.01$). Thus, our subjects' rating scores were consistent with the standard valence scores from IAPS (see Method section).

Memory performance. As expected, memory performance was affected by the emotional content of the pictures. The proportion of pictures recalled was 0.57 for pleasant pictures (SD = 0.091), .58 for unpleasant pictures (SD = 0.095), and .48 for neutral pictures (SD = 0.078). A one-way (emotion: pleasant, unpleasant, and neutral) ANOVA yielded a significant main effect of emotion ($F(2,32) = 16.44$, $p < 0.0001$), and post-hoc contrasts yielded significant differences between pleasant and neutral pictures ($p < 0.05$) and between unpleasant and neutral pictures ($p < 0.05$), but not between pleasant and unpleasant pictures ($p > 0.05$). Thus, memory performance was higher for emotional than for neutral pictures with no difference between pleasant and unpleasant pictures.

ERP results

To investigate the emotion effect, ERPs were separately averaged for pleasant, unpleasant, and neutral pictures. To calculate the subsequent memory (Dm) effect, ERPs in each emotional category were further subdivided into ERPs for remembered and forgotten items. Finally, to investigate the modulatory influence of emotion on the subsequent memory effect, the emotional Dm (emotional remembered-emotional forgotten) and the neutral Dm (neutral remembered-neutral forgotten) were compared to each other. Averaged ERP data were analyzed using repeated measures ANOVAs and post-hoc Tukey-Kramer tests.

Emotion effect - Effect of arousal and valence on ERP correlates of emotional evaluation. The overall shape of encoding ERPs was similar for pleasant, unpleasant, and neutral pictures, and was characterized by a N200-N300-P300b-Slow Wave complex (Figure 2-1). As expected, there was an emotion effect: ERPs for emotional pictures were more positive-going than ERPs for neutral pictures. Overall, the emotion effect reflected mainly differences in arousal, which where most prominent in the amplitude of slow waves (SW), and at parietal electrodes. However, during an earlier epoch (i.e., 500-800 ms) and at frontocentral electrodes (e.g., FCZ in Figure 2-2), the emotion effect was sensitive mainly to valence. As Figure 2-2 suggests, the emotion effect was different at parietal vs. frontocentral electrodes. At parietal electrodes, the emotion effect appeared at the same time (500 ms) for both categories of high arousing pictures (i.e., pleasant and unpleasant), whereas at frontocentral areas, it appeared earlier for pleasant pictures (500 ms) than for unpleasant pictures (after 800 ms). No noticeable valence-related hemispheric asymmetry was present (Figure 2-1). To test these ideas, ANOVAs were computed on ERPs from PZ and FCZ, at two time windows (Figure 2-2). These locations and time windows were chosen based on previous evidence that showed a tendency for a posterior/anterior topographical dissociation of the arousal/valence effects, at similar locations and ERP components (Cuthbert et al., 2000).

To verify whether the emotion effect was different at parietal vs. frontocentral electrodes at 500-800 ms, a 2 (electrode site: PZ vs. FCZ) x 3 (emotion: pleasant, unpleasant, neutral) ANOVA was computed. It yielded significant main effects of both

electrode site ($F(1,14) = 16.25$, $p < 0.0012$) and emotion ($F(2,28)=27.84$, $p < 0.0001$), and a significant electrode site x emotion interaction ($F(2,28)=4.57$, $p < 0.019$). To elucidate this interaction, separate one-way (pleasant/unpleasant/neutral) ANOVAs were computed on PZ and FCZ. At PZ, the ANOVA yielded a significant effect of emotion ($F(2, 28)=31.02$, $p <.0001$), and the post-hoc tests showed a significant difference between pleasant pictures and neutral pictures ($p < 0.05$), and between unpleasant and neutral pictures ($p < 0.05$), but not between pleasant and unpleasant pictures ($p > 0.05$). At FCZ, in contrast, the ANOVA yielded a significant effect of emotion ($F(2, 28)=18.29$), $p < 0.0001$, and post-hoc tests showed a significant difference between pleasant pictures and both unpleasant ($p < 0.05$) and neutral pictures ($p < 0.05$), but not between unpleasant and neutral pictures ($p > 0.05$). Thus, the two separate ANOVAs confirmed a difference between emotional (both pleasant and unpleasant) and neutral pictures in parietal regions, but a difference between pleasant and both unpleasant and neutral pictures in frontocentral regions (compare FCZ and PZ graphs for the early epoch in Figure 2-2).

To verify whether the emotion effect at FCZ was different over time, a 2 (epoch: 500-800 ms vs. 800-1200 ms) x 3 (emotion: pleasant, unpleasant, and neutral) ANOVA was performed. It yielded significant main effects of both epoch ($F(1, 14)=56.53$, $p < 0.0001$) and emotion ($F(2, 28)=22.6$, $p < 0.0001$), and a significant epoch x emotion interaction ($F(2,28)=10.28$, $p < 0.0004$). To further quantify these effects, an additional one-way (emotion: pleasant, unpleasant, and neutral) ANOVA was performed at the late epoch of FCZ. It yielded a significant main effect of emotion ($F(2, 28)= 25.24$, $p < 0.0001$), and post-hoc tests showed a significant difference for both pleasant and unpleasant when compared to neutral pictures ($p < 0.05$), but no significant difference between pleasant and unpleasant pictures ($p > 0.05$).

Finally, to check for hemispheric differences in the emotion effect, 3 (emotion: pleasant, unpleasant, and neutral) x 2 (hemisphere: left vs right) ANOVAs where computed on ERPs from left (F3, FP1) and right (F4, FP2) frontal locations. The ANOVAs performed on ERPs from F3/F4 did not yield a significant emotion x hemisphere interaction, neither during an early epoch (500-800 ms) nor during a late

epoch (800-1200), suggesting that the emotion effect at these locations was similar across hemispheres. However, the same 3 x 2 design computed on ERPs from FP1/FP2 and during the early epoch (500-800 ms) yielded a significant emotion x hemisphere interaction ($F(2, 28)=3.94$, $p <.032$), suggesting that the emotion effect was different across hemispheres during this early interval. Follow-up ANOVAs and post-hoc analyses showed that this interaction was due to a larger emotion effect for pleasant pictures in the left compared to the right hemisphere ($T(1, 14)=3.35$, $p <.005$). Although this finding is consistent with the valence hypothesis of hemispheric asymmetry (Davidson, 1995), because the analyses did not yield analogous results for unpleasant pictures (larger emotion effect in the right compared to the left hemisphere), it does not bring clear ERP evidence for the valence hypothesis. However, the fact that this lateralization is seen in the frontal electrodes is consistent with the proposed role of the frontal lobes in the processing of emotional valence (Davidson, 1995; Heller, 1993).

Taken together, these results show that the emotion effect was different at parietal vs. frontocentral locations, and suggest that at parietal locations, the emotion effect was sensitive mainly to arousal (pleasant = unpleasant > neutral), whereas at frontocentral locations, it was sensitive mainly to valence during an earlier epoch (pleasant > unpleasant = neutral) and then later to overall arousal (pleasant = unpleasant > neutral).

Subsequent memory effect - ERP correlates of the modulatory effect of emotion on memory formation. As illustrated by Figure 2-3, the distribution of the subsequent memory effect was different during an early epoch than during a late epoch. During an early epoch (400-600 ms), the subsequent memory effect at midline locations (e.g., CPZ, CZ, FCZ) was greater for pleasant and unpleasant pictures than for neutral pictures. The difference was maximal at CZ, and it can be clearly observed on the subtraction data (remembered-forgotten) depicted in Figure 2-4. During a late epoch (600-800 ms) however, the distribution of the subsequent memory effect was more similar for pleasant, unpleasant, and neutral pictures: it extended over centroparietal, frontocentral regions, and it was maximal at midline electrodes. In addition to the overall similarity in the general patter of activation, some differences in the subsequent memory effect can also be noticed. As Figure 2-3 suggests, the subsequent memory effect at frontal electrodes seems

bilateral for pleasant pictures, right-lateralized for unpleasant pictures, and left-lateralized for neutral pictures.

To investigate the effect of arousal on the latency of the subsequent memory effect, ANOVAs were conducted on subtraction data (remembered-forgotten) from CZ, at two different epochs: 400-600 and 600-800 (see Figure 2-4). These locations and time windows were selected because, as mentioned above, the subsequent memory effect is likely to occur at midline electrodes, and as early as 300-400 ms after stimulus onset (Rugg, 1995). Since a preliminary ANOVA yielded no difference between pleasant and unpleasant pictures either at the early ($F(1,14)=0.002$, $p < 0.97$) or at the late epoch (600-800; $F(1, 14)=0.11$, $p <.75$), statistical power was increased by collapsing pleasant and unpleasant conditions into one emotional category. The 2 (epoch: 400-600 ms vs. 600-800 ms) x 2 (arousal: emotional vs. neutral) ANOVA yielded a significant main effect of epoch ($F(1, 14)=24.76$, $p < 0.00025$), and a reliable epoch x arousal interaction ($F(1, 14)=5.56$, $p < 0.035$). To clarify this interaction, separate ANOVAs were computed on early (400-600 ms) and late (600-800 ms) epochs. A one-way (arousal: emotional vs. neutral) ANOVA showed that the subsequent memory effect was greater for emotional than for neutral pictures in the early epoch ($F(1, 14)=6.01$, $p < 0.028$), but not in the late epoch ($F(1, 14)=.1$, $p < 0.8$). Consistent with these results, separate ANOVAs directly comparing the waves for remembered and forgotten pictures for each emotion condition (pleasant, unpleasant, and neutral) and epoch (early and late) showed that the subsequent memory effect (remembered vs. forgotten) for both pleasant and unpleasant pictures was significant during both early ($F(1, 14)=10.29$, $p < 0.0064$, for pleasant, and $F(1, 14)=9.56$, $p < 0.0081$, for unpleasant) and late epochs ($F(1, 14)=8.07$, $p < 0.0132$, for pleasant, and $F(1, 14)=14.14$, $p < 0.0022$, for unpleasant), whereas for neutral pictures it was significant during the late epoch ($F(1, 14)=12.13$, $p < 0.0038$) but not during the early epoch ($F(1, 14)=.85$, $p < 0.3732$) (see also the remembered/forgotten wave graphs for pleasant, unpleasant, and neutral pictures in Figure 2-4A). In other words, the subsequent memory effect at CZ occurred earlier for emotional than for neutral pictures.

To investigate the possible lateralization of the subsequent memory effect at frontal electrodes, ANOVAs were conducted on ERPs for remembered and forgotten

pleasant, unpleasant, and neutral pictures from left (F3) and right (F4) electrodes and for both early (400-600 ms) and late (600-800) epochs. A 3 (emotion: pleasant, unpleasant, and neutral) x 2 (memory: remembered vs. forgotten) x 2 (hemisphere: left vs. right) repeated measures ANOVA design did not yield any significant hemisphere x memory, emotion x memory, or hemisphere x emotion x memory interactions, during the early epoch (400-600 ms); these results suggest that the subsequent memory effect was not different across emotion conditions or hemispheres. However, during the late epoch (600-800 ms), similar 3 x 2 x 2 ANOVAs yielded significant main effects of both memory ($F(1, 14)=27.33$, $p= .0001$) and emotion ($F(2, 28)=11.01$, $p= .0003$) and a significant hemisphere x emotion x memory interaction ($F(2, 28)=5.68$, $p < 0.009$). Additional ANOVAs meant to elucidate this complex interaction, computed on the subtraction (remembered–forgotten) data, showed that the subsequent memory effect differed across hemispheres only for neutral pictures (left > right; $T(1, 14)=2.26$, $p <.041$), but not for pleasant ($T(1, 14)=-.57$, $p>.575$) and unpleasant pictures ($T(1, 14)= -1.24$, $p>.234$). Also, direct comparisons of the subsequent memory effect for pleasant, unpleasant, and neutral pictures did not yield any significant differences, suggesting that, despite the hemispheric differences encountered for neutral pictures, the subsequent memory effect for emotional and neutral pictures was similar at these frontal locations. These results suggest that the ERPs from these locations may reflect comparable involvement of the same frontal neural generators as those associated with successful encoding in functional neuroimaging studies (e.g., Brewer et al., 1998, Wagner et al., 1998).

Collectively, the subsequent memory data show that, compared to forgotten pictures, remembered pictures elicited larger potentials over centroparietal and frontocentral regions, for both emotional and neutral pictures. However, at central locations (i.e., CZ) and during an early epoch (400-600 ms), the subsequent memory effect was larger for emotional than for neutral pictures, suggesting faster encoding for emotional pictures.

Discussion

The study yielded two main results, which were both consistent with the predictions. First, there was a clear topographical difference between arousal-related and valence-related components of the emotion effect: the emotion effect was sensitive to arousal at parietal sites, whereas it was sensitive to both arousal and valence at frontocentral sites. Second, there was a difference between the subsequent memory effect for emotional and neutral pictures: the subsequent memory effect was greater in an early epoch for emotional than for neutral stimuli, suggesting better encoding of high arousing than low arousing stimuli.

Effect of arousal and valence on ERP correlates of emotional evaluation

At parietal sites, the emotion effect reflected differences in arousal, whereas at frontocentral sites, it reflected differences in both arousal and valence. These findings are consistent with lesion (see Heilman, 2000) and neuroimaging (LaBar et al., 1999) evidence about the role of parietal areas in the processing of emotional arousal, and with ERP evidence that the valence-related differences tend to be larger in anterior electrodes than at posterior electrodes (Cuthbert et al., 2000; Diedrich et al., 1997). The findings are also consistent with a neuropsychological model developed by Heller and collaborators (Heller, 1993; Heller & Nitschke, 1998), which proposes the existence of two distinct neural systems involved in the processing of emotional information: one involved in the processing of emotional arousal located in the parietal lobes, and one involved in the modulation of emotional valence located in the frontal lobes.

It is possible that the ERP differences between emotional and neutral pictures reflected attentional differences that follow from viewing emotional content, rather that direct effects of emotion. The fact that ERPs for emotional and neutral pictures differed mainly in amplitude constitutes evidence for different levels of engagement of the same neural/functional processes (Allan, Edward, & Rugg, 1998). Consistent with this idea, there is evidence showing that, because of their motivational significance, emotionally salient stimuli are selected by the brain for sustained attentional processing (Lang, Bradley, & Cuthbert, 1997b).

The neural generators of ERP differences reported are unclear, but one may speculate that arousal-related differences in the emotion effect primarily reflected the contribution of amygdala-cortical interactions (Amaral et al., 1992) whereas valence-related differences primarily reflected the contribution of the prefrontal cortex (Davidson, 1995; Heller 1993). In addition, because emotion effect could reflect attentional modulation, these differences may also be related to activity in "attention" areas from parietal and prefrontal regions (e.g., Hopfinger, Buonocore, & Mangun, 2000).

The suggestion of a possible involvement of the amygdala as the neural generator of the emotion effect at parietal electrodes seems in disagreement with evidence suggesting that the amygdala is important in arousal-mediated memory effects, rather than in arousal *per se* (Cahill et al., 1995; LaBar & Phelps, 1998). That is, it has been shown that amygdala patients did not show enhanced memory to emotional items despite normal skin conductance responses to emotional words (LaBar & Phelps, 1998) or normal arousal ratings of emotional scenes of a narrated slide show (Cahill et al., 1995). One possible explanation is that the amygdala is involved in emotional arousal but is not necessary for it. Thus, damage to the amygdala may not impair emotional arousal even if this region participates in emotional arousal in the normal brain (Dolcos, Graham, LaBar, & Cabeza, 2003). Another possible explanation is that the ERP emotion effect from parietal electrodes reflects activity in other brain areas involved in the processing of emotional arousal, such as the parietal lobes. This interpretation is consistent with the proposed role of the parietal areas in the processing of emotional arousal (Heller, 1993) and can reconcile the above-mentioned lines of evidence.

The valence-related difference in the emotion effect at frontocentral electrodes could reflect a difference in arousal between the pleasant and unpleasant pictures, but the fact that pleasant and unpleasant pictures were equated for arousal suggests that this difference could reflect a real valence difference at the cortical level of affective processing (Cuthbert et al., 2000). This difference occurred because the emotion effect started earlier for pleasant than for unpleasant pictures (Figure 2-2) and could reflect a preference toward pleasant pictures. This interpretation has ecological validity in the sense that, normally, people are more likely to show preference for pleasant than for

unpleasant stimuli (Pollyanna effect; Matlin & Stang, 1978). It is also consistent with the notion proposed by Diedrich et al. (1997) that the emotion effect in the 400-600 ms epoch reflects the processing of the emotional qualities of the stimuli, depending on the amount of attention paid to the emotional content.

This earlier emotion effect for pleasant pictures may seem surprising if one considers the evidence coming from work on the potentiated startle reflex that suggests enhanced response to unpleasant relative to pleasant stimuli (e.g., Lang, Bradley, Cuthbert, 1990; Schupp, Cuthbert, Bradley, Birbaumer, & Lang, 1997). A simple explanation of these differences could be that they may reflect different processes. While the affective modulation of the startle reflex is thought of as reflecting motivational priming in which a defensive reflex is augmented when the ongoing motivational state is aversive in nature (Lang, 1995, cited by Schupp et al., 1997), the modulation of the ERP may be interpreted as reflecting earlier processing due to preference. Given these differences, it would be interesting to design studies intended to dissociate these phenomena.

In sum, the emotion effect results show a clear ERP topographical dissociation of arousal and valence. These results are consistent with previous ERP evidence (Cuthbert et al., 2000; Diedrich et al., 1997), and with evidence supporting the general notion that parietal areas are involved in the processing of emotional arousal (Heilman, 2000; Heller, 1993; LaBar et al., 1999), whereas prefrontal areas are involved in the evaluation of the emotional valence of stimuli (Davidson & Irwin, 1999; Davidson & Tomarken, 1989; Heller, 1993).

ERP correlates of the modulatory effect of emotion on memory formation

The main result of the present study is the finding that the subsequent memory effect was larger, during an early epoch, for emotional than for neutral pictures. There is a considerable amount of evidence that emotional stimuli are processed faster than neutral stimuli (Ohman, Flykt, & Ludqvist, 2000). If we assume that shorter ERP latencies reflect privileged access to processing resources (Ganis, Kutas, & Sereno, 1996), and that this advantage in processing leads to better encoding, then the present finding of an earlier

subsequent memory effect for emotional pictures could be one of the mechanisms underlying better memory for emotional than neutral events.

However, a question still remains: why would an earlier engagement of processing resources confer an encoding advantage to emotional stimuli? According to Salthouse (1996), two distinct mechanisms are responsible for the relationship between speed and cognition: the *limited time mechanism*, and the *simultaneity mechanism*. The limited time mechanism is based on the idea that more processing results in higher performance, and the amount of processing is greater when the speed of processing is faster. The simultaneity mechanism is based on the idea that higher level processing depends on the amount of the products of early processing simultaneously available for further processing. Consequently, the faster the speed of processing, the more information that is simultaneously available for high level processing, and thus, the higher the performance. Adapted to our experiment, these principles could explain our subsequent memory results for high arousing pictures: the emotional content granted a privileged access to processing resources that resulted in a better encoding of high arousing pictures. This, in turn, resulted in better retrieval of pleasant and unpleasant pictures compared to neutral pictures. If true, this interpretation could explain the beneficial effect of emotion on memory performance.

As for the neural generators of this ERP effect, given the aforementioned pharmacological (Cahill & McGaugh, 1998; McGaugh et al., 1996), lesion (Adolphs et al., 2000; Cahill et al., 1995; LaBar & Phelps, 1998) and neuroimaging (Cahill et al., 1996; Canli et al., 2000; Canli et al., 1999; Hamann et al., 1999) evidence linking the amygdala to emotional memory formation, it is reasonable to assume that the earlier subsequent memory effect for emotional pictures indirectly reflects activity in this structure. Although activity in the amygdala is unlikely to volume-conduct to the scalp, this region has intimate connections with a number of neocortical regions (Amaral et al., 1992), and hence, it is likely to influence scalp ERP recordings. The neocortical generators of the emotional modulation of the subsequent memory effect are unclear, but they may involve prefrontal and parietal regions associated with emotional processing (Barbas, 2000; Davidson & Irwin, 1999; LaBar et al., 1999; Lane et al., 1997; Lang et al.,

1998). Finally, the similarity of the subsequent memory effect for emotional and neutral pictures at frontal electrodes may suggest that the ERP from these locations reflect comparable involvement of the same neural generators as those associated with successful encoding in functional neuroimaging studies (Brewer et al., 1998, Wagner et al., 1998).

Conclusions

The present study yielded two novel results. First, it yielded a dissociation between arousal and valence. The *emotion effect* results clearly showed that the processing of emotional content of pictures is sensitive to both arousal and valence, and their effects can be dissociated over the scalp: ERPs from parietal areas were sensitive to arousal, whereas ERPs from frontocentral areas were sensitive to both arousal and valence. Second, this is the first study investigating the subsequent memory effect for emotional pictorial stimuli. The *subsequent memory effect* results show that this effect occurred earlier for pleasant and unpleasant pictures than for neutral pictures, and suggest that emotional stimuli have privileged access to processing resources, possibly resulting in better encoding. These results are compatible with previous evidence about the role of different brain areas in the processing of emotional information, and with evidence about the beneficial effect of emotion on memory formation. The present study provides the first available evidence of a link between two seemingly unrelated ERP phenomena: the *emotion effect* and the *subsequent memory effect*.

References

Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. (1994). Impaired recognition of emotions in facial expressions following bilateral damage to the human amygdala. *Nature, 372*, 699-672.

Adolphs, R., Tranel, D., & Denburg, N. (2000). Impaired emotional declarative memory following unilateral amygdala damage. *Learning & Memory, 7*, 180-186.

Allan, K., Edward, L., & Rugg, M. D. (1998). Electrophysiological evidence for dissociable processes contributing to recollection. *Acta Psychologica,* 1998: 231-252.

Amaral, D. G., Price, J. L., Pitkanen, A., & Carmichael, S. T. (1992). Anatomical organization of the primate amygdaloid complex. In J. P. Aggleton (Ed.), *The Amygdala, Neurobiological Aspects, of Emotion, Memory and Mental Dysfunction.* (pp. 1-66). New York: Wiley-Liss.

Barbas, H. (2000). Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices. *Brain Research Bulletin, 52*(5), 319-330.

Bechara, A., Damasio, H., Damasio, A. R., & Lee, P. L. (1999). Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. *The Journal of Neuroscience, 19*(13), 5473-5481.

Borod, J. C., Koff, E., & Caron, H. (1983). Right hemisphere specialization for the expression and appreciation of emotion: A focus on the face. In E. Perecman (Ed.), *Cognitive Processing in the Right Hemisphere.* (pp. 83-110). New York: Academic Press.

Borod, J. C., Obler, L. K., Erhan, H. M., Grunwald, I. S., Cicero, B. A., Welkowitz, J., Santschi, C., Agosti, R. M., & Whalen, J. R. (1998). Right hemisphere emotional perception: Evidence across multiple channels. *Neuropsychology, 12*(3), 446-458.

Bradley, M. M., Greenwald, M. K., Petry, M. C., & Lang, P. J. (1992). Remembering pictures: Pleasure and arousal in memory. *Journal of Experimental Psychology: Learning Memory and Cognition, 18*(2), 379-390.

Bradley, M. M., & Lang, P. J. (1994). Measuring emotion: The self-assessment manikin and the semantic differential. *Journal of Behavior Therapy and Experimental Psychiatry, 25*(1), 49-59.

Brewer, J. B., Zhao, Z., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (1998). Making memories: Brain activity that predicts how well visual experience will be remembered. *Science, 281*, 1185-1187.

Cahill, L. (1996). *Neurobiology of memory for emotional events: Converging evidence from infra-human and human studies.* Paper presented at the Cold Spring Symposia on Quantitative Biology. Cold Spring Harbor Laboratory Press, Vol. LXI.

Cahill, L. , Babinsky, R., Markowitsch, H., & McGaugh, J. L. (1995). The amygdala and emotional memory. *Nature, 377*, 295-296.

Cahill, L., & McGaugh, J. L. (1998). Mechanisms of emotional arousal and lasting declarative memory. *Trends in Neurosciences, 21*(7), 294-299.

Cahill, L., Haier, R. J., Fallon, J., Alkire, M. T., Tang, C., Keator, D., Wu, J., & McGaugh, J. L. (1996). Amygdala activity at encoding correlated with long-term, free recall of emotional information. *PNAS: Proceedings of the National Academy of Sciences of The United States of America, 93*, 8016-8021.

Canli, T., Desmond, J. E., Zhao, Z., Glover, G., & Gabrieli, J. D. E. (1998). Hemispheric asymmetry for emotional stimuli detected with fMRI. *NeuroReport, 9*, 3233-3239.

Canli, T., Zhao, Z., Brewer, J., Gabrieli, J. D. E., & Cahill, L. (2000). Event-related activation in the human amygdala associated with later memory for individual emotional experience. *The Journal of Neuroscience, 20*(RC99), 1-5.

Canli, T., Zhao, Z., Desmond, J. E., Glover, G., & Gabrieli, J. D. E. (1999). fMRI identifies a network of structures correlated with retention of positive and negative emotional memory. *Psychobiology, 27*, 441-452.

Carretie, L., Iglesias, J., Garcia, T., & Ballesteros, M. (1997). N300, P300 and the emotional processing of visual stimuli. *Electroencephalography and Clinical Neurophysiology, 103*(2), 298-303.

Carretie, L., Iglesias, J., & Garcia, T. (1997). A study on the emotional processing of visual stimuli through event-related potentials. *Brain and Cognition, 34*, 207-217.

Christianson, S.-A. (1992). *The Handbook of Emotion and Memory: Research and Theory.* Lawrence Erlbaum Associates.

Cuthbert, B. N., Schupp, H. T., Bradley, M. M., Birbaumer, N., & Lang, P. J. (2000). Brain potentials in affective picture processing: Covariation with autonomic arousal and affective report. *Biological Psychology, 52*, 95-111.

Davidson, R. J. (1995). Cerebral asymmetry, emotion and affective style. In R. J. H. Davidson & K. Hugdahl (Eds.), *Brain Asymmetry.* (pp. 361-387): MIT Press.

Davidson, R. J., & Irwin, W. (1999). The functional neuroanatomy of emotion and affective style. *Trends in Cognitive Sciences, 3*(1), 11-20.

Davidson, R. J., & Tomarken, A. J. (1989). Laterality and emotion: An electrophysiological approach. In F. Boller & J. Grafman (Eds.), *Handbook of Neuropsychology* (Vol. 3, pp. 419-441). New York: Elsevier.

Dolcos, F., Graham, R., LaBar, K. S., & Cabeza, R. (in press). Coactivation of the amygdala and hippocampus predicts better recall for emotional than for neutral pictures. *Brain and Cognition, 51*, 221-223.

Diedrich, O., Naumann, E., Maier, S., & Becker, G. (1997). A frontal positive slow wave in the ERP associated with emotional slides. *Journal of Psychophysiology, 11*(1), 71-84.

Fabiani, M., Karis, D., & Donchin, E. (1986). P300 and recall in an incidental memory paradigm. *Psychophysiology, 23*, 298-308.

Ganis, G., Kutas, M., & Sereno, M. I. (1996). The search for 'common sense': An electrophysiological study of the comprehension of words and pictures in reading. *Journal of Cognitive Neuroscience, 8*(2), 89-106.

Halgren, E., & Marinkovic, K. (1995). Neurophysiological networks integrating human emotions. In M. S. Gazzaniga (Ed.), *The Cognitive Neurosciences* (pp. 1137-1151). Cambridge, Massachusetts: The MIT Press.

Hamann, S. B., Ely, T. D., Grafton, S. T., & Kilts, C. D. (1999). Amygdala activity related to enhanced memory for pleasant and aversive stimuli. *Nature Neuroscience, 2*(3), 289-293.

Heilman, K. M. (2000). Emotional experience: A neurological model. In D. R. Lane & L. Nadel (Eds.), *Cognitive Neuroscience of Emotion.* (pp. 328-344). New York: Oxford University Press, Inc.

Heller, W. (1993). Neuropsychological mechanisms of individual differences in emotion, personality, and arousal. *Neuropsychology, 7*(4): 476-489.

Heller, W. and Nitschke, J. B. (1998). The puzzle of regional brain activity in depression and anxiety: The importance of subtypes and comorbidity. *Cognition and Emotion,* 12(3): 421-447.

Hopfinger, J. B., Buonocore, M. H., & Mangun, G. R. (2000). The neural mechanisms of top-down attentional control. *Nature Neuroscience,* 3(3): 284-91.

Irwin, W., Davidson, R. J., Lowe, M. J., Mock, B. J., Sorenson, J. A., & Turski, P. A. (1996). Human amygdala activation detected with echo-planar functional magnetic resonance imaging. *NeuroReport, 7*(11), 1765-1769.

Jasper, H. H. (1958). The ten-twenty electrode system of the International Federation. *Electroencephalography and Clinical Neurophysiology, 10*, 371-375.

Johnston, V. S., Miller, D. R., & Burleson, M. H. (1986). Multiple P3s to emotional stimuli and their theoretical significance. *Psychophysiology, 23*(6), 684-694.

LaBar, K. S., & Phelps, E. A. (1998). Arousal-mediated memory consolidation: Role of the medial temporal lobe in humans. *Psychological Science, 9*(6), 490-493.

LaBar, K. S., Rabinovici, G. D., Ranganath, C., Gitelman, D. R., Parish, T. B., Paller, K. A., & Mesulam, M.-M. (1999). *Spatiotemporal dynamics of a neural network for emotional picture encoding revealed by parallel evoked potential and fMRI measurements.* Paper presented at the Society for Neuroscience Annual Meeting, *25*: 2146.

Lane, D. R., & Nadel, L. (2000). *Cognitive Neuroscience of Emotion.* New York: Oxford University Press, Inc.

Lane, R. D., Reiman, E. M., Bradley, M. M., Lang, P. J., Ahern, G. L., Davidson, R. J., & Schwartz, G. E. (1997). Neuroanatomical correlates of pleasant and unpleasant emotion. *Neuropsychologia, 35*(11), 1437-1444.

Lang, P. J. (1995). The emotion probe. Studies of motivation and attention. *American Psychologist, 50*: 372-385.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1990). Emotion, attention, and the startle reflex. *Psychogical Review,* 97(3): 377-395.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1997a). *International Affective Picture System.* [Pictures]. Gainesville: NIMH Center for the Study of Emotion and Attention.

Lang, P. J., Bradley, M. M., Cuthbert, B. N. (1997b). Motivated attention: Affect, activation, and action. In P. J. Lang, R. F. Simons, & M. Balaban (Eds.),

Attention and Orienting: Sensory and Motivational Processes. Erlbaum Associates, Hillsdale, NJ.

Lang, P. J., Bradley, M. M., Fitzsimmons, J. R., Cuthbert, B. N., Scott, J. D., Moulder, B., & Nangia, V. (1998). Emotional arousal and activation of the visual cortex: An fMRI analysis. *Psychophysiology, 35*, 199-210.

Lang, P. J., Greenwald, M. K., Bradley, M. M., & Hamm, A. O. (1993). Looking at pictures: affective, facial, visceral, and behavioral reactions. *Psychophysiology, 30*(3), 261-273.

LeDoux, J. E. (1993). Emotional memory systems in the brain. *Behavioural Brain Research, 58*(1-2), 69-79.

Leiphart, J., Rosenfeld, J. P., & Gabrieli, J. D. (1993). Event-related potential correlates of implicit priming and explicit memory tasks. *International Journal of Psychophysiology, 15*(3), 197-206.

Maratos, E. J., Allan, K., & Rugg, M. D. (2000). Recognition memory for emotionally negative and neutral words: An ERP study. *Neuropsychologia,* 38(11): 1452-1465.

Maratos, E. J. & Rugg, M. D. (2001). Electrophysiological correlates of the retrieval of emotional and non-emotional context. *Journal of Cognitive Neuroscience,* 13(7): 877-891.

Matlin, M. W., & Stang, D. J. (1978). *The Pollyanna Principle: Selectivity in Language, Memory, and Thought.* Cambridge, MA: Shenkman.

McGaugh, J. L., Cahill, L., & Roozendaal, B. (1996). Involvement of the amygdala in memory storage: Interaction with other brain systems. *PNAS: Proceedings of the National Academy of Sciences of The United States of America, 93*, 13508-13514.

Morris, J. S., Frith, C. D., Perrett, D. I., Rowland, D., Young, A. W., Calder, A. J., & Dolan, R. J. (1996). A differential neural response in the human amygdala to fearful and happy facial expressions. *Nature, 383*, 812-815.

Naumann, E., Bartussek, D., Diedrich, O., & Laufer, M. E. (1992). Assessing cognitive and affective information processing functions of the brain by means of the late positive complex of the event-related potential. *Journal of Psychophysiology, 6*, 285-298.

Naumann, E., Maier, S., Diedrich, O., Becker, G., & Bartussek, D. (1997). Structural, semantic, and emotion-focused processing of neutral and negative nouns: Event-related potential correlates. *Journal of Psychophysiology, 11*(2), 158-172.

Ohman, A., Flykt, A., & Ludqvist, D. (2000). Unconscious emotion: Evolutionary perspectives, psychophysiological data and neuropsychological mechanisms. In R. D. Lane, & L. Nadel (Eds.), *Cognitive Neuroscience of Emotion.* (pp. 296-327). New York: Oxford University Press, Inc.

Paller, K. A., Kutas, M., & Mayes, A. R. (1987). Neural correlates of encoding in an incidental learning paradigm. *Electroencephalography and Clinical Neuropsychology, 67*, 360-371.

Palomba, D., Angrilli, A., & Mini, A. (1997). Visual evoked potentials, heart rate responses and memory to emotional pictorial stimuli. *International Journal of Psychophysiology, 27*(1), 55-67.

Phelps, E. A., & Anderson, A. K. (1997). Emotional memory: What does the amygdala do? *Current Biology: CB, 7*(5), R311-314.

Rugg, M. D. (1995). ERP studies of memory. In M. G. H. Coles & M. D. Rugg (Eds.), *Electrophysiology of mind: Event-related brain potentials and cognition.* (pp. 132-170). Oxford, New York: Oxford University Press.

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review, 103*(3), 403-428.

Sanquist, T. F., Rohrbaugh, J. W., Syndulko, K., & Lindsley, D. B. (1980). Electrophysiological signs of level of processing: Perceptual analysis and recognition memory. *Psychophysiology, 17*, 568-576.

Schneider, F., Grodd, W., Weiss, U., Klose, U., Mayer, K. R., Nagele, T., & Gur, R. C. (1997). Functional MRI reveals left amygdala activation during emotion. *Psychiatry Research: Neuroimaging Section, 76*, 75-82.

Schupp, H. T., Cuthbert, B. N., Bradley, M. M., Birbaumer, N., & Lang, P. J. (1997). Probe P3 and blinks: Two measures of afective startle modulation. *Psychophysiology,* 34: 1-6.

Shields, S. (1991). Gender in the psychology of emotion: A selective research review. In K. Strongman (Ed.), *International Review of Studies on Emotion* (pp. 227-245). New York: Wiley.

Vanderploeg, R. D., Brown, W. S., & Marsh, J. T. (1987). Judgments of emotion in words and faces: ERP correlates. *International Journal of Psychophysiology, 5*(3), 193-205.

Wagner, A. D., Koutstaal, W., & Schacter, D. L. (1999). When encoding yields remembering: Insights from event-related neuroimaging. *Philosophical Transactions of The Royal Society of London: Biological Sciences, 354*, 1307-1324.

Wagner, A. D., Schacter, D. L., Rotte, M., Koutstaal, W., Maril, A., Dale, A. M., Rosen, B. R., & Buckner, R. L. (1998). Building memories: Remembering and forgetting of verbal experiences as predicted by brain activity. *Science, 281*, 1188-1191.

Wheeler, R. E., Davidson, R. J., & Tomarken, A. J. (1993). Frontal brain asymmetry and emotional reactivity: A biological substrate of affective style. *Psychophysiology, 30*, 82-89.

Windmann, S. & Kutas, M. (2001). Electrophysiological correlates of emotion-induced recognition bias. *Journal of Cognitive Neuroscience,* 13(5): 577-592.

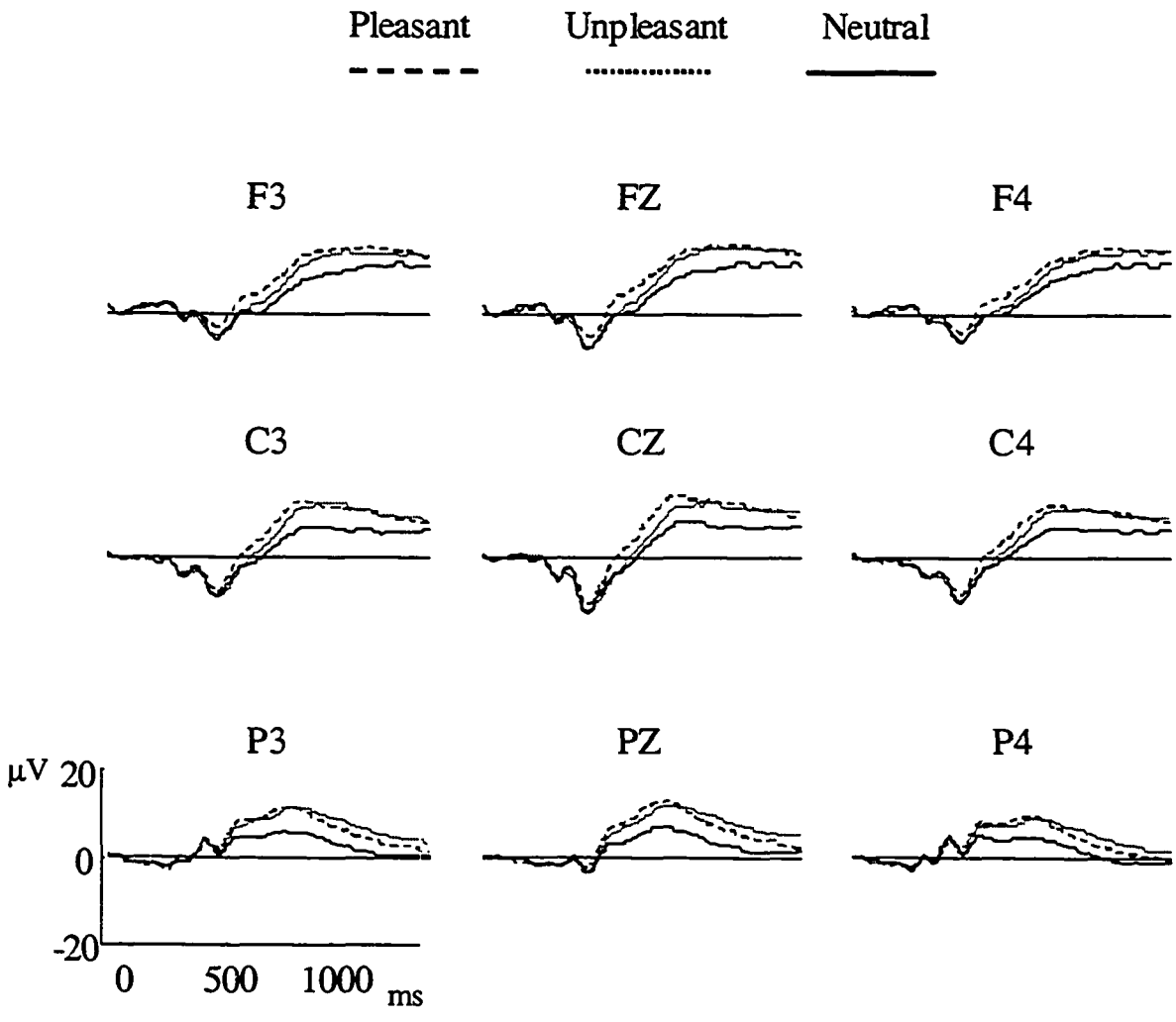

Figure 2-1. ERP Emotion effect. ERPs for both pleasant and unpleasant pictures were more positive-going than ERPs for neutral pictures. The electrode locations are topographically arranged as viewed from above the subjects' heads. Vertical and horizontal scales represent the voltage amplitude (microvolts) and the time from stimulus onset (milliseconds), respectively.

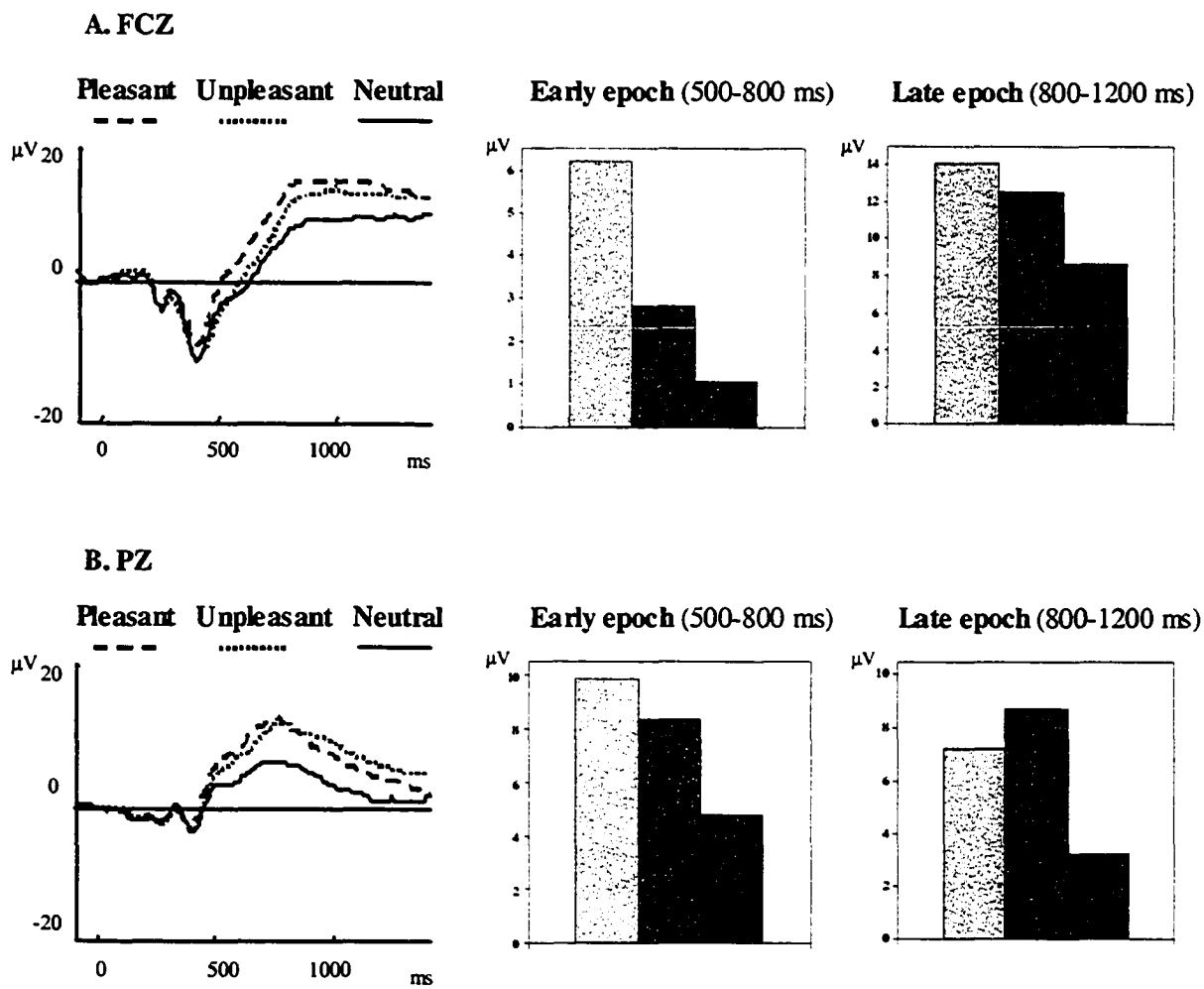

Figure 2-2. Dissociable effects of arousal and valence at frontal vs. parietal electrodes. **A.** At frontocentral electrodes, it appeared earlier for pleasant pictures (500-800 ms) than for unpleasant pictures (after 800 ms). **B.** At parietal electrodes, it appeared at the same time (500-800 ms) for both pleasant and unpleasant pictures. Light gray=Pleasant; Dark gray=Unpleasant; Black=Neutral.

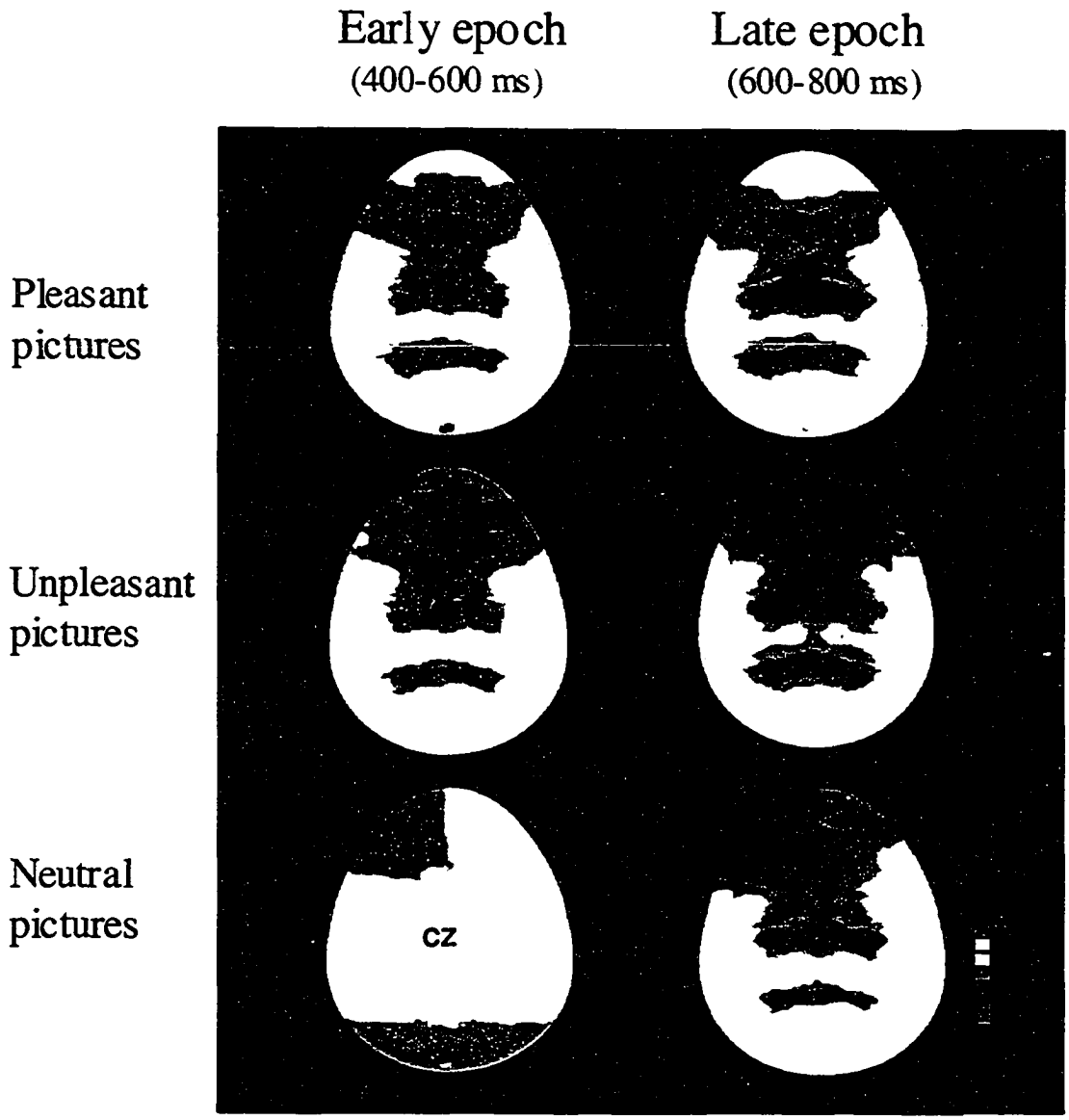

Figure 2-3. Subtraction (Recalled–Forgotten) topomaps comparing the subsequent memory effect for emotional and neutral pictures at different epochs. Subsequent memory effect over centroparietal areas occurred earlier for pleasant and unpleasant pictures (400-600 ms) than for neutral pictures (after 600 ms). The maximal difference occurred at CZ.

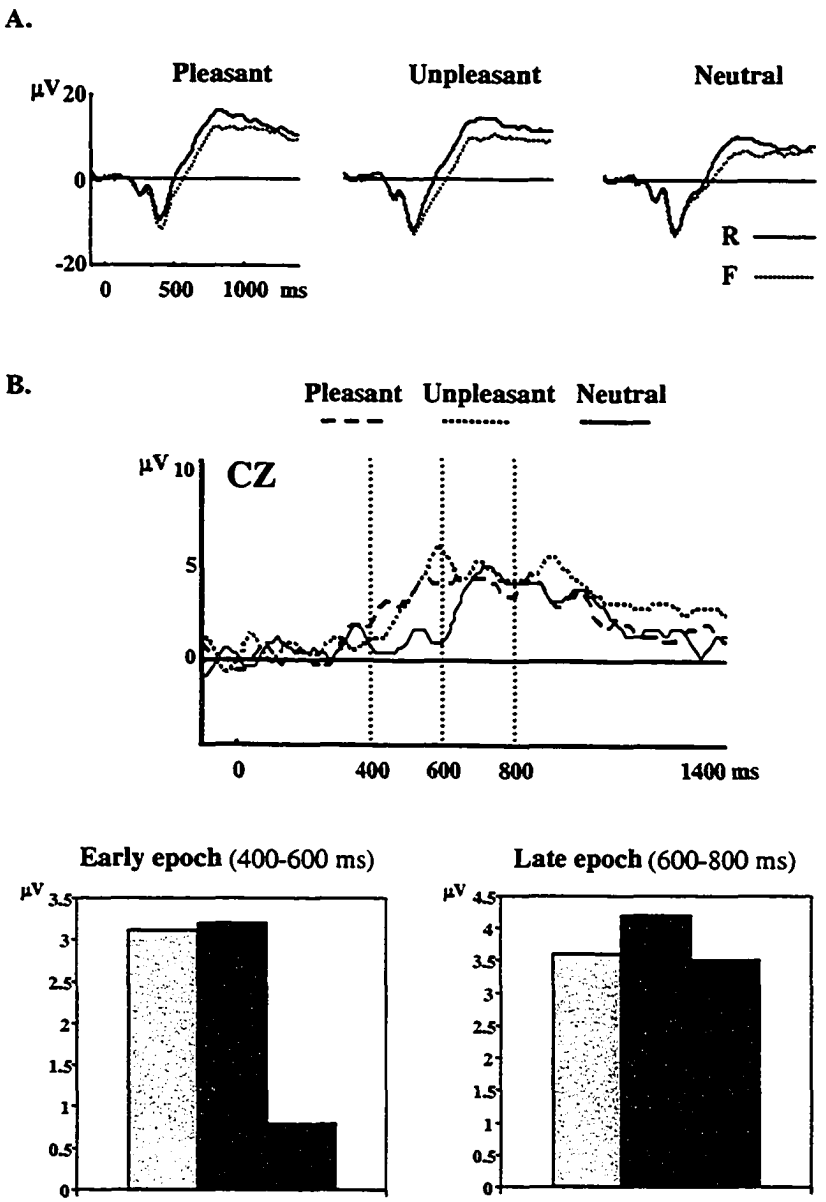

Figure 2-4. Modulatory effect of emotion on memory formation at CZ. **A.** Wave graphs comparing the ERPs for remembered (R) and forgotten (F) pictures. **B.** Subtraction (Recalled–Forgotten) wave and bar graphs comparing the subsequent memory effect for pleasant, unpleasant, and neutral pictures. During an early epoch (400-600 ms), the subsequent memory effect was larger for emotional than for neutral pictures; Light gray=Pleasant; Dark gray=Unpleasant; Black=Neutral.

CHAPTER 3

EFFECT OF EMOTION ON BRAIN ACTIVITY ASSOCIATED WITH EMOTIONAL EVALUATION AND EMOTIONAL MEMORY ENCODING – FMRI EVIDENCE

PART I

Coactivation of the Amygdala and Hippocampus Predicts Better Recall for Emotional than for Neutral Pictures

A version of this chapter had been published as a short report in *Brain and Cognition,* Vol. 51, 2003

Emotionally charged events tend to be better remembered than nonemotional events. This difference has been attributed to a modulatory effect of the amygdala on the hippocampus during memory encoding and consolidation (modulation hypothesis, McGaugh, 2000). This hypothesis is based mainly on animal evidence, but some functional neuroimaging evidence with humans is also available (Hamann, 2001). Here, the neural mechanisms underlying the formation of emotional memory were explored using event-related fMRI.

Two effects were measured: the *emotion effect* and the *subsequent memory effect*. The *emotion effect* refers to brain activity that is greater for emotional than for neutral stimuli. Previous functional neuroimaging studies have identified emotion effects in several regions including the amygdala, prefrontal cortex, anterior cingulate, posterior parietal, and insula (Davidson & Irwin, 1999). The *subsequent memory effect* refers to encoding activity that is greater for items that are subsequently remembered than for items that are subsequently forgotten. Previous event-related fMRI studies have identified subsequent memory effects in hippocampal and prefrontal regions (Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998). On the basis of emotion and subsequent memory effects, the following two issues were investigated.

1. Role of the amygdala during emotional evaluation. Neuroimaging studies of emotion have strongly associated the amygdala with the processing of unpleasant stimuli, but it is less clear how this region is involved in the processing of pleasant stimuli (Davidson & Irwin, 1999). To investigate this issue, we measured amygdalar activity during the processing of pleasant and unpleasant pictures.

2. Co-activation of the amygdala and hippocampus during emotional encoding

Previous neuroimaging studies have reported that amygdalar activity was correlated with the number of subsequently remembered emotional items (for a review, see Hamann, 2001). However, the modulation hypothesis assumes not only amygdalar activation, but also an effect of the amygdala on the hippocampus, and therefore it predicts that both the amygdala and the hippocampus are involved in emotional encoding. To investigate this issue, activity in these regions was compared for subsequently

remembered emotional and subsequently remembered neutral pictures, using event-related fMRI.

Methods

Participants

Fourteen young (mean age = 24.3 years) healthy right-handed female Duke University area participated in this study. All subjects gave informed consent to a protocol approved by the Duke University Institutional Review Board. Female participants were chosen because previous studies using similar stimuli have found that women are more physiologically reactive to emotional stimuli, and because women are more likely to report intense emotional experiences (Lang, Greenwald, Bradley, & Hamm, 1993; Shields, 1991).

Stimuli

Stimuli consisted of a pool of 180 pictures selected mainly from the International Affective Picture System (IAPS) and complemented with additional neutral pictures equated for complexity and human presence. IAPS pictures (Lang, Bradley, & Cuthberg, 1997) are rated on a 9-point scale both in terms of emotional arousal (1=calm and 9=excited) and emotional valence (1=unpleasant, 5=neutral, 9=pleasant). Based on these scores, 60 high-arousing and pleasant, 60 high-arousing and unpleasant, and 60 low-arousing and neutral pictures were compared. The pleasant and unpleasant pictures differed from each other in terms of emotional valence, but not in terms of emotional arousal, whereas both pleasant and unpleasant pictures differed from neutral pictures in terms of both arousal and valence.

Procedure

Similar to the procedure we employed in the event-related potential (ERP) study described in the previous chapter (Dolcos & Cabeza, 2002), subjects completed 6 consecutive study blocks of 30 pictures each (10 pleasant, 10 unpleasant, 10 neutral), which were randomly presented using an LCD projector. Pictures were presented for 3 sec, and followed by a 12-sec fixation. Participants were instructed to rate the pictures for pleasantness, using a 3-point scale (1=unpleasant, 2=neutral, 3=pleasant). Nothing was

mentioned about the subsequent memory test, so that learning was incidental. Following the scanning session, subjects performed a 45 min. cued-recall test, in which they were provided with a written cue for each picture, and had to describe in writing and in as many details as they could the pictures they remembered. Subjects were asked to provide enough details so that an outsider could identify each picture and discriminate it from similar studied pictures. Only pictures whose description was detailed enough to allow both identification and discrimination were classified as remembered.

fMRI Methods

Anatomical scanning. Thirty-four axial high-resolution T1-weighted structural images were acquired with a 450-ms TR (repetition time), a 9-ms TE (echo time), a 24-cm FOV (field of view), a 256^2 matrix, and a slice thickness of 3.75mm. Forty-six coronal T1-weighted images were then acquired using the same imaging parameters.

Functional scanning. Thirty-four contiguous gradient-echo echoplanar axial images (EPIs) sensitive to blood-oxygen level dependent contrast were acquired using the same slice prescription described above for the near-axial structural images. The EPIs were acquired as follows: TR = 3s, TE = 40ms, one radio frequency excitation, FOV = 24cm, image matrix = 64^2, and flip angle (FA) = 90°. Slice thickness was 3.75mm, resulting in cubic 3.75-mm^3 isotropic voxels.

Image preprocessing: All image preprocessing and statistical analyses were performed using SPM99. Functional images were corrected for acquisition order, and realigned to correct for motion artifacts. Anatomical images were coregistered with the first functional images for each subject, and both anatomical and functional images were spatially normalized to a standard stereotactic space. Functional images were spatially smoothed using an 8-mm isotropic Gaussian kernel.

Statistical analyses. For each subject, task-related activity was identified by a convolving vector of the onset times of the stimuli with a synthetic hemodynamic response and its temporal derivative. The general linear model, as implemented in SPM99, was used to model the effects of interest. Group analyses were conducted using random-effects models, as follows. (1) The emotion effect was calculated by comparing brain activity for pleasant and unpleasant pictures vs. neutral pictures. (2) The subsequent memory effect

was calculated by comparing brain activity for subsequently remembered pictures vs. subsequently forgotten pictures. The significance threshold was set at $p < 0.001$, uncorrected ($t > 3.85$). Additionally, ANOVAs were performed on the percent signal change measures extracted from regions of interest (ROIs) drawn on amygdala and hippocampus using custom software from the Brain Imaging and Analysis Center (BIAC) of Duke University.

Results

Behavioral Results

As expected, recall was better for emotional pictures (pleasant: 54%, unpleasant: 54%) than for neutral pictures (40%). An ANOVA yielded a significant picture type effect ($F(2,13) = 73.07$, $p < 0.0001$), and post-hoc contrasts indicated that recall of pleasant and unpleasant pictures was similar ($p > 0.05$) and higher than recall of neutral pictures (both $ps < 0.001$).

fMRI Results

Emotion effect. Compared to neutral pictures, emotional pictures (pleasant and unpleasant) were associated with greater activity in several brain regions, including the amygdala, medial frontal, medial and lateral parietal, and occipitotemporal cortices (Figure 3-1). Interestingly, the amygdala was activated by both unpleasant and pleasant pictures, and in the right amygdala activity was greater for unpleasant than for pleasant pictures (Figure 3-2).

Subsequent memory effect / modulatory effect of emotion on memory formation. Concerning the overall subsequent memory effect, compared to forgotten pictures, remembered pictures were associated with activations in several brain regions, including medial temporal lobe (MTL) and prefrontal cortex (PFC; Figure 3-3). The effect of emotion on brain activity during encoding was calculated by comparing brain activity for remembered-emotional vs. remembered-neutral pictures. As illustrated in Figure 3-4, this contrast revealed activity in both the amygdala and the hippocampus (Figure).

Discussion

The main result of the study was that both the amygdala and the hippocampus were more activated for remembered emotional than for remembered neutral pictures. Activity in these two structures paralleled the difference in memory performance, which was greater for emotional than for neutral pictures. This finding provides support for the idea that emotional stimuli exert their beneficial effect on memory performance by enhancing activity in the medial-temporal lobe memory system (*modulation hypothesis*).

A second finding of the study was that the amygdala is involved in the processing of both positive and negative stimuli. This result is consistent with evidence of amygdalar involvement in the processing of high-arousing pleasant stimuli (Hamann, Ely, Hoffman, & Kilts, 2002). At the same time, the finding that the right amygdala was more activated for unpleasant than for pleasant pictures is consistent with evidence suggesting that the amygdala is particularly sensitive to negative emotions (Davidson & Irwin, 1999). Thus, the present results suggest that the amygdala is involved in the processing of emotional arousal, while showing preference for negative valence.

References

Brewer, J. B., Zhao, Z., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (1998). Making memories: Brain activity that predicts how well visual experience will be remembered. *Science, 281*, 1185-1187.

Davidson, R. J., & Irwin, W. (1999). The functional neuroanatomy of emotion and affective style. *Trends in Cognitive Sciences, 3*(1), 11-20.

Dolcos, F., & Cabeza, R. (2002). Event-related potentials of emotional memory: Encoding pleasant, unpleasant, and neutral Pictures. *Cogn, Affect, & Behav Neurosci, 2*(3), 252-263.

Hamann, S. (2001). Cognitive and Neural Mechanisms of Emotional Memory. *Trends in Cognitive Sciences, 5*(9), 394-400.

Hamann, S. B., Ely, T. D., Hoffman, J. M., & Kilts, C. D. (2002). Ecstasy and agony: Activation of the human amygdala in positive and negative emotion. *Psychol Sci, 13*(2), 135-141.

Lang, P. J., Bradley, M. M., & Cuthberg, B. N. (1997). *International Affective Picture System* [Pictures]. Gainesville: NIMH Center for the Study of Emotion and Attention.

Lang, P. J., Greenwald, M. K., Bradley, M. M., & Hamm, A. O. (1993). Looking at pictures: Affective, facial, visceral, and behavioral reactions. *Psychophysiol, 30*(3), 261-273.

McGaugh, J. L. (2000). Memory-a century of consolidation. *Science, 287*(5451), 248-251.

Shields, S. (1991). Gender in the psychology of emotion: A selective research review. In K. Strongman (Ed.), *International Review of Studies on Emotion* (pp. 227-245). New York: Wiley.

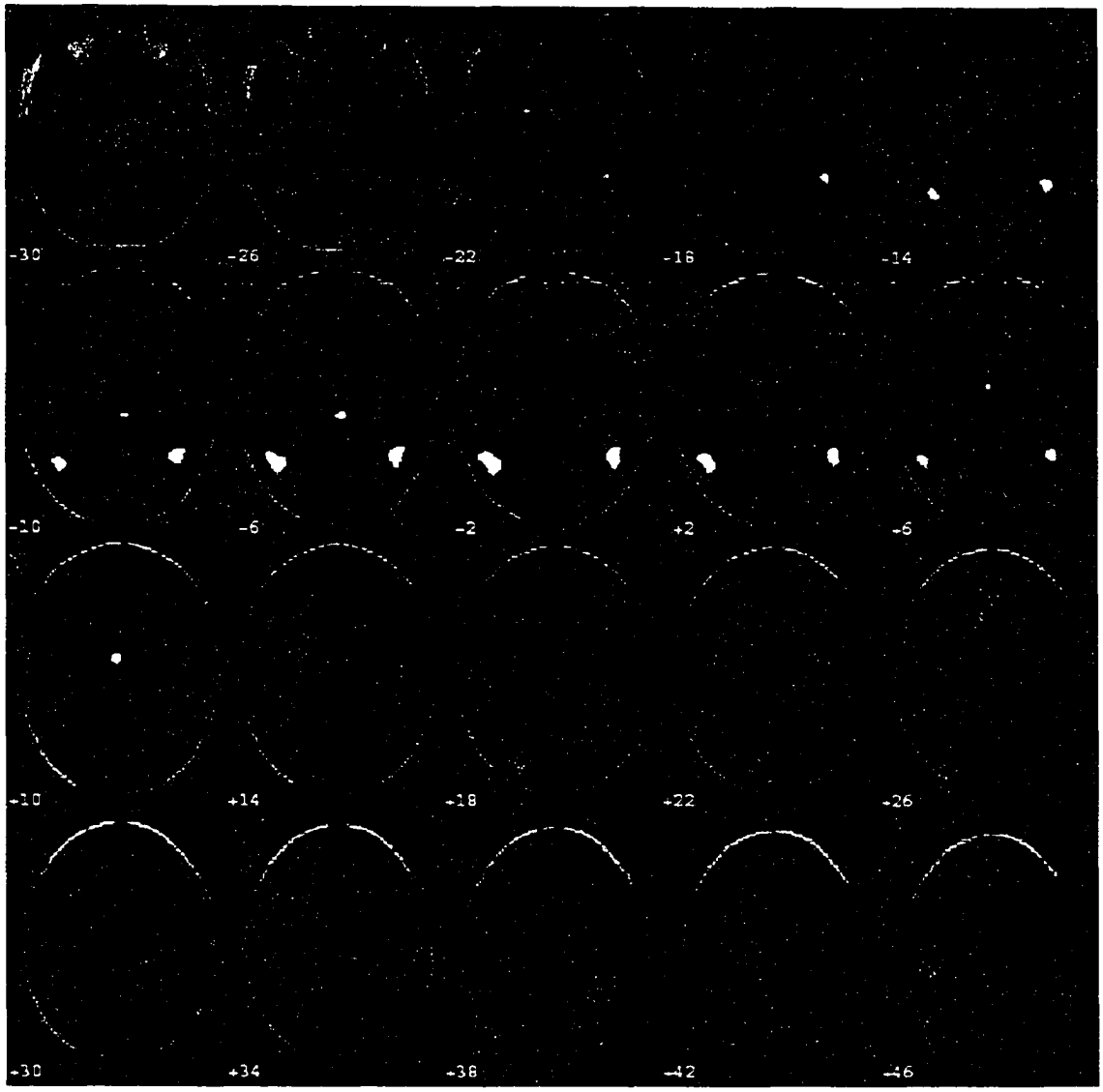

Figure 3-1. Greater activity for emotional than for neutral pictures (Emotion Effect). Compared to neutral pictures, emotional pictures were associated with greater activity in subcortical (i.e., amygdala, midbrain, and thalamus) and cortical (medial frontal, medial and lateral parietal, and occipitotemporal cortices) brain regions. The panel shows the SPM results superimposed on a standard high-resolution anatomical image. The results are plotted at a threshold of $p < 0.005$, uncorrected. Left side of the brain slices corresponds to the left side of the brain.

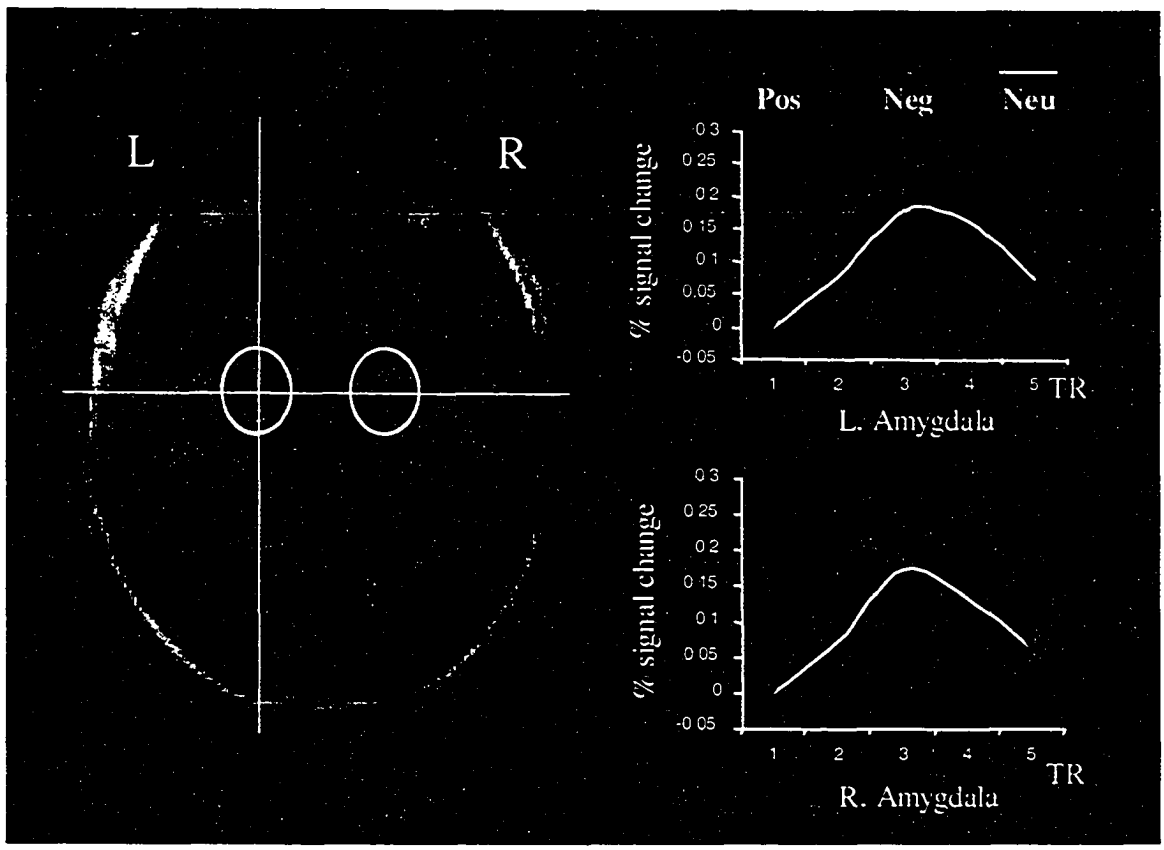

Figure 3-2. Greater amygdalar activity for emotional than for neutral pictures. The panel on the left side of the figure shows the SPM results superimposed on a standard high-resolution anatomical image (amygdalar activations are highlighted by the white circles). The results are plotted at a threshold of $p < 0.005$, uncorrected. The graphs compare the percent signal change for pleasant, unpleasant, and neutral pictures, as extracted from the most active amygdalar voxels. L = Left, R = Righ; Pos = Positive, Neg = Negative, Neu = Neutral; TR = Repetition Time (1 TR = 3 seconds).

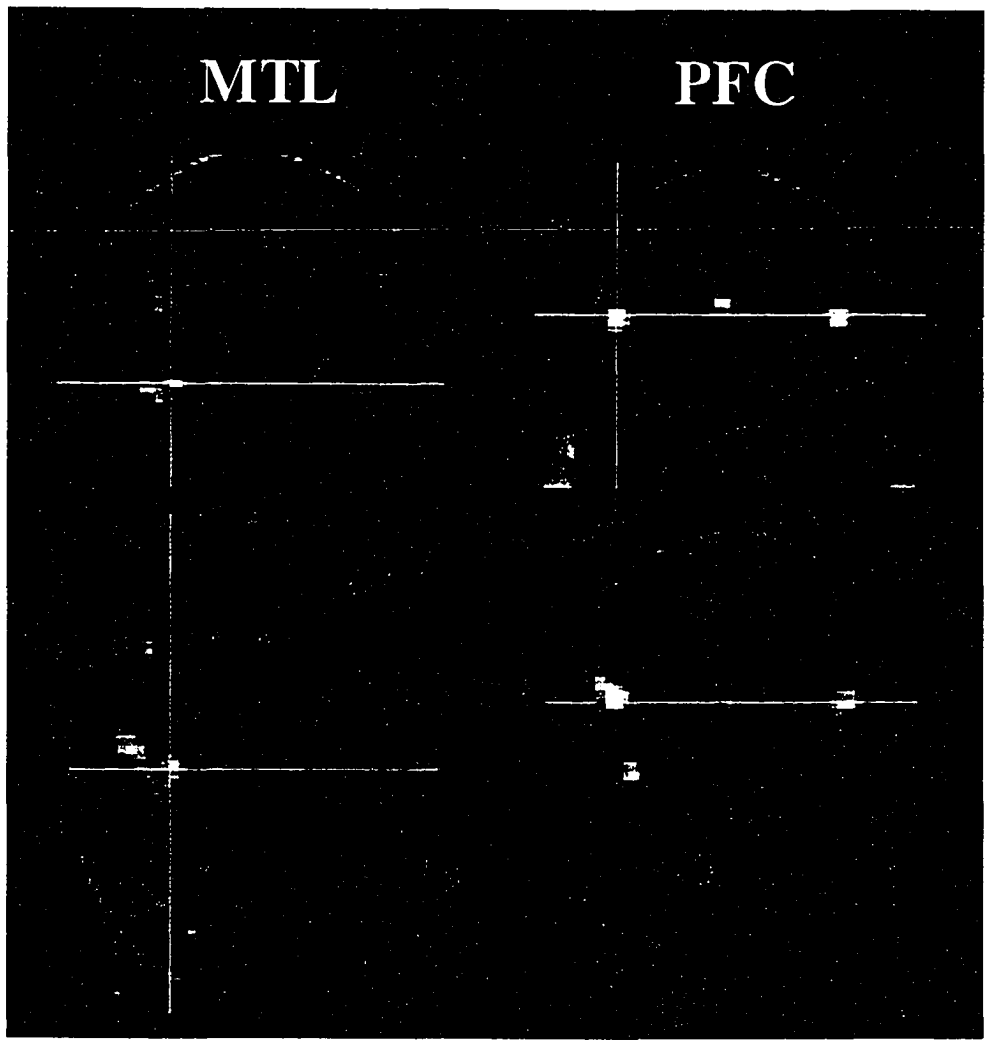

Figure 3-3. Greater MTL and PFC activity for remembered than for forgotten pictures (Subsequent memory effect). Compared to forgotten pictures, remembered pictures were associated with greater activity in the left medial temporal lobe (MTL) memory regions and bilaterally in the prefrontal cortex (PFC); left MTL and PFC activations are highlighted by the crosshairs. The panel shows the SPM results superimposed on a standard high-resolution anatomical image. The results are plotted at a threshold of $p < 0.01$, uncorrected. Left side of the brain slices corresponds to the left side of the brain.

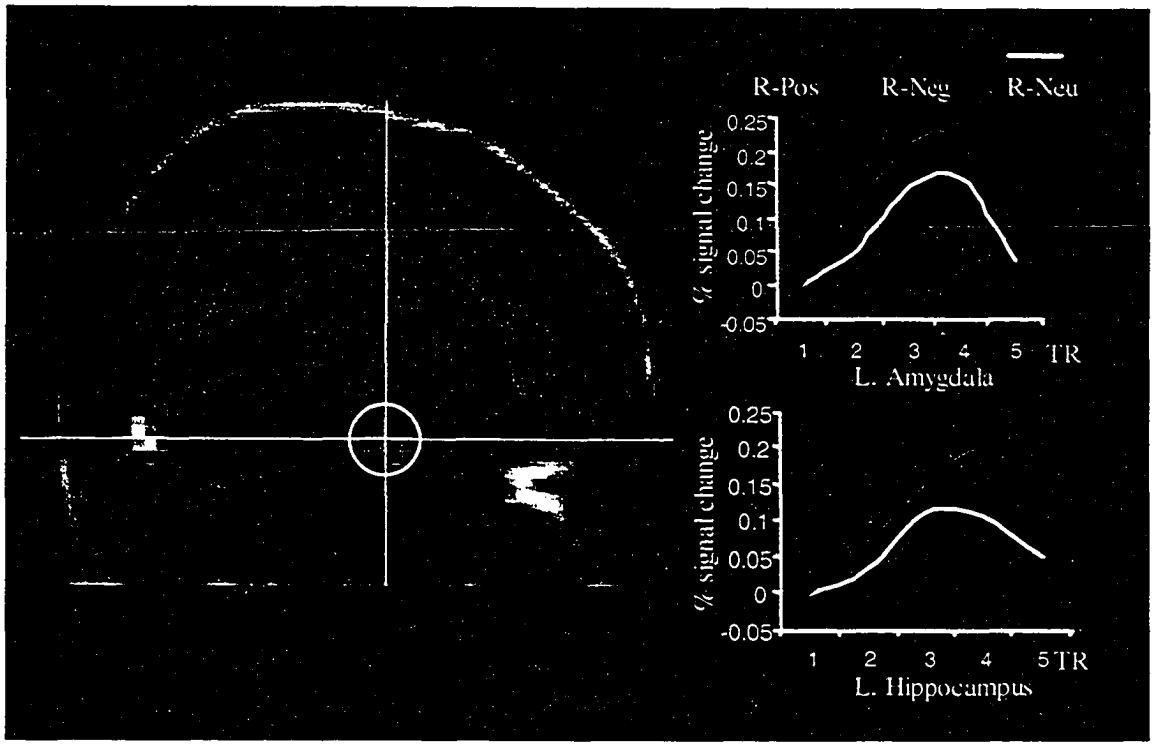

Figure 3-4. Greater amygdalar-hippocampal activity for remembered-emotional than for remembered-neutral pictures. The panel on the left side of the figure shows the SPM results superimposed on a standard high-resolution anatomical image (overlapping amygdalar-hippocampal activations from left hemisphere are highlighted by the white circle). The results are plotted at a threshold of $p < 0.01$, uncorrected. The graphs compare the percent signal change for positive, negative, and neutral pictures, as extracted from the most active amygdalar and hippocampal voxels. R = Remembered; Pos = Positive, Neg = Negative, Neu = Neutral; TR = Repetition Time (1 TR = 3 seconds).

CHAPTER 4

EFFECT OF EMOTION ON BRAIN ACTIVITY ASSOCIATED WITH EMOTIONAL EVALUATION AND EMOTIONAL MEMORY ENCODING – FMRI EVIDENCE

PART II

Interaction Between the Amygdala and the Medial Temporal Lobe Memory System Predicts Better Memory for Emotional Events

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Scientific and anecdotal evidence shows that emotionally arousing events tend to be better remembered than non-arousing and neutral events (Bradley et al., 1992; Christianson, 1992). According to the *modulation hypothesis* (McGaugh, 2000; McGaugh et al., 1996; McGaugh et al., 2002), the beneficial effect of emotion on memory is due to modulatory influences of the basolateral amygdala (BLA) on encoding and consolidation processes occurring in medial temporal lobe (MTL) memory structures, including the hippocampus and associated parahippocampal regions (i.e., entorhinal, perirhinal, and parahippocampal cortices; Squire and Zola-Morgan, 1991). Early evidence supporting the modulation hypothesis identified the hippocampus as a putative target for the modulatory influences from BLA (McGaugh et al., 1996), but more recent studies have also identified anterior parahippocampal regions, particularly the entorhinal cortex, as brain sites sensitive to amygdalar modulatory influences (McGaugh et al., 2002; Roesler et al., 2002).

Although the modulation hypothesis is supported by a considerable amount of evidence from nonhuman animals (McGaugh, 2000; McGaugh, 2002; McGaugh et al., 2002), direct evidence from humans is scarce. Neuropsychological studies of patients with amygdalar lesions have shown that these patients are impaired in some explicit tests of emotional memory (Adolphs et al., 1997; Adolphs et al., 2000; Cahill et al., 1995; LaBar and Phelps, 1998; Phelps et al., 1998). However, it is unclear if these deficits reflect a lack of amygdalar modulation or the damage of neighboring MTL regions. Also, lesion studies cannot easily distinguish whether memory difficulties reflect deficits during encoding, consolidation, or retrieval (LaBar and Phelps, 1998). Functional neuroimaging studies provide a greater spatial resolution and the ability to distinguish between encoding and retrieval, but they have not yet provided complete evidence for the modulation hypothesis.

The ideal neuroimaging method to investigate the modulation hypothesis is the *subsequent memory paradigm* (Paller et al., 1987; Paller and Wagner, 2002), which has been applied to both event-related potentials (ERP) and event-related functional magnetic resonance imaging (fMRI). In this paradigm, brain activity while items were encoded is analyzed according to whether the items were remembered or forgotten in a subsequent

memory test. Greater activity for subsequently remembered than for subsequently forgotten items is known as *Dm* (difference due to memory; Paller et al., 1987) and is assumed to reflect successful encoding processes. In the present study, we partitioned the Dm (remembered stimuli – forgotten stimuli) according to the emotional content of stimuli involved. More specifically, we measured an *emotional Dm* (remembered emotional stimuli – forgotten emotional stimuli) and a *neutral Dm* (remembered neutral stimuli – forgotten neutral stimuli). Using this method, the effects of emotion on successful encoding activity can be revealed by identifying regions where the emotional Dm is greater than the neutral Dm. In a previous ERP study, Dolcos & Cabeza (Dolcos and Cabeza, 2002) identified several significant differences between emotional and neutral Dms, but the ERP method did not provide a precise localization of the neural generators of the observed differences. Thus, in the present study the emotional Dm and the neutral Dm were compared using event-related fMRI.

The main goal of the study was to test the hypothesis that better memory for emotionally arousing than for non-arousing and neutral events is due to an effect of the amygdala on the MTL memory system during memory formation (modulation hypothesis). The following two predictions were derived from this hypothesis: (1) the *emotional Dm* (emotional remembered – emotional forgotten) should be greater than the *neutral Dm* (neutral remembered – neutral forgotten) in both the amygdala and the MTL memory system; and (2) the correlation between activity in the amygdala and the MTL memory system should be greater for the *emotional Dm* than for the *neutral Dm*. Additionally, a second goal of the study was to explore the possibility of anatomical specialization within the MTL memory system for effects of emotion on memory formation. Although little evidence is available, reasonable candidates are anterior MTL memory regions, particularly the hippocampus and the entorhinal cortex, which are not only richly interconnected with the amygdala (Amaral et al., 1992; Pitkanen et al., 2000) but have also been identified as potential targets of amygdalar modulatory influences in pharmacological and lesion studies (McGaugh et al., 2002; Roesler et al., 2002). Thus, the possibility that the effect of emotion on Dm activity would be more pronounced in anterior than in posterior MTL memory regions was also investigated.

To investigate these ideas, encoding-related activity from MTL regions was obtained using event-related fMRI while participants rated high-arousing emotional (both pleasant and unpleasant) and low-arousing neutral pictures for pleasantness. Cued recall for the pictures was assessed following scanning, and used to identify the *emotional Dm* and the *neutral Dm,* which were then compared to each other. Correlations between the Dm in amygdala and the MTL memory regions were also calculated for emotional and neutral stimuli. Emotional Dm was calculated by collapsing both categories of high-arousing pictures to form the *emotional* category. Activity in the amygdala and the MTL memory regions was identified using manually traced anatomical regions-of-interest (ROIs). The ROI approach was used because it provides a precise localization of the fMRI signal recorded from neighboring brain regions, such as those in the MTL. In the amygdala, the main focus was on separating the signal from BLA, which has been identified as the main site of amygdalar modulatory influences on memory-related activity in other brain regions. In the MTL memory system, ROI tracing first identified the main regions (i.e., the hippocampus and the parahippocampal gyrus), which were then further subdivided into their major subregions. Thus, following a rostro-caudal organization, the hippocampus was subdivided into head, body, and tail, and the parahippocampal gyrus (PHG) was subdivided into anterior and posterior PHG. Posterior PHG included the parahippocampal cortex. Finally, anterior PHG was further subdivided into entorhinal and perirhinal cortices.

Methods

Subjects

Sixteen young (mean age = 25 $\pm$ 4.6 yrs, all female), right-handed, healthy adults participated in the study. Female participants were chosen because previous studies showed that, compared to men, women are physiologically more reactive to emotional stimuli (Lang et al., 1993) and are more likely to report intense emotional experiences (Shields, 1991). All subjects provided written informed consent for a protocol approved by the Duke University Institutional Review Board.

Materials

Stimuli consisted of 120 high-arousing emotional (60 pleasant and 60 unpleasant), and 60 low-arousing neutral pictures selected from the International Affective Picture System (IAPS) series (Lang et al., 1997), based on their standard scores for emotional arousal and emotional valence. Pleasant and unpleasant pictures were equally arousing, and both were more arousing than the neutral pictures. The mean arousal score was 6.0 for pleasant (SD = 2.2), 6.15 for unpleasant (SD = 2.2), and 3.15 for neutral pictures (SD = 2.0). The mean valence score was 7.1 for pleasant (SD= 1.7), 2.3 for unpleasant (SD = 1.5), and 5.2 for neutral (SD = 1.4). To equate the emotional and neutral categories for visual complexity and content (e.g., human presence), the IAPS pictures were supplemented with neutral pictures from other sources (Yamasaki et al., 2002).

Procedure

The pool of 180 pictures was divided into six sets of 30 pictures (10 pleasant, 10 unpleasant, and 10 neutral), which were randomly assigned to six study blocks. Six different block orders were randomly assigned to the participants. To avoid the induction of long-lasting mood states, the pictures within each block were pseudo-randomized so that no more than two pictures of the same valence were consecutively presented. Functional MR images were recorded while subjects viewed the emotional and neutral pictures. Participants were instructed to experience any feelings or thoughts the pictures might trigger in them and to rate each picture for pleasantness using a 3-point scale (1 = unpleasant, 2 = neutral, 3 = pleasant). Nothing was mentioned about the subsequent memory test, before or during the encoding task (incidental learning). The pictures were presented, using an LCD projector, to a screen located behind the subjects' crown that subjects could see via an angled mirror. Each picture was presented for 3 sec and followed by a 12-sec fixation cross. This long inter stimulus interval (ISI) was used to allow the fMRI signal to come back to baseline and avoid elevated baseline activity prior to the onset of the next stimulus (Yamasaki, et al, 2002). This is an important issue to consider particularly in the context of comparing emotional and neutral stimuli using selective averaging of fMRI signal relative to ISI baseline. That is, it is possible that experiencing the emotion might continue into the fixation period, and thus selective

averaging relative to ISI baseline may reduce the magnitude of the response for these trials. Therefore, the use of long ISI and pseudo-randomization stimulus presentation, as well as the use of stimulus onset, rather than ISI, as baseline (see below) avoided a possible confound of the baseline with the trial types.

Forty-five minutes after the scanning session, subjects performed a surprise cued-recall test conducted outside the MRI suite. Subjects were provided with one- or two-word written cues for each picture (e.g., snake, building, skydivers) and had to describe in writing, and in as much detail as they could, the pictures they remembered. Participants were asked to provide enough relevant details (e.g., about the number of elements, color, action, etc.) so that an outsider could identify each picture and discriminate it from similar studied pictures (e.g., a brown snake facing viewer vs. several small green snakes). The test lasted until participants could not recall any additional pictures or until a maximum of 50 min had elapsed. Two raters were involved in the evaluation of the written descriptions provided by the subjects and only the pictures whose description was detailed enough to allow both identification and discrimination were classified as remembered. To illustrate this, consider the example of two similar pictures presented in Table 4-1. In this example, both pictures contain a snake with open mouth and both can be recalled based on this single cue. If the subjects only remember that they saw a snake with an open mouth, the raters can identify several possible pictures that fit the description, but they cannot distinguish among them. Hence, none of these pictures would be considered "recalled" without additional distinguishing details.

Functional MRI signal recorded during encoding was selectively averaged based on the emotion category (i.e., emotional vs. neutral) and on subsequent memory performance (i.e., remembered vs. forgotten = Dm). Since the main goal of the study was to compare the emotional Dm with the neutral Dm, the Dm was first calculated for both emotional and neutral pictures, separately. Then, emotional and neutral Dms were directly compared to each other. The basic assumption was that activity in brain regions showing greater emotional Dm than neutral Dm reflects emotional arousal modulations of encoding mechanisms.

Given the fact that subjects' rating scores were highly consistent with the IAPS standard scores (see Behavioral Results), the latter were used to separate the emotional and neutral categories. Also, behavioral (Bradley et al., 1992) and neuroimaging (Anderson et al., 2003; Hamann et al., 2002) evidence suggests that the emotional intensity rather than the emotional valence is the main factor determining amygdalar activity and long-term explicit memory for emotional stimuli. Therefore, the pleasant and unpleasant pictures were collapsed to form the *emotional* category. This procedure was methodologically suitable since pleasant and unpleasant pictures were equated for emotional arousal.

MRI Aquisition

Neuroimaging was performed using a 1.5 Tesla GE scanner. Two series of high-resolution T1-weighted structural images were acquired relative to the anterior commissure - posterior commissure (AC-PC) plane. Thirty-four axial (parallel to AC-PC plane) and forty-six coronal (perpendicular to AC-PC plane) were acquired using the following parameters: TR = 450 ms; TE = 9 ms; FOV = 24; matrix size = 256^2; slice thickness = 3.75 mm. Thirty-four contiguous functional images (gradient-echo echoplanar images sensitive to BOLD contrast) were acquired parallel to the AC-PC plane (TR = ms; TE = 40 ms; FOV = 24; matrix size = 64^2; FA = 90°; one radio frequency excitation; slice thickness = 3.75 mm, resulting in cubic voxels).

fMRI Data Analysis

Region of interest (ROI) analysis was performed using in-house software developed at Duke University's Brain Imaging and Analysis Center (Jha and McCarthy, 2000; Yamasaki et al., 2002). In this analysis, the fMRI signal is extracted from ROIs that are manually-traced on each subject's anatomical brain image. Consequently, it can provide a precise localization of the fMRI signal recorded from anatomically proximal brain regions, such as those from MTL.

Pre-processing and ROI tracing. Image preprocessing involved slice timing correction and coregistration. ROIs were manually-drawn on each participant's coronal brain images, based on corroborated guidelines for MTL tracing (Brierley et al., 2002;

Duvernoy et al., 1999; Insausti et al., 1998; Pruessner et al., 2002; Pruessner et al., 2000). In-house software packages were used for tracing ROIs in the following MTL regions: amygdala, hippocampus, and parahippocampal gyrus (PHG; see Figure 4-1A and B). The amygdalar ROIs were additionally divided into four quadrants. Particularly, we were interested in activity from the basolateral quadrant (BLA), since this region has been identified by animal research as the main site through which the amygdala modulates the memory-related activity in other brain regions (McGaugh, 2002; McGaugh et al., 2002). The hippocampal and PHG ROIs were also subdivided into their main anatomical components. Following a rostro-caudal organization, the hippocampus was subdivided into head, body, and tail, and the PHG was subdivided into anterior and posterior PHG. This anterior-posterior separation was employed as a result of evidence suggesting possible functional dissociations along the longitudinal axis of the MTL memory system (Amaral et al., 1992; Pitkanen et al., 2000; McGaugh et al., 2002; Roesler et al., 2002). The anterior PHG was further subdivided into medial and lateral portions corresponding to its anatomical subregions (i.e., entorhinal and perirhinal cortices, respectively). The boundaries among the hippocampal and PHG subregions, were identified in each subject using anatomical landmarks (Duvernoy et al, 1999; Insausti, et al., 1998; Pruessner et al., 2002). Consistent with anatomical nomenclature for MTL regions, in the present article the term "parahippocampal" refers generically to PHG regions. If it is associated with more specific terms (e.g., anterior vs. posterior), it refers either to both entorhinal and perirhinal cortices (anterior PHG) or to parahippocampal cortex proper (posterior PHG). The terms entorhinal and perirhinal both refer to specific subregions of the anterior PHG.

Statistical Analyses. ROI analysis employed two levels: individual and group analyses. For individual analyses, the fMRI signal extracted from all voxels contained in the ROIs was selectively averaged in each subject as a function of stimulus condition (e.g., remembered vs. forgotten), hemisphere, slice, and time point (one pre-stimulus and four post-stimulus onset time points were employed). For group analyses, ANOVAs were performed on the percent signal change relative to stimulus onset for each effect of interest (e.g., emotional Dm vs. neutral Dm) and MTL region. Furthermore, the ROI approach also involved correlation analyses. Across-subject pairwise Pearson correlation

tests between the Dm in the amygdala and in memory-related MTL regions (PHG and hippocampus) were performed on the average data extracted from each subject's ROIs and hemispheres, and compared for emotional and neutral pictures. For all analyses involving the fMRI signal extracted from *a priori* anatomically defined ROIs, the significance threshold was set at $p < 0.05$, uncorrected.

Results

Behavioral Results

Valence Ratings. The average valence scores (1 = unpleasant, 2 = neutral, 3 = pleasant) as rated by the participants in the scanner were 1.14 for unpleasant pictures (SD = 0.16), 2.18 for neutral pictures (SD= 0.40), and 2.64 for pleasant pictures (SD = 0.26). All pairwise comparisons were significant (ps < 0.0001). Thus, the subjects' rating scores were consistent with the normative scores provided by the International Affective Picture System (IAPS; Lang et al., 1997), which is the source of stimuli used in the present study. Further validating this consistency, the correlation between our subjects' average scores and the normed IAPS scores of the pictures used in the present study was highly significant ($R = 0.90$, $p < 0.0001$).

Memory Performance. As expected, mean recall ($\pm$ SD) was better for high-arousing and emotional pictures (pleasant: 52 $\pm$ 4.5 %, unpleasant: 53 $\pm$ 4.8 %) than for low-arousing and neutral pictures (38 $\pm$ 4.8 %). An ANOVA yielded a significant picture type effect ($F(2, 15) = 41.21$, $p < 0.0001$). Post-hoc contrasts showed that recall of pleasant and unpleasant pictures was similar ($p > 0.05$), and recall for both high-arousing categories was higher than that for neutral pictures (ps < 0.0001).

FMRI Results

Effect of Emotion on Dm in the Amygdala and MTL memory system

Confirming the first prediction, the emotional Dm was greater than the neutral Dm in both the amygdala and the MTL memory system. As seen in Figure 4-1 and Table 4-1, ANOVAs computed on data extracted from anatomically-defined ROIs at peak time

points and activation slices / subregions yielded a significant emotion effect on Dm in the amygdala, hippocampus, and anterior PHG but not in the posterior PHG. Interestingly, in the amygdala this difference occurred in the basolateral (BLA) aspect of the amygdalar ROI, in the hippocampus it occurred in its most anterior part (the head), and in the anterior PHG it occurred in the entorhinal cortex.

Correlation between emotional Dm in amygdala and MTL memory system

Confirming the second prediction, greater correlations between the amygdala and MTL memory system were found for the emotional Dm than for the neutral Dm. Correlations were calculated for both the regions showing the greatest differences between the emotional Dm and the neutral Dm (i.e., BLA, head of the hippocampus, and the entorhinal cortex) and for those whose Dm activity was not modulated by emotion (i.e., the body and tail of the hippocampus, and the parahippocampal cortex). As illustrated by Table 4-1, Pearson coefficients calculated across subjects showed that the correlation between the emotional Dm in the amygdala and the MTL memory regions were highly significant and greater for emotional than for neutral pictures. In other words, the subjects showing greater emotional Dm in the amygdala also showed greater emotional Dm in the MTL memory regions. Correlations between the Dm in amygdala and hippocampus were significant and greater for emotional than for neutral pictures when they involved the whole hippocampal structure or when the correlations where calculated separately for the head and the body, but not when Dm activity from the tail was involved. The maximum difference in correlation between the Dm for emotional and neutral stimuli occurred for the amygdala-entorhinal cortex correlation, which was highly significant for the emotional pictures ($R = 0.77$, $p < 0.0003$) but not for the neutral pictures ($R = 0.02$, $p > 0.9$; see Table 4-1 and Figure 4-2), and the difference between these two correlations was also significant ($p < 0.01$). Taken together, the present results suggest that the amygdala and the MTL memory regions are coactivated more consistently during successful encoding of emotional pictures than during successful encoding of neutral pictures.

Double dissociation between emotional and neutral Dm along the longitudinal axis of MTL memory system

As expected, the emotional Dm was greater in the anterior than in the posterior MTL memory regions. Additionally, the reverse pattern was found for the neutral Dm, demonstrating a double dissociation between the anterior and the posterior regions. To test for this double dissociation in the hippocampus, an ANOVA was conducted to compare the Dm for emotional and neutral stimuli in the most anterior (head) and most posterior (tail) hippocampal regions, calculated at the peak time point and averaged across hemispheres. Confirming the double dissociation, this 2 (Region: head vs. tail) by 2 (Emotion: emotional vs. neutral) ANOVA yielded a significant interaction ($F(1, 15) = 5.7$, $p < 0.05$). To test for this double dissociation in PHG, a similar ANOVA was conducted to compare the Dm for emotional and neutral stimuli in anterior vs. posterior PHG regions. Again, confirming the anterior-posterior double dissociation, a 2 (Region: anterior vs. posterior) x 2 (Emotion: emotional vs. neutral) design yielded a significant interaction ($F(1, 15) = 11.25$, $p < 0.005$), which was more significant when the entorhinal ($F(1, 15) = 10.9$, $p < 0.005$; see also Figure 4-3) rather than the perirhinal cortex was compared to the posterior PHG ($F(1, 15) = 5.8$, $p < 0.03$).

Discussion

The present study yielded three main findings. The first two findings are consistent with the modulation hypothesis: (1) the emotional Dm was greater than the neutral Dm in both the amygdala and the MTL memory system, and (2) the correlation between the amygdala and the MTL memory system was greater for the emotional Dm than for the neutral Dm. The third finding was a dissociation between anterior and posterior MTL memory regions: whereas anterior regions showed a greater emotional Dm, posterior regions showed a greater neutral Dm.

Evidence for the modulation hypothesis

Successful encoding activity in the amygdala and MTL memory structures was greater and more strongly correlated for emotionally-arousing than for neutral pictures. Initial positron emission tomography (PET) studies exploring the neural correlates of emotional encoding suggested a link between amygdala activity at encoding and memory for emotionally-arousing material (Cahill et al., 1996; Hamann et al., 1999). However,

these studies used blocked designs that cannot accommodate the subsequent memory paradigm to distinguish brain activity for successfully vs. unsuccessfully encoded stimuli within participants. More recent fMRI studies by Canli and colleagues (Canli et al., 2002; Canli et al., 2000) used event-related designs to examine emotional memory formation, but they focused primarily on the amygdala and did not report correlations between the amygdala and the MTL memory regions. Moreover, these previous PET and fMRI studies used voxel-wise analyses, which, because of the normalization of individual variations in human anatomy to a standard brain template and image smoothing, do not provide an accurate localization in neighboring MTL regions. The extant human literature thus implicates involvement of the amygdala in emotional memory but has not revealed the mechanisms by which the amygdala interfaces with other memory processing areas of the brain. By addressing these limitations, the present study provides more direct evidence for the modulation hypothesis in humans.

The use of anatomical ROIs also allowed identification of specific subregions of the amygdala and MTL memory system that are sensitive to emotion effects during encoding. Within the amygdala, the emotional memory effects (i.e., emotional Dm > neutral Dm) were largest in its basolateral aspect (BLA), which is anatomically interconnected with the fronto-temporal neocortex (Amaral et al., 1992) and has been identified by animal research on emotional memory as the main site through which the amygdala modulates memory-related activity in other brain regions (McGaugh, 2000; McGaugh, 2002; McGaugh et al., 2002). Within the MTL memory system, the effect of emotion on Dm was most pronounced in its anterior portion, comprising both hippocampal and parahippocampal regions. The involvement of these regions in successful encoding is consistent with the results of fMRI studies using the subsequent memory paradigm (Brewer et al., 1998; Davachi and Wagner, 2002; Kirchhoff et al., 2000; Otten et al., 2001; Otten and Rugg, 2001; Strange et al., 2002; Wagner et al., 1998; for a review see Paller and Wagner, 2002), and with animal studies that place the PHG, particularly the entorhinal cortex, in a key position within the MTL memory system (Eichenbaum, 2000; Squire and Zola-Morgan, 1991). The fact that the emotion effect on Dm activity in the MTL memory system was maximal in the anterior hippocampus and

entorhinal cortex fits well with anatomical evidence that these regions are recipients of rich feedback projections from the amygdala (Amaral et al., 1992; Pitkanen et al., 2000). Moreover, these regions have been also associated with the effects of emotion on memory in pharmacological and lesion studies (McGaugh et al., 2002; Roesler et al., 2002).

In addition to the finding that the emotional Dm was greater than the neutral Dm in both the amygdala and the anterior MTL memory regions, the present results showed that the correlation between Dm activity in these regions was greater for the emotional than for the neutral stimuli. This finding suggests that these regions interact more intimately during the encoding of emotional stimuli than during the encoding of neutral stimuli. Although correlations do not imply causation, our findings are consistent with the hypothesis that the amygdala enhances processing of emotional stimuli in MTL memory regions, thereby leading to better memory for emotional than for neutral information (McGaugh, 2002). Thus, the combined finding that successful encoding activity in the amygdala and MTL memory regions were both greater and more strongly correlated for emotional than for neutral stimuli is strong evidence for the modulation hypothesis in humans. The left-sided bias of the amygdala-entorhinal correlation is consistent with previous studies of emotional memory in female participants (Cahill et al., 1996; Canli et al., 2002), and may reflect deeper semantic processing or other verbal strategies (Funayama et al., 2001).

It is unclear why the effect of emotion on successful encoding activity was stronger for the entorhinal cortex than the hippocampus. This difference may be related to factors influencing the detection of Dm with fMRI. In fact, several fMRI studies found the Dm in parahippocampal regions but not in the hippocampus (Brewer et al., 1998; Otten and Rugg, 2001; Wagner et al., 1998), and it is uncertain why other studies found it in both regions (e.g. Davachi and Wagner, 2002; Kirchhoff et al., 2000; Otten et al., 2001; Strange et al., 2002). Alternatively, larger effect of emotion on entorhinal cortex vs. hippocampus may be related to the timing of the modulatory influence. That is, the neurohormonal influences of the amygdala on the consolidation processes occurring in the hippocampus, as reported in animal studies, are typically found after longer retention intervals (i.e., several hours or days; McGaugh and Roozendaal, 2002; Roesler et al,

2002), whereas the present results are based on a shorter retention interval (less than an hour). Thus, the present entorhinal findings may reflect short-term neuronal effects rather than long-term neurohormonal effects. At any rate, the present results are consistent with the notion that emotional arousal exerts its beneficial effect on explicit memory through interactions between the amygdala and memory-related MTL regions.

Functional dissociation along the longitudinal axis of MTL

The second goal of the study was to investigate the existence of MTL memory regions differentially sensitive to the effects of emotion on successful encoding. Confirming this idea, the emotional Dm was greater in anterior rather than posterior sectors of the MTL memory system. Additionally, the neutral Dm was greater in posterior than in anterior MTL memory regions. In other words, a double dissociation along the longitudinal axis of the MTL was identified (see Figure 4-3). The emotional Dm was greater in the anterior hippocampus (the head) and anterior PHG (particularly in the entorhinal cortex), whereas the neutral Dm was greater in the posterior hippocampus (the tail) and posterior PHG (i.e., parahippocampal cortex). The finding that the emotional Dm was greater in anterior MTL memory regions is consistent with anatomical evidence that these regions are richly interconnected with the amygdala (Amaral et al., 1992; Pitkanen et al., 2000), and with animal evidence specifically identifying amygdalar modulation of emotional memory formation in both hippocampal and entorhinal regions (McGaugh et al., 2002; Roesler et al., 2002). This finding is also consistent with a neuroimaging study that found activity related to emotional memory in anterior PHG (Alkire et al., 1998), although this evidence was not conclusive since activity in this region was also related to neutral memory. Even though greater neutral Dm in the posterior than in the anterior MTL was not predicted, it is consistent with the results of several neuroimaging studies of successful encoding of neutral stimuli (Alkire et al., 1998; Brewer et al., 1998; Wagner et al., 1998; for a review, see Paller and Wagner, 2002).

It could be argued that the greater neutral Dm in posterior MTL, particularly in the posterior PHG, reflected a confound with the amount of scene information in neutral pictures, as compared to emotional pictures. Given that posterior PHG ("parahippocampal

place area") is activated by scene perception (Epstein and Kanwisher, 1998) and during the encoding of complex scenes (Brewer et al., 1998; Gabrieli et al., 1997), it is important to determine that scene content did not differ between emotional and neutral stimuli. To investigate this idea, 10 participants were asked to rate the stimuli using a scene content scale (1 = no scene content, 4 = very high scene content). The ratings for emotional (1.86) and neutral (1.93) pictures were similar ($T = 0.64$, $p > 0.5$), suggesting an equivalent amount of scene information in the two classes of stimuli. Nevertheless, Dm activity in PHG was analyzed using a 3-way ANOVA with scene content (low vs. high), PHG region (anterior vs. posterior), and emotion (emotional vs. neutral) as the factors. A nonsignificant 3-way interaction ($F(1, 15) = 0.62$, $p > 0.44$) confirmed that neutral Dm in posterior PHG was not differentially greater for pictures with high scene content. This non-significant interaction was also confirmed when the same ANOVA was performed separately for the entorhinal ($F(1, 15) = 2.5$, $p > 0.13$; see Figure 4-3) and perirhinal ($F(1, 15) = 0.53$, $p > 0.47$) cortices vs. parahippocampal cortex, and when anterior and posterior hippocampal regions (head vs. tail) where compared to each other ($F(1, 15) = 0.67$, $p > 0.42$). These results, together with the fact that emotional and neutral pictures were equated for complexity, presence of human figures, and other lower-level visual features (Yamasaki et al., 2002), suggest that scene content or perceptual factors cannot account for the differences between anterior and posterior PHG activity. Thus, the present double dissociation represents the first direct evidence that different regions of the MTL memory system are differentially involved in the successful encoding of emotional vs. neutral stimuli.

Several hypotheses with respect to possible rostrocaudal segregations of MTL function have been proposed. One model suggests that anterior MTL regions may be more important for relational aspects of encoding, whereas posterior regions are more important in item-related aspects of encoding (Schacter and Wagner, 1999). Another dissociation following the functional organization along the ventral visual pathway (Ungerleider, 1995) proposes that posterior regions, closer to the primary visual cortex, are more associated with lower-level perceptual processes, whereas more anterior regions are associated with higher-level mnemonic processes. The present results are consistent

with both kinds of models. One possibility is that the greater emotional Dm in the anterior MTL memory regions reflects enhanced semantic and relational processing for emotional stimuli, whereas the greater neutral Dm in the posterior MTL reflects enhanced perceptual processing for neutral stimuli. This idea is compatible with evidence that anterior MTL regions are associated with memory for semantic information and posterior MTL regions with memory for perceptual information (Cabeza et al., 2001). Although future research is needed to clarify the specific mechanism involved, the double dissociation revealed by the present study clearly indicates that different MTL sectors are specialized to encode emotional and neutral information into long-term memory.

Conclusions

Remembering emotionally-arousing events entails concomitant activity in an amygdala-based emotional processing system and in MTL regions that support various mnemonic functions. Results from the present study provided novel insights into the neural mechanisms associated with the formation of explicit emotional memories in the intact human brain. Successful encoding activity in the amygdala and MTL memory structures was greater and more strongly correlated for emotional than for neutral pictures. Furthermore, a double dissociation was observed along the longitudinal axis of the MTL memory system for successful encoding of emotional and neutral stimuli. The results support the modulation hypothesis of emotional memory as developed from animal models and provide clear neuroimaging evidence that emotionally-arousing stimuli exert their beneficial effect on episodic memory by enhancing activity in both the amygdala and the MTL memory system in the human brain. The present study also highlights the key position of the entorhinal cortex in this process. Taken together, the findings advance an understanding of the MTL mechanisms underlying emotional memory formation and their conservation across species.

References

Adolphs, R., Cahill, L., Schul, R., and Babinsky, R. (1997). Impaired declarative memory for emotional material following bilateral amygdala damage in humans. Learn Mem 4, 291-300.

Adolphs, R., Tranel, D., and Denburg, N. (2000). Impaired emotional declarative memory following unilateral amygdala damage. Learn Mem 7, 180-186.

Alkire, M. T., Haier, R. J., Fallon, J. H., and Cahill, L. (1998). Hippocampal, but not amygdala, activity at encoding correlates with long-term, free recall of nonemotional information. Proc Natl Acad Sci U S A 95, 14506-14510.

Amaral, D. G., Price, J. L., Pitkanen, A., and Carmichael, S. T. (1992). Anatomical organization of the primate amygdaloid complex. In The Amygdala, Neurobiological Aspects of Emotion, Memory and Mental Dysfunction, J. P. Aggleton, ed. (New York, Wiley-Liss), pp. 1-66.

Anderson, A. K., Christoff, K., Stappen, I., Panitz, D., Ghahremani, D. G., Glover, G., Gabrieli, J. D., and Sobel, N. (2003). Dissociated neural representations of intensity and valence in human olfaction. Nat Neurosci 6, 196-202.

Bradley, M. M., Greenwald, M. K., Petry, M. C., and Lang, P. J. (1992). Remembering pictures: Pleasure and arousal in memory. J Exp Psychol: Learn, Mem, & Cogn 18, 379-390.

Brewer, J. B., Zhao, Z., Desmond, J. E., Glover, G. H., and Gabrieli, J. D. (1998). Making memories: Brain activity that predicts how well visual experience will be remembered. Science 281, 1185-1187.

Brierley, B., Shaw, P., and David, A. S. (2002). The human amygdala: A systematic review and meta-analysis of volumetric magnetic resonance imaging. Brain Res Rev 39, 84-105.

Cabeza, R., Rao, S. M., Wagner, A. D., Mayer, A. R., and Schacter, D. L. (2001). Can medial temporal lobe regions distinguish true from false? An event- related functional MRI study of veridical and illusory recognition memory. Proc Natl Acad Sci U S A 98, 4805-4810.

Cahill, L. (1998). Interactions between Catecholamines and the Amygdala in Emotional Memory: Subclinical and Clinical Evidence. Advances in Pharmacology 42, 964-967.

Cahill, L., Babinsky, R., Markowitsch, H., and McGaugh, J. L. (1995). The amygdala and emotional memory. Nature 377, 295-296.

Cahill, L., Haier, R. J., Fallon, J., Alkire, M. T., Tang, C., Keator, D., Wu, J., and McGaugh, J. L. (1996). Amygdala activity at encoding correlated with long-term, free recall of emotional information. Proc Natl Acad Sci U S A 93, 8016-8021.

Canli, T., Desmond, J. E., Zhao, Z., and Gabrieli, J. D. E. (2002). Sex differences in the neural basis of emotional memories. Proc Natl Acad Sci U S A 99, 10789-10794.

Canli, T., Zhao, Z., Brewer, J., Gabrieli, J. D. E., and Cahill, L. (2000). Event-related activation in the human amygdala associated with later memory for individual emotional experience. J Neurosci 20, 1-5.

Christianson, S.-A. (1992). The Handbook of Emotion and Memory: Research and Theory, (Lawrence Erlbaum Associates).

Davachi, L., and Wagner, A. D. (2002). Hippocampal contributions to episodic encoding: Insights from relational and item-based learning. J Neurophysiol 88, 982–990.

Dolcos, F., and Cabeza, R. (2002). Event-related potentials of emotional memory: Encoding pleasant, unpleasant, and neutral Pictures. Cogn, Affect, & Behav Neurosci 2, 252-263.

Duvernoy, H. M., Bourgouin, P., Cabanis, E. A., Cattin, F., Guyot, J., Iba-Zizen, M. T., Maeder, P., Parratte, B., Tatu, L., and Fuillier, F. (1999). The Human Brain: Surface, Three-Dimensional Sectional Anatomy With Mri, and Blood Supply, 2nd Edition edn (Wien, Springer-Verlag Wien New York).

Eichenbaum, H. (2000). A cortical-hippocampal system for declarative memory. Nat Rev Neurosci 1, 41-50.

Epstein, R., and Kanwisher, N. (1998). A cortical representation of the local visual environment. Nature 392, 598-601.

Funayama, E. S., Grillon, C., Davis, M., and Phelps, E. A. (2001). A double dissociation in the affective modulation of startle in humans: Effects of unilateral temporal lobectomy. J Cogn Neurosci 13, 721-729.

Gabrieli, J. D. E., Brewer, J. B., Desmond, J. E., and Glover, G. H. (1997). Separate neural bases of two fundamental memory processes in the human medial temporal lobe. Science 276, 264–266.

Hamann, S. B., Ely, T. D., Grafton, S. T., and Kilts, C. D. (1999). Amygdala activity related to enhanced memory for pleasant and aversive stimuli. Nat Neurosci 2, 289-293.

Hamann, S. B., Ely, T. D., Hoffman, J. M., and Kilts, C. D. (2002). Ecstasy and agony: Activation of the human amygdala in positive and negative emotion. Psychol Sci 13, 135-141.

Insausti, R., Juottonen, K., Soininen, H., Insausti, A. M., Partanen, K., Vainio, P., Laakso, M. P., and Pitkanen, A. (1998). MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. Am J Neuroradiol 19, 659-671.

Jha, A. P., and McCarthy, G. (2000). The influence of memory load upon delay-interval activity in a working-memory task: An event-related functional MRI study. J Cogn Neurosci 12 Suppl 2, 90-105.

Kirchhoff, B. A., Wagner, A. D., Maril, A., and Stern, C. E. (2000). Prefrontal-temporal circuitry for episodic encoding and subsequent memory. J Neurosci 20, 6173-6180.

LaBar, K. S., and Phelps, E. A. (1998). Arousal-mediated memory consolidation: Role of the medial temporal lobe in humans. Psychol Sci 9, 490-493.

Lang, P. J., Bradley, M. M., and Cuthberg, B. N. (1997). International Affective Picture System (Gainesville, NIMH Center for the Study of Emotion and Attention).

Lang, P. J., Greenwald, M. K., Bradley, M. M., and Hamm, A. O. (1993). Looking at pictures: Affective, facial, visceral, and behavioral reactions. Psychophysiol 30, 261-273.

McGaugh, J. L. (2000). Memory-a century of consolidation. Science 287, 248-251.

McGaugh, J. L. (2002). Memory consolidation and the amygdala: A systems perspective. Trends Neurosci 25, 456-461.

McGaugh, J. L., Cahill, L., and Roozendaal, B. (1996). Involvement of the amygdala in memory storage: Interaction with other brain systems. Proc Natl Acad Sci U S A 93, 13508-13514.

McGaugh, J. L., McIntyre, C. K., and Power, A. E. (2002). Amygdala modulation of memory consolidation: interaction with other brain systems. Neurobiology of Learning and Memory 78, 539-552.

McGaugh, J. L., and Roozendaal, B. (2002). Role of adrenal stress hormones in forming lasting memories in the brain. Curr Opin Neurobiol 12, 205-210.

Otten, L. J., Henson, R. N., and Rugg, M. D. (2001). Depth of processing effects on neural correlates of memory encoding: relationship between findings from across- and within-task comparisons. Brain 124, 399-412.

Otten, L. J., and Rugg, M. D. (2001). Task-dependency of the neural correlates of episodic encoding as measured by fMRI. Cerebral Cortex 11, 1150–1160.

Paller, K. A., Kutas, M., and Mayes, A. R. (1987). Neural correlates of encoding in an incidental learning paradigm. Electroenc Clin Neuropsychol 67, 360-371.

Paller, K. A., and Wagner, A. D. (2002). Observing the transformation of experience into memory. Trends Cogn Sci 6, 93-102.

Phelps, E. A., LaBar, K. S., Anderson, A. K., O'Connor, K. J., Fulbright, R. K., and Spencer, D. D. (1998). Specifying the contributions of the human amygdala to emotional memory: A case study. Neurocase 4, 527-540.

Pitkanen, A., Pikkarainen, M., Nurminen, N., & Ylinen, A. (2000). Reciprocal connections between the amygdala and the hippocampal formation, perirhinal cortex, and postrhinal cortex in rat. A review. Annals NY Academy of Sciences, 911, 369-391.

Pruessner, J. C., Kohler, S., Crane, J., Pruessner, M., Lord, C., Byrne, A., Kabani, N., Collins, D. L., and Evans, A. C. (2002). Volumetry of temporopolar, perirhinal, entorhinal and parahippocampal cortex from high-resolution MR images: considering the variability of the collateral sulcus. Cereb Cortex 12, 1342-1353.

Pruessner, J. C., Li, L. M., Serles, W., Pruessner, M., Collins, D. L., Kabani, N., Lupien, S., and Evans, A. C. (2000). Volumetry of hippocampus and amygdala with high-resolution MRI and three-dimensional analysis software: minimizing the discrepancies between laboratories. Cereb Cortex 10, 433-442.

Roesler, R., Roozendaal, B., and McGaugh, J. L. (2002). Basolateral amygdala lesions block the memory-enhancing effect of 8-Br-cAMP infused into the entorhinal cortex of rats after training. European Journal of Neuroscience 15, 905-910.

Schacter, D. L., and Wagner, A. D. (1999). Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. Hippocampus 9, 7-24.

Shields, S. (1991). Gender in the psychology of emotion: A selective research review. In International Review of Studies on Emotion, K. Strongman, ed. (New York, Wiley), pp. 227-245.

Squire, L. R., and Zola-Morgan, S. (1991). The medial temporal lobe memory system. Science 253, 1380-1386.

Strange, B. A., Otten, L. J., Josephs, O., Rugg, M. D., and Dolan, R. J. (2002). Dissociable human perirhinal, hippocampal, and parahippocampal roles during verbal encoding. The Journal of Neuroscience 22, 523–528.

Ungerleider, L. G. (1995). Functional brain imaging studies of cortical mechanisms for memory. Science 270, 769-775.

Wagner, A. D., Schacter, D. L., Rotte, M., Koutstaal, W., Maril, A., Dale, A. M., Rosen, B. R., and Buckner, R. L. (1998). Building memories: Remembering and forgetting of verbal experiences as predicted by brain activity. Science 281, 1188-1191.

Yamasaki, H., Labar, K. S., and McCarthy, G. (2002). Dissociable prefrontal brain systems for attention and emotion. Proc Natl Acad Sci U S A 99, 11447-11451.

MTL Regions	EmoDm > NeuDm (F scores)	Amygdala - MTL Correlations (R scores - EmoDm)	Amygdala - MTL Correlations (R scores - NeuDm)
Amygdala	5.09*; (BLA)	N/A	N/A
Hippocampus (whole)	-	0.67**	0.54*
Hippocampus (head)	6.67*; (L)	0.78****	0.60*
Hippocampus (body)	-	0.75***; (R)	0.46
Hippocampus (tail)	-	-	-
Anterior PHG (whole)	6.63*	0.77***; (BLA / L)	0.03
Anterior PHG (entorhinal ctx.)	6.43*	0.77***; (BLA / L)	0.02
Anterior PHG (perirhinal ctx.)	-	0.59*; (BLA / L)	- 0.05
Posterior PHG (parahippocampal ctx.)	-	0.75***; (R)	0.62*

Table 4-1. MTL regions showing significantly greater emotional than neutral Dm and greater amygdala-MTL correlations for emotional than for neutral Dm. Unless specified, the results are based on the averaged signal from both hemispheres. BLA = Basolateral Amygdala, PHG = Parahippocampal Gyrus, Dm = Remembered – Forgotten, EmoDm = Emotional Dm, NeuDm = Neutral Dm, L = Left, R = Right. * $p < 0.05$, ** $p < 0.005$, *** $p < 0.0005$, **** $p < 0.0001$.

Actual picture description	Picture Cue	Subject's description	Raters' decision
Green snake on black background; open mouth facing viewer	Snake	Open mouth	Not-Recalled
Brown snake on tree branch; open mouth facing left	Snake	Open mouth / Brown / on tree branch	Recalled

Table 4-2. Example of scoring criteria for cued recall procedure conducted outside the scanner.

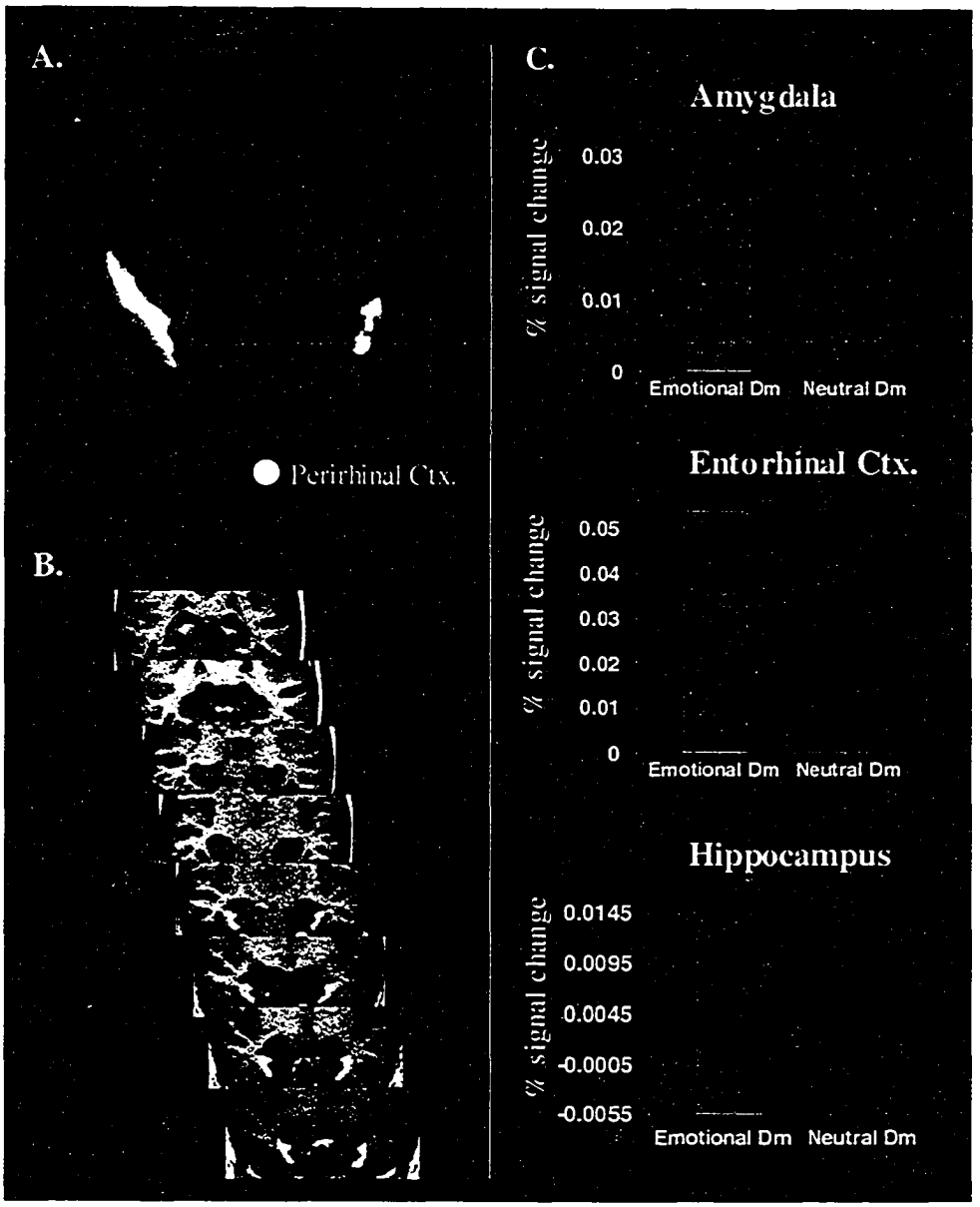

Figure 4-1. Greater emotional Dm than neutral Dm in the amygdala and MTL memory system. A) Three-dimensional view of the anatomically-defined ROIs from one representative subject. B) Coronal view of eight representative slices showing the location in the brain of the MTL regions. C) Bar graphs comparing the percent signal change for emotional and neutral Dms, as extracted from the peak activation slice/subregion in the amygdala (BLA), hippocampus (the head / left hemisphere), and anterior PHG. Unless specified, the graphs are based on the fMRI signal averaged across hemispheres and emotion conditions (pleasant and unpleasant collapsed). Ctx. = Cortex, Dm = Remembered – Forgotten.

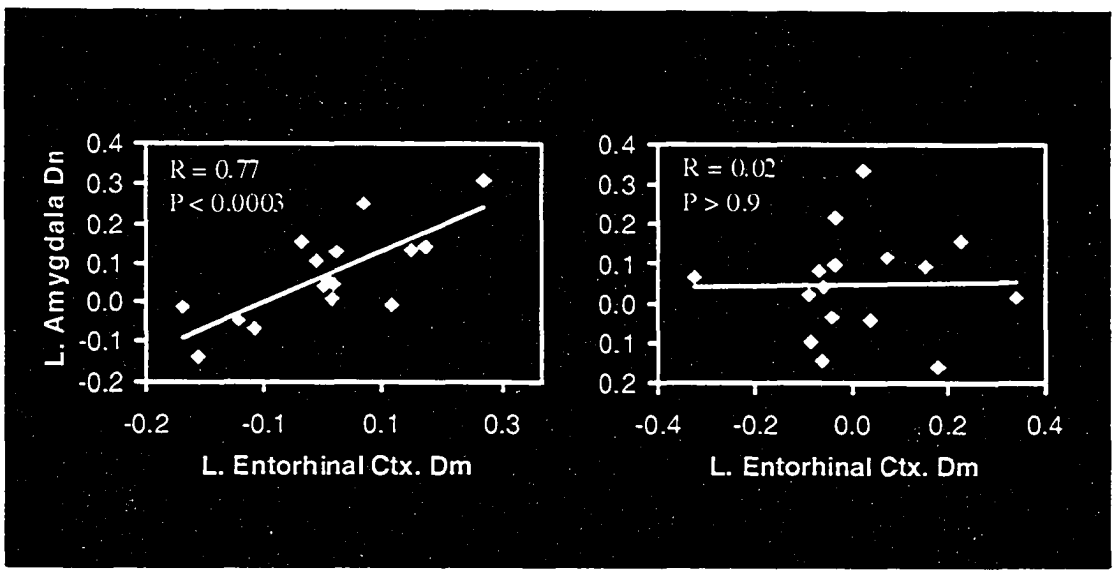

Figure 4-2. Stronger correlations between activity in the amygdala and the entorhinal cortex for the emotional Dm (left panel) than for the neutral Dm (right panel). The plots are based on the emotional and neutral Dms, as extracted from left amygdala (the peak activation slice in BLA) and left entorhinal cortex. Ctx. = Cortex, Dm = Remembered – Forgotten, L = Left.

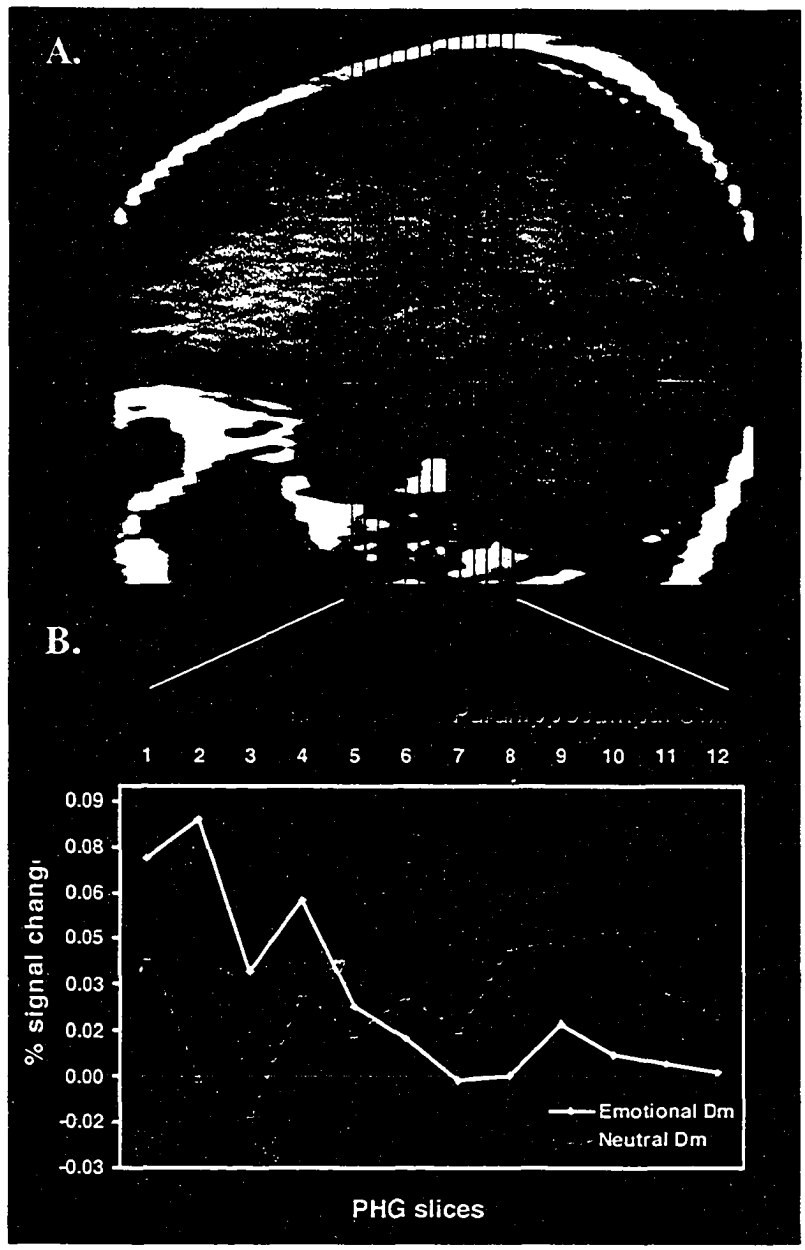

Figure 4-3. Functional dissociation along the longitudinal axis of the PHG. Anterior PHG, particularly the entorhinal cortex, was associated with subsequent memory for emotional pictures, whereas posterior PHG (i.e., parahippocampal cortex) was associated with subsequent memory for neutral pictures. The upper panel (A) shows a sagittal view of the entorhinal and parahippocampal cortices as traced on the anatomical brain image of one representative subject. The bottom graph (B) compares the emotional Dm and the neutral Dm as extracted slice-by-slice from anatomical ROIs traced in the entorhinal and parahippocampal cortices. The numbers from the upper part of the graph correspond to the PHG slices as they are shown on the upper brain image. PHG regions are color-coded as follows: Entorhinal cortex = Magenta, Parahippocampal cortex = Green. PHG = Parahippocampal gyrus, Ctx. = Cortex, Dm = Remembered – Forgotten.

CHAPTER 5

EFFECT OF EMOTION ON BRAIN ACTIVITY ASSOCIATED WITH EMOTIONAL EVALUATION AND EMOTIONAL MEMORY ENCODING – FMRI EVIDENCE

PART III

Dissociable Effects of Arousal and Valence on Prefrontal Activity Indexing Emotional Evaluation and Subsequent Memory: An Event-Related fMRI Study

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The domain of cognitive neuroscience of emotion has grown dramatically during the last decade. As a result of this development, various effects of emotion on brain activation associated with different perceptual and cognitive functions have been revealed (reviewed in Davidson & Irwin, 1999; Lane & Nadel, 2000; Phan, Wager, Taylor, & Liberzon, 2002). To understand these diverse effects, researchers have often divided emotion into its basic underlying constructs. One dimensional approach to emotion emphasizes the contribution of two orthogonal components, namely *arousal* and *valence* (Lang, Greenwald, Bradley, & Hamm, 1993; Russell, 1980). *Arousal* refers to a continuum that varies from calm to excitement, whereas *valence* refers to a continuum that varies from positive to negative with neutral in the middle (for methods to assess these two dimensions, see Bradley & Lang, 1994). The vast majority of studies have focused on the limbic system and particularly on the amygdala, whereas other components of the emotional processing network, such as the prefrontal cortex (PFC), have received relatively less attention. Recent studies of amygdala function have attempted to tease apart the relative contributions of the aforementioned affective dimensions to task performance (e.g., Anderson et al., 2003; Hamann, Ely, Hoffman, & Kilts, 2002; Phelps & Anderson, 1997; Phelps et al., 1998). However, the contribution of these factors to emotional processing in other frontolimbic regions is not well understood, and the available evidence is contradictory. To address this imbalance, the present functional MRI (fMRI) study focused on the role of PFC regions in emotional processing.

In particular, the study investigated the effects of arousal and valence on *emotional evaluation* and *emotional memory*. *Emotional evaluation* refers to the perception and categorization of emotional stimuli, and *emotional memory* refers to the modulatory effect of emotion on different stages of memory processing, including encoding, consolidation and retrieval. In the domain of emotional evaluation, the amygdala is assumed to be involved in the rapid detection of the basic emotional properties of incoming stimuli, whereas PFC is assumed to be involved in higher-order emotional evaluation processes, which operate in close interaction with other cognitive functions and with behavioral goals (Davidson & Irwin, 1999). In the domain of emotional memory, the existing studies have focused on the amygdala and identified arousal-mediated effects at encoding that predict subsequent memory (Cahill et al., 1996;

Canli, Desmond, Zhao, & Gabrieli, 2002; Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000; Dolcos, LaBar, & Cabeza, 2004; Hamann, Ely, Grafton, & Kilts, 1999), but there is little understanding of the contribution of other brain regions, such as PFC regions. Although it is assumed that activation during emotional evaluation tasks plays a role in memory, few studies have explicitly examined the relationship between emotional evaluation and memory. Thus, the overarching goal of the present study was to carefully investigate the contribution of the PFC to arousal and valence effects on emotional evaluation and memory.

Different PFC subregions are likely to make distinct contributions to emotional evaluation, but information about this issue is scarce. A basic anatomical distinction in this domain is between lateral and medial PFC regions. According to one prevailing view, the role of lateral PFC regions in emotional evaluation is primarily related to valence. The *valence hypothesis* states that the left PFC is dominant in the processing of positive emotions, whereas the right PFC is dominant in the processing of negative emotions (Davidson, 1995; Davidson & Irwin, 1999). This hypothesis is inspired by evidence from lesion literature and is mainly supported by electrophysiological evidence from EEG recordings. Neuropsychological evidence shows that patients with left hemisphere lesions tend to experience negative emotions, such as sadness (Morris, Robinson, Raphael, & Hopwood, 1996; Paradiso, Chemerinski, Yazici, Tartaro, & Robinson, 1999), whereas patients with right hemisphere damage are biased towards experiencing positive emotions, such as euphoria (e.g., Starkstein et al., 1989). The results of some electrophysiological studies are consistent with the valence hypothesis and support the idea that this valence-related PFC lateralization may depend either on transiently induced affective states or on stable personality traits (Aftanas, Varlamov, Pavlov, Makhnev, & Reva, 2001; Davidson, 1995; Davidson & Irwin, 1999; Tomarken, Davidson, Wheeler, & Doss, 1992; Wheeler, Davidson, & Tomarken, 1993).

However, electrophysiological studies do not provide an accurate localization of the sources of these valence effects, and, overall, the evidence supporting the valence hypothesis has been mixed. First, neither lesion nor electrophysiological evidence has always been consistent with the valence hypothesis (e.g., Borod, 1992; Borod et al., 1998; Dolcos & Cabeza, 2002; Hagemann, Naumann, Becker, Maier, & Bartussek,

1998). Second, functional neuroimaging evidence is also inconclusive. Whereas some studies support the valence hypothesis (e.g., Canli, Desmond, Zhao, Glover, & Gabrieli, 1998), a number of studies do not report valence-related hemispheric asymmetry in PFC (e.g., Baker, Frith, & Dolan, 1997; George et al., 1995; Lane, Fink, Chau, & Dolan, 1997; Lane, Reiman, Ahern, Schwartz, & Davidson, 1997; Lane, Reiman, Bradley et al., 1997; Pardo, Pardo, & Raichle, 1993; Teasdale et al., 1999). One possible reason why the results have been mixed is that arousal and valence are often not distinguished carefully (but see Canli et al., 1998); hence, valence effects might have been confounded with arousal effects. Thus, the first goal of the present study was to investigate the valence hypothesis and identify the specific PFC regions involved, in conditions where positive and negative stimuli were matched in arousal and other potentially confounding factors were controlled.

As for the role of medial PFC regions in emotional evaluation, different hypotheses have been suggested. For instance, orbitofrontal areas of medial PFC have been linked to the rewarding nature of stimuli (e.g., O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001; Rolls, 2000), and anteromedial areas have been related to more personal and subjective aspects of experiencing internal states (e.g., Frith & Frith, 1999). Although medial PFC regions have been strongly associated with emotional processing, it is unclear whether the role of these regions is related to arousal or to valence. Given that medial PFC regions are systematically activated by emotional stimuli, regardless of their valence (for a review, see Phan et al., 2002), PFC involvement could be attributed to its role in the processing of arousal. This notion is consistent with evidence supporting medial PFC involvement in processing emotionally arousing stimuli irrespective of valence (Lane, Fink et al., 1997; Lane, Reiman, Ahern et al., 1997; Lane, Reiman, Bradley et al., 1997; Reiman, 1997; Reiman et al., 1997; Schneider et al., 1995; Teasdale et al., 1999). On the other hand, there is also evidence suggesting valence-related specificity in medial PFC (e.g., George et al., 1995;Paradiso, Johnson et al., 1999). In particular, medial PFC has been associated with affiliative behaviors and appetitive/reward circuits (e.g., Rolls, 2000). A recent meta-analysis of functional neuroimaging studies of emotion (Wager, Phan, Liberzon, & Taylor, 2003) found that, overall, medial PFC activity was associated with approach/appetitive tasks. To address

this issue, the second goal of the present study was to determine whether the role of medial PFC in emotional processing is primarily related to arousal or to valence, or whether there are subregions within medial PFC differently involved in arousal and valence.

Turning to emotional memory, the most basic phenomenon to explain in this domain is why arousing events (both positive and negative) are better remembered than neutral events (Bradley, Greenwald, Petry, & Lang, 1992; Christianson, 1992). This effect has been attributed to the modulatory effect of the amygdala on the medial temporal lobe (MTL) memory system (McGaugh, McIntyre, & Power, 2002), and this modulation hypothesis has been confirmed by functional neuroimaging studies (Cahill et at., 1996; Canli et al., 2002; Dolcos et al., 2004; Hamann et al., 1999). For example, Dolcos et al. (2004) investigated this hypothesis using event-related fMRI and the *subsequent memory paradigm* (Paller & Wagner, 2002). In this paradigm, memory performance on a subsequent memory task is used to sort encoding items into two categories: remembered vs. forgotten. Greater encoding activity for remembered than forgotten items, sometimes known as "the Dm (difference in memory) effect", is assumed to reflect successful encoding operations. Consistent with the modulation hypothesis, Dolcos at al. (2004) found that the Dm effect in the amygdala and the MTL memory regions were greater for emotionally arousing pictures than for neutral pictures, and that the two Dm effects were more strongly correlated in the case of arousing pictures than in the case of neutral pictures.

Although this evidence strongly links the memory-enhancing effect of emotion to an MTL mechanism, it does not exclude the possibility that other brain regions, such as PFC, also play a major role. In fact, in functional neuroimaging studies, PFC regions are as strongly associated with successful encoding operations as MTL regions (e.g., Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Paller & Wagner, 2002; Wagner et al., 1998). Also, the effects of several factors affecting encoding success, such as organizational strategies and attention, have been found to be mediated by changes in PFC activity (Anderson et al., 2000; Fletcher, Shallice, & Dolan, 1998; Kensinger, Clarke, & Corkin, 2003). Moreover, studies using transcranial magnetic stimulation (TMS) have shown that PFC activity is actually necessary for successful encoding (Epstein, Sekino, Yamaguchi,

Kamiya, & Ueno, 2002; Grafman & Wassermann, 1999; Rossi et al., 2001). Thus, it is quite likely that the enhancing effect of emotion on encoding is mediated not only by MTL but also by PFC. Yet, very little is known about the role of PFC on emotional memory formation (see however Canli et al., 2002). For example, it is uncertain if the Dm effect in PFC is enhanced by emotion, similar to what we found in MTL (Dolcos et al., 2004). It is also unclear whether this putative effect is due to arousal or valence, and which specific PFC regions are involved. Thus, the third goal of the study was to investigate the role of PFC in the formation of emotional memory.

The method employed has two main features: (1) it distinguishes between activity associated with emotional evaluation and emotional memory, and (2) it distinguishes between the effects of arousal and valence. Participants were scanned while rating the pleasantness of arousing pictures (positive and negative) and nonarousing pictures (neutral), and after scanning they recalled the contents of the pictures. Stimuli were selected from a standardized set of pictures that allows experimental control over arousal and valence characteristics (Lang, Bradley, & Cuthberg, 1997), which has been largely used in neuroimaging studies of emotion (e.g., Dolan, Lane, Chua, & Fletcher, 2000; Hamann et al., 1999; Hamann et al., 2002; Lane, Chua, & Dolan, 1999; Lane, Fink et al., 1997; Lane, Reiman, Ahern et al., 1997; Lane, Reiman, Bradley et al., 1997; Liberzon et al., 2000; Paradiso, Johnson et al., 1999; Taylor et al., 1998; Taylor, Liberzon, & Koeppe, 2000). *Evaluation activity* was measured by comparing activity during picture rating to the baseline activity, and *successful encoding activity* was measured by comparing activity for subsequently remembered vs. subsequently forgotten pictures (Dm effect). Given that positive and negative pictures were both more arousing than neutral pictures, arousal effects should affect both positive and negative pictures. Given that positive and negative pictures were matched in arousal, differences between them should reflect valence effects rather than arousal effects. Thus, the *effect of arousal* was defined as greater activity for both positive and negative pictures than for neutral pictures, and the *effect of valence,* as differences between activity for positive and negative pictures.

To summarize, three main issues were investigated. First, it investigated the valence hypothesis, and in particular, what specific left and right PFC subregions would be sensitive to valence effects. Second, it investigated the role of medial PFC in

emotional evaluation, and specifically, whether activity in this region is primarily sensitive to arousal or valence, or whether subregions can be distinguished. Finally, it also investigated the role of PFC in emotional memory, and particularly, the relationship of Dm effects with stimulus arousal and valence, and their localization within PFC.

Methods

Subjects

Sixteen young (25 ± 4.6 yrs), right-handed, healthy women participated in the study. Female participants were chosen because evidence suggests that they are more likely to display strong physiological responses to emotional stimuli (Lang et al., 1993) and report more intense emotional experiences (Shields, 1991) than men. All participants consented to a protocol approved by Duke University Institutional Review Board.

Materials

Stimuli consisted of 60 positive, 60 negative, and 60 neutral pictures selected from the International Affective Picture System (IAPS) picture database (Lang et al., 1997), on the basis of their normative arousal and valence scores. The mean arousal scores (1 = calm, 9 = excited) were 6.0 for positive (SD = 2.2), 6.15 for negative (SD = 2.2), and 3.15 for neutral pictures (SD = 2.0). Thus, positive and negative pictures had similar high arousal scores, whereas neutral pictures had low arousal scores. The mean valence scores (1 = negative, 5 = neutral, 9 = positive) were 7.1 for positive (SD= 1.7), 2.3 for negative (SD = 1.5), and 5.2 for neutral (SD = 1.4). To equate the emotional and neutral categories for visual complexity and content (e.g., human presence), the IAPS pictures were supplemented with neutral pictures from other sources (Yamasaki, LaBar, & McCarthy, 2002). Also, given the evidence that dorsal/ventral PFC regions are differently involved in the processing of visual stimuli depending on their spatial content (e.g., Goldman-Rakic, 1995), it was important to determine that spatial/scene content did not differ between emotional and neutral stimuli. To investigate this idea, 10 participants rated the pictorial stimuli using a scene content scale (1 = no scene, 4 = very high scene content). The ratings for emotional (1.86) and neutral (1.93) pictures were similar (T =

0.64, $p > 0.5$), suggesting an equivalent amount of scene/spatial information across the stimulus categories.

Experimental Design

The pool of 180 pictures was divided into six sets of 30 pictures (10 positive, 10 negative, and 10 neutral), which were randomly assigned to six study blocks. Six different block orders were randomly assigned to the participants. To avoid the induction of long-lasting mood states, the pictures within each block where pseudo-randomized so that no more than two pictures of the same valence were consecutively presented. Functional MR images were recorded while subjects viewed emotional and neutral pictures. The pictures were presented, using an LCD projector, to a screen located behind the subjects' crown that subjects could see via an angled mirror. Each picture was presented for 3 sec and followed by a 12-sec fixation cross. Participants were instructed to experience any feelings or thoughts the pictures might elicit in them, and to rate each picture in a 3-point pleasantness scale (1 = negative, 2 = neutral, 3 = positive). Rating the emotional valence of stimuli was employed because paying attention to emotional responses elicited by various stimuli is associated with deep encoding, which results in better subsequent memory performance. This task also provides an estimation of subjects' emotional responses. Nothing was mentioned about a subsequent memory test, before or during the encoding task, and hence learning was incidental. Incidental learning was preferred because intentional learning may interfere with the experience of emotions, and because differences in voluntary attention may complicate the interpretation of subsequent memory effects.

Forty-five minutes after the scanning session, subjects performed an unexpected cued-recall test conducted outside the MRI suite. Subjects were provided with one- or two-word written cues for each picture (e.g., snake, building, skydivers), and had to describe in writing, and in as much detail as they could, the pictures that they remembered. Similar to the procedure employed in our previous ERP study (Dolcos & Cabeza, 2002), participants were asked to provide enough relevant details (e.g., about the number of elements, color, action, etc.) so that an outsider could identify each picture and discriminate it from similar studied pictures (e.g., a brown snake facing viewer vs.

several small green snakes; see also Dolcos et al., 2004). The test lasted until participants could not recall any additional pictures or until a maximum of 50 min had elapsed. Two raters were involved in scoring participants' responses, and only those pictures whose description was detailed enough to allow both identification and discrimination were classified as remembered.

MRI Data Aquisition

Anatomical scanning. Neuroimaging was performed using a 1.5 Tesla GE scanner. A T1-weighted sagittal localizer series was first acquired. The anterior (AC) and posterior commissures (PC) were identified in the midsagittal slice, and 34 contiguous oblique slices were prescribed parallel to the AC-PC plane. High-resolution T1-weighted structural images were acquired with a 450-ms TR (repetition time), a 9-ms TE (echo time), a 24-cm FOV (field of view), a 256^2 matrix, and a slice thickness of 3.75-mm. A second series of 46 oblique T1-weighted images perpendicular to the AC-PC was then acquired using the same imaging parameters.

Functional scanning. Thirty-four contiguous gradient- echo echoplanar images (EPIs) sensitive to blood oxygen level dependent (BOLD) contrast were acquired parallel to the AC–PC plane, using the same slice prescription described above for the near-axial structural images. The EPIs were acquired with a 3-s TR, 40-ms TE, one radio frequency excitation, 24-cm FOV, 64^2 image matrix, and a 90° flip angle. Slice thickness was 3.75-mm, resulting in cubic 3.75-mm3 isotropic voxels.

FMRI Data Analysis

Image preprocessing. Image preprocessing and statistical analyses were performed using SPM99 (*http://www.fil.ion.ucl.ac.uk/spm/*). Functional images were corrected for acquisition order, and realigned to correct for motion artifacts. Anatomical images were coregistered with the first functional images for each subject, and then both anatomical and functional images were spatially normalized to a standard stereotactic space, using the Montreal Neurological Institute (MNI) templates implemented in SPM99. Subsequently, functional images were spatially smoothed using an 8-mm isotropic Gaussian kernel.

Statistical analyses. Statistical analyses were separately performed to assess both emotion-related (emotional evaluation) and memory-related differences (emotional encoding) between emotional and neutral pictures. The images were defined as unpleasant, neutral or pleasant based on the IAPS ratings. The use of the IAPS score was justified by two reasons. First, different from the rating scores, which due to technical limitations during scanning (i.e., the response box had only 3 response options) did not allow fine evaluations of the subjects' emotional response, the IAPS scores are based on more sophisticated methods of assessing emotional arousal and valence, and allow much finer dissociations. Second, although some subjects classified some of the images differently than the norms, the high correlation between the average picture scores as rated by the subjects and the IAPS valence scores ($R = 0.9$, $p < 0.0001$) suggests that participants' classification was highly consistent with the normative data. Therefore, the latter scores were used to dissociate the effect of arousal and valence on brain activity associated with emotional evaluation and emotional memory formation. For each subject, task-related activity was identified by convolving a vector of the onset times of the stimuli with a synthetic hemodynamic response (HDR) and its temporal derivative. The general linear model, as implemented in SPM99, was used to model the effects of interest and other confounding effects (e.g., session effects and magnetic field drift). Functional images were proportionally scaled to the whole-brain signal.

Group analyses were conducted using random-effects models to assess the effect of arousal and valence on emotional evaluation and emotional encoding. In the present manuscript we report the PFC results, with a focus on lateral and medial cortices, excepting motor and cingulate regions. The MTL results were reported in a different manuscript (Dolcos et al., 2004). Conjunction analyses were used to identify brain regions more activated in two conditions (e.g., positive and negative) than in a third condition (e.g., neutral). This was done using the ImCalc feature in SPM, and according to the following formula: [(Condition 1 T score > 2.01) .* (Condition 2 T score > 2.01)]. This procedure yields a mask containing only those voxels that were significantly activated above $T = 2.01$ ($p = 0.0316$) in each and both contrasts. The probability of finding a voxel that is independently significant in each and both contrasts (i.e., the joint probability) can be estimated by multiplying the probabilities for each contrast: 0.0316 *

$0.0316 = p < 0.001$ (e.g., Allan, Dolan, Fletcher, & Rugg, 2000; Cabeza, Dolcos, Graham, & Nyberg, 2002).

The resulting conjunction masks provided information about the extent of the overlapping activations associated with the conditions involved in the conjunction, but not about the intensity of the overlapping activity. For this, conjunction T maps were calculated by multiplying the T values for the conditions of interest in the overlapping regions. The conjunction T maps were calculated according to the following formula: [(Condition 1 T score) .* (Condition 2 T score) .* (Conjunction mask of Condition 1 & Condition 2)]. These are the T values we report.

For emotional evaluation, the effect of arousal was measured as greater activity (compared to baseline) for arousing stimuli (positive and negative pictures) than for non-arousing stimuli (neutral pictures). This was done by identifying regions that showed *both* (1) greater activity for positive than for neutral pictures, and (2) greater activity for negative than for neutral pictures. That is, the *effect of arousal on emotional evaluation* was defined as [(positive > neutral) *conj* (negative > neutral)]. The effect of valence was measured as significant differences between positive and negative pictures. Since the valence scales had neutral as an intermediate value between positive and negative, it was further required that regions associated with positive or negative valence had to be more activated in these conditions than in the neutral condition. That is, the *effect of positive valence on emotional evaluation* was defined as [(positive > negative) *conj* (positive > neutral)] and the *effect of negative valence on emotional evaluation* was defined as [(negative > positive) *conj* (negative > neutral)].

The same kind of analyses were performed for emotional encoding, except that instead of using activity during picture rating compared to baseline, differences in activity between remembered and forgotten items (Dm = activity for remembered pictures – activity for forgotten pictures) were used. Dm activity was separately calculated for each picture category (e.g., Dm positive = positive remembered –positive forgotten), and then the effects of arousal and valence were identified by comparing the three types of Dm activity. The *effect of arousal on emotional memory* was defined as [(Dm positive > Dm neutral) *conj* (Dm negative > Dm neutral)]. The *effect of positive valence on emotional memory* was defined as [(Dm positive > Dm negative) *conj* (Dm

positive > Dm neutral)] and the *effect of negative valence on emotional memory* was defined as [(Dm negative > Dm positive) *conj* (Dm negative > Dm neutral)]. To make sure that the differences between Dms occurred due to positive activations in the condition of interest and were not driven by deactivations in the other conditions, the conjunction maps were masked with the activation maps showing the main effect of memory (Dm) for the condition of interest at $p < 0.05$. For instance, for the latter comparison (i.e., [(Dm negative > Dm positive) *conj* (Dm negative > Dm neutral)]), the resulting map was masked with the activation map for Dm negative. Thus, the final conjunction map contained only the voxels that showed a significant Dm for negative pictures.

The bar graphs of fMRI activations were examined by extracting the mean effect size from the peak voxel of each region, as identified by the SPM conjunction analyses for each condition of interest and subject. The data extraction was accomplished using SPM99. The xyz coordinates provided by SPM, which are in MNI (Montreal Neurological Institute) brain space, were converted to xyz coordinates in Tailarach and Tournoux's brain space (Talairach & Tournoux, 1988).

Results

Behavioral Results

Valence Ratings. The average valence scores (1 = negative, 2 = neutral, 3 = positive) as rated by the participants in the scanner were 1.14 (SD = 0.16) for negative pictures, 2.18 (SD= 0.40) for neutral pictures, and 2.64 (SD = 0.26) for positive pictures. All pairwise comparisons were significant ($p < 0.0001$). Thus, the subjects' rating scores were consistent with those provided in the IAPS norms (Lang et al., 1997). Further validating this consistency, the correlation between our subjects' average scores and the normed IAPS scores of the pictures used in the present study was highly significant ($R = 0.90$, $p < 0.0001$).

Memory Performance. Arousing pictures, both positive and negative, were better recalled than neutral pictures. Out of 60 pictures per category, participants recalled an average of 52% positive, 53% negative, and 38% neutral pictures (SDs were 4.5, 4.8, and

4.8, respectively). An ANOVA yielded a significant picture type effect ($F(2, 15) = 41.21$, $p < 0.0001$), and post-hoc contrasts showed that recall of positive and negative pictures was similar ($p > 0.05$), and greater than recall of neutral pictures ($p < 0.0001$).

fMRI Results

The analyses on activity associated with emotional evaluation (rating - baseline) yielded dissociable PFC regions showing effects of arousal and valence. In lateral PFC, the main goal was to test the valence hypothesis. Consistent with this hypothesis, a valence-related hemispheric asymmetry was found: a left dorsolateral PFC region (BA 8/9; xyz = -41, 21, 48; T = 8.63) showed an effect of positive valence, whereas a right ventrolateral PFC region (BA 47; xyz = 49, 33, -2; T = 17.03) showed an effect of negative valence. As illustrated by Table 5-1, the left PFC region was more activated for positive than for negative pictures, whereas the right PFC region was more activated for negative than for positive pictures. However, this asymmetry was not present in the entire lateral PFC: other dorsolateral PFC areas (BA 9) showed a bilateral (xyz = 49, 9, 24 / -38, 9, 24; T = 20.02 / T = 15.41) effect of negative valence. The effect of arousal in lateral PFC was evident in an area of the right inferior frontal gyrus (BA 47; xyz = 30, 18, -17; T = 9.57).

In medial PFC, a dorsal-ventral distinction was found during emotional evaluation in which arousal effects were located in a dorsal region (BA 9; xyz = -4, 52, 19; T = 11.45), whereas valence effects were found in more ventral locations - orbitofrontal and anteromedial cortices (BA 10; xyz = 0, 58, -10 / 0, 58, 4; T = 14.72 / T = 30.2). As illustrated by Table 5-2, the dorsomedial PFC region was more activated during evaluation of both pleasant and unpleasant pictures than during evaluation of neutral pictures, whereas the ventral regions were more activated during the evaluation of positive pictures.

The analysis of activity associated with emotional memory (Dm = remembered - forgotten) also yielded PFC regions showing effects of arousal and valence. The areas showing effects of arousal were found only in the lateral PFC, and included both ventral (BA 47; xyz = -49, 29, -1; T = 5.48) and dorsal (BA 9/6; xyz = -38, 2, 31; T = 8.64) locations. As illustrated by Table 5-3, in these lateral PFC regions the Dm for positive

pictures and the Dm for negative pictures were both greater than the Dm for neutral pictures. The average effect size values for remembered and forgotten pleasant, unpleasant, and neutral items, respectively, are as follows: BA 47 (-0.22, -0.46, -0.13, -0.30, -0.31, and -0.22) and BA 9/6 (-0.24, -0.41, -0.09, -0.22, -0.31, and -0.16). The areas showing effects of valence included medial (BA 9; xyz = -11, 38, 29; T = 6.41) and lateral (BA 45; xyz = -49, 22, 3; T = 8.51) locations, both showing an effect of positive valence.

Discussion

The present study yielded three main findings relevant for understanding PFC contributions to emotional evaluation and memory. First, consistent with the valence hypothesis, during emotional evaluation, specific left dorsolateral PFC areas showed greater activity for positive than for negative pictures whereas right ventrolateral PFC areas showed the converse pattern. Second, also during emotional evaluation, dorsomedial PFC activity was sensitive to arousal (greater activation for both positive and negative pictures relative to neutral ones), whereas ventromedial PFC activity was sensitive to valence (greater activation for positive pictures relative to negative ones). Finally, demonstrating the role of lateral PFC in emotional memory, arousal enhanced successful encoding activity in left ventrolateral and dorsolateral PFC. These results provide evidence for multiple, regionally-specific emotional influences on PFC function. The implications of the findings are discussed in separate sections below.

Lateral PFC showed a hemispheric asymmetry consistent with the valence hypothesis

As illustrated by Figure 5-1, a left PFC region was more activated for positive than for negative pictures and a right PFC region showed the converse pattern. This finding is consistent with other evidence supporting the valence hypothesis (Aftanas et al., 2001; Canli et al., 1998; Davidson, 1995; Tomarken et al., 1992; Wheeler et al., 1993) but it extends this evidence in two ways.

First, the present finding demonstrates hemispheric asymmetry effects predicted by the valence hypothesis under conditions in which positive and negative stimuli were matched for arousal and visual properties, and in which the effects of valence could be

distinguished from the effects of arousal on a trial-by-trial basis. As noted before (see Methods), positive and negative stimuli had similar normative scores of arousal and were equivalent in terms of complexity, presence of human figures, and other lower-level visual features. Participant ratings obtained on-line during encoding confirmed the valence manipulation and were highly correlated with normative valence scores. Moreover, the inclusion of neutral pictures allowed us to disentangle valence effects from arousal effects. Since arousal effects are by definition common to positive and negative pictures, these effects should appear as greater activity for both positive and negative pictures than for neutral pictures. As illustrated by Figure 5-1, this was not the case in either the left or the right PFC regions comprising valence-related hemispheric asymmetry. Additionally, in contrast to previous findings (Canli et al., 1998), which could not determine whether hemispheric asymmetries were stimulus-specific or reflected sustained changes in affective states, the present study provides evidence supporting the valence hypothesis using an event-related design in which stimuli were randomized during scanning.

Second, the present results not only demonstrated a valence-related hemispheric asymmetry but also identified the specific left and right PFC regions associated with positive and negative valence. The valence hypothesis has been primarily supported using electrophysiological methods (Aftanas et al., 2001; Davidson, 1995; Tomarken et al., 1992; Wheeler et al., 1993), which do not allow a good localization of neural sources. Evidence for the valence hypothesis was also found using fMRI (Canli et al., 1998) but using analyses that collapsed activity over a whole hemisphere. In contrast, the present result shows that the left PFC region specifically sensitive to positive valence is in dorsolateral cortex (middle frontal gyrus; BA 8/9) whereas the right PFC region particularly sensitive to negative valence is in ventrolateral cortex (inferior frontal gyrus; BA 47). A more inferior sector of BA9, in contrast, did not show such asymmetry effects, and was sensitive to negative valence bilaterally.

What are the implications of this region-specific hemispheric asymmetry in the processing of emotional valence? As described above, lesion, electrophysiological, as well as the available neuroimaging evidence supporting the valence hypothesis lacks the regional specificity necessary to link activity in the regions identified here with possible

differential involvement in processing emotional valence. One possibility is to broadly explain the role of these regions based on the available neuroimaging evidence concerning their involvement in various tasks. Another possibility is to link our findings with more specific evidence concerning dorsal-ventral dissociations in the lateral PFC. As concerning the former, neuroimaging evidence has associated the dorsolateral sectors of PFC, including the BAs 8 & 9 with a variety of tasks, involving perceptual, attentional, imagistic, and mnemonic operations, but typically they have been associated with working memory tasks (see Cabeza & Nyberg, 2000, for a review). In addition, portions of BA 8 are thought to be part of the so-called frontal eye field, although the overlap between this region in human and non-human primates is still controversial (Koyoma et al., 2004). Interestingly, related to its role in emotional processing, BA 8 has been identified in tasks involving rating the pleasantness of facial stimuli (Nakamura et al., 1998). As concerning the role of ventrolateral PFC regions, including BA 47, their function have been associated with semantic memory operations, as well as with interference control and inhibitory processes (Miller & Cohen, 2001; Smith & Jonides, 1999; see also Cabeza & Nyberg, 2000). Specifically related to the involvement in emotional processing, right ventrolateral PFC has been implicated in the inhibition of negative emotions (Petrovic, Kalso, Petersson, & Ingvar, 2002).

Turning to the evidence concerning the asymmetry in the dorsal-ventral dimension, two main views have been identified regarding the role of lateral PFC. According to one view, dorsolateral PFC regions are more involved in manipulating working memory contents whereas ventrolateral PFC regions are more involved in simple maintenance operations (D'Esposito, Postle, & Rypma, 2000; Owen et al., 1999; Petrides, 1995). Another view (Davidson & Irwin, 1999) specifically relates the function of lateral PFC to the role of emotion in guiding and organizing behavior in a motivationally consistent manner (Frijda, 1988). According to this view, dorsolateral PFC is involved in a particular form of working memory - *affective working memory* - responsible for the representation of goal-related emotional states, whereas the ventrolateral sector of the PFC is involved in the simple representation of elementary emotional states (Davidson & Irwin, 1999).

Combining these ideas, one may speculate that the left dorsolateral PFC activity for positive stimuli reflects the maintenance and manipulation of positive information in working memory during the valence-rating task, whereas the right ventrolateral PFC activity reflects the inhibition (avoidance) of negative information. Of course, these ideas are *ad hoc* and require independent confirmation. For instance, since other dorsolateral PFC regions were associated with evaluation of negative pictures, it would be important to clarify that working memory-related activity in the left PFC region specifically associated with positive pictures is related to the maintenance of appetitive goals (e.g, detection and processing of positive stimuli).

Dissociable regions of medial PFC were associated with arousal and positive valence

As illustrated by Table 5-2, dorsomedial PFC activity was sensitive to arousal, whereas ventromedial PFC activity was sensitive to positive valence. Previous evidence is consistent with the idea of possible segregation among medial PFC regions with respect to their involvement in emotional processing, but it is unclear whether the role of these regions is related to arousal or to valence. On the one hand, a meta-analysis of neuroimaging studies of emotion suggests that medial PFC regions are systematically activated by emotional stimuli, regardless of their valence (for a review, see Phan et al., 2002). This finding suggests a non-specific involvement of medial PFC in emotional processing, probably mediated by arousal, and is consistent with a number of neuroimaging studies reporting dorsomedial activations associated with the processing of emotional stimuli, regardless of their valence (Lane, Fink et al., 1997; Lane, Reiman, Ahern et al., 1997; Lane, Reiman, Bradley et al., 1997; Reiman, 1997; Reiman et al., 1997; Teasdale et al., 1999). On the other hand, another meta-analysis (Wager et al., 2003) found that, overall, medial PFC activity was associated with approach/appetitive tasks. Although approach-withdrawal and valence dimensions are not identical, they do overlap, and thus this finding suggests possible valence-related specificity in medial PFC function (see also George et al., 1995; Paradiso et al., 1997; Paradiso, Johnson et al., 1999). However, comparisons across studies are complicated by differences in stimuli, methods, and participants.

In the present study, we demonstrated a dorsal-ventral dissociation in the medial PFC, within-subjects and under controlled conditions. By identifying specific medial PFC regions sensitive to arousal and valence, this finding complements and reconciles previous functional neuroimaging evidence suggesting non-specific (Lane, Fink et al., 1997; Lane, Reiman, Ahern et al., 1997; Lane, Reiman, Bradley et al., 1997; Reiman, 1997; Reiman et al., 1997; Teasdale et al., 1999) vs. valence-specific involvement of medial PFC during emotional processing (George et al., 1995; Paradiso et al., 1997; Paradiso, Johnson et al., 1999). This finding is also consistent with the results of an ERP study (Dolcos & Cabeza, 2002) where we found arousal vs. valence dissociations at midline frontal electrodes. Although spatial resolution of ERP did not allow us to separate these effects topographically, it allowed dissociations in timing: there was a faster effect (500-800 ms) of positive valence (positive > negative = neutral), and a delayed effect (after 800 ms) of arousal (positive = negative > neutral). Since the valence-related ERP effect occurred in an earlier time-window (see also Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000), it was interpreted as reflecting a bias towards detecting and processing positive stimuli. Given the fact that, overall, the medial PFC in the present study was more activated for positive than for negative pictures, this interpretation may also apply to the current finding.

An alternative account is that the sensitivity of medial PFC to positive valence reflected greater self-engagement in the processing of positive pictures compared to negative and neutral pictures. A number of recent neuroimaging studies associated medial PFC activity with self-referential processing (e.g., Cabeza et al, 2004; Frith & Frith, 1999; Gusnard, Akbudak, Shulman, & Raichle, 2001; Kelley et al., 2002). For instance, in a review of the literature, Frith and Frith (1999) suggested that activity in ventral medial PFC was specifically associated with emotional aspects of self-processing. It should be noted, however, that the appetitive and self-engagement accounts of the present medial PFC activation are not incompatible. For example, participants could have been more likely to relate the pictures to their own self and life in the case of positive pictures than in the case of negative and neutral pictures. The medial PFC this is frequently activated in functional neuroimaging studies of autobiographical memories. For example, this region was found to be more activated during the recognition of photographs taken

by oneself than during the recognition of photographs taken by others (Cabeza et al., 2004).

Arousal enhanced successful encoding activity in left PFC

Emotional arousal enhanced successful encoding (Dm) activity in lateral PFC. As illustrated by Table 5-3, compared to the Dm for neutral pictures, the Dm for arousing pictures was greater in left ventrolateral and dorsolateral PFC. These findings suggest that the enhancing effect of emotion on memory formation (i) is partly mediated by changes in PFC activity; (ii) is mainly related to arousal, and (iii) may involve an amplification of semantic processing and working memory operations mediated by lateral PFC regions.

Research on the neural bases of the enhancing effect of emotion on memory formation has emphasized the role of the amygdala and its interactions with MTL memory regions (Cahill et al., 1996; Canli et al., 2002; Dolcos et al. 2004; Hamann et al., 1999; McGaugh et al., 2002). The present results expand this line of research by showing that the enhancing effect of emotion on memory formation is also mediated by changes in PFC activity. However, the effects of emotion on MTL and PFC are likely to enhance different memory mechanisms. Given the functions typically attributed to these regions (Moscovitch, 1992; Simons & Spiers, 2003), it is reasonable to assume that in MTL, emotion enhances the storage and consolidation of memory representations, whereas in PFC, it enhances strategic encoding processes.

A second implication of the present findings is that the enhancing effect of emotion on memory formation is primarily related to arousal rather than to valence. In our MTL study Dolcos et al. (2004) also found that the Dm increase was related to arousal rather than to valence. Thus, although valence-related Dm increases also occur, it seems fair to conclude that arousal is the main factor modulating the neural mechanisms of memory formation. This conclusion is consistent with the behavioral results, which showed that compared to non-arousing and neutral events, memory was better for both arousing categories (positive and negative), with no significant difference between these two conditions. Thus, from the point of view of memory, a negative event can be as "good" as a positive event (see also Talarico, LaBar, & Rubin, 2004).

The specific PFC regions where the Dm was increased by arousal suggest that arousing events are better remembered because they receive deeper semantic processing and working memory resources during encoding. The Dm was enhanced by arousal in left ventrolateral (BA 47) and dorsolateral (BA 9/6) PFC regions (see Table 5-3). The left ventrolateral region is an area that many functional neuroimaging studies have associated with encoding processes (for a review, see Cabeza & Nyberg, 2000), including event-related fMRI studies using the subsequent memory paradigm (Brewer et al., 1998; Kirchhoff, Wagner, Maril, & Stern, 2000; Paller & Wagner, 2002; Wagner et al., 1998). Since the role of this region in encoding is generally attributed to semantic processing (Kapur et al., 1996; Poldrack et al., 1999; Shallice et al., 1994), the present finding suggests that arousal facilitated successful encoding by increasing semantic processing of the information in the pictures. It is possible that arousal also enhanced perceptual encoding processes mediated by right PFC (Brewer et al., 1998). However, since picture memory was tested using verbal recall, the effects of arousal on perceptual encoding were probably not detected. To detect such effects, it would be necessary to test memory with a nonverbal task, such as picture recognition (e.g., Brewer et al., 1998).

Finally, the effect of arousal on left dorsolateral PFC is likely to reflect the augmentation of the working memory processes typically associated with this region (D'Esposito et al., 2000; Owen et al., 1999; Petrides, 1995). Thus, it is possible that the contents of arousing events not only receive deeper semantic processing but are also maintained longer or manipulated more intensely in working memory, leading to better retention. It should be noted that this interpretation is not incompatible with the idea of dorsolateral PFC involvement during emotional evaluation of positive pictures, since the specific regions involved during positive evaluation vs. successful encoding of arousing pictures are slightly different. It is possible that in one case the involvement of working memory operations is related to the maintenance of appetitive-goals, whereas in the latter the maintenance/manipulation of emotionally-arousing information leads to better subsequent memory.

Conclusions

Using an fMRI paradigm that distinguished between activity related to emotional evaluation and emotional memory and between the effects of arousal and valence, the present study yielded three main results. First, during emotional evaluation, PFC activity showed a hemispheric asymmetry consistent with the valence hypothesis. A left dorsolateral PFC region was sensitive to positive valence, possibly reflecting the maintenance of positive information in working memory, whereas a right ventrolateral PFC region was sensitive to negative valence, possibly reflecting the inhibition of negative information. Second, dorsomedial PFC activity was sensitive to arousal, whereas ventromedial PFC activity was sensitive to positive valence, possibly reflecting the involvement of these regions in general processing of emotional information (dorsomedial PFC), and self-awareness / appetitive behavior (ventromedial PFC).

Finally, successful encoding activity was enhanced by arousal in left ventrolateral and dorsolateral PFC regions, possibly reflecting an enhancement of strategic, semantic, and working memory operations. Although further research is required, these findings strongly suggest that different PFC regions are sensitive to arousal and to valence, and that they play an important role in the evaluation of emotional stimuli and in processes that lead to better memory for emotional events.

References

Aftanas, L., Varlamov, A., Pavlov, S., Makhnev, V., & Reva, N. (2001). Event-related synchronization and desynchronization during affective processing: emergence of valence-related time-dependent hemispheric asymmetries in theta and upper alpha band. *Int J Neurosci, 110*(3-4), 197-219.

Allan, K., Dolan, R. J., Fletcher, P. C., & Rugg, M. D. (2000). The role of the right anterior prefrontal cortex in episodic retrieval. *Neuroimage, 11*(3), 217-227.

Anderson, A. K., Christoff, K., Stappen, I., Panitz, D., Ghahremani, D. G., Glover, G., Gabrieli, J. D., & Sobel, N. (2003). Dissociated neural representations of intensity and valence in human olfaction. *Nat Neurosci, 6*(2), 196-202.

Anderson, N. D., Iidaka, T., Cabeza, R., Kapur, S., McIntosh, A. R., & Craik, F. I. (2000). The effects of divided attention on encoding- and retrieval-related brain activity: A PET study of younger and older adults. *J Cogn Neurosci, 12*(5), 775-792.

Baker, S. C., Frith, C. D., & Dolan, R. J. (1997). The interaction between mood and cognitive function studied with PET. *Psychol Med, 27*(3), 565-578.

Borod, J. C. (1992). Interhemispheric and intrahemispheric control of emotion: A focus on unilateral brain damage. *Journal of Consulting and Clinical Psychology, 60*, 339-348.

Borod, J. C., Obler, L. K., Erhan, H. M., Grunwald, I. S., Cicero, B. A., Welkowitz, J., Santschi, C., Agosti, R. M., & Whalen, J. R. (1998). Right hemisphere emotional perception: Evidence across multiple channels. *Neuropsychology, 12*(3), 446-458.

Bradley, M. M., Greenwald, M. K., Petry, M. C., & Lang, P. J. (1992). Remembering pictures: Pleasure and arousal in memory. *J Exp Psychol: Learn, Mem, & Cogn, 18*(2), 379-390.

Bradley, M. M., & Lang, P. J. (1994). Measuring emotion: The self-assessment manikin and the semantic differential. *J. Behav. Ther. & Exp.Psychiat., 25*(1), 49-59.

Brewer, J. B., Zhao, Z., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (1998). Making memories: Brain activity that predicts how well visual experience will be remembered. *Science, 281*, 1185-1187.

Cabeza, R., Dolcos, F., Graham, R., & Nyberg, L. (2002). Similarities and differences in the neural correlates of episodic memory retrieval and working memory. *Neuroimage, 16*(2), 317-330.

Cabeza, R., & Nyberg, L. (2000). Imaging cognition II: An empirical review of 275 PET and fMRI studies. *J of Cogn Neurosci., 12*(1), 1-47.

Cabeza, R., Prince, S. E., Daselaar, S. M, Greenberg, D. L., Budde, M., Dolcos, F., LaBar, K. S., Rubin, D. C. (2004). Brain activity during episodic retrieval of autobiographical and laboratory events: An fMRI study using a novel photo paradigm. *Journal of Cognitive Neuroscience, in press.*

Cahill, L., Haier, R. J., Fallon, J., Alkire, M. T., Tang, C., Keator, D., Wu, J., & McGaugh, J. L. (1996). Amygdala activity at encoding correlated with long-term, free recall of emotional information. *Proc Natl Acad Sci U S A, 93*, 8016-8021.

Canli, T., Desmond, J. E., Zhao, Z., & Gabrieli, J. D. E. (2002). Sex differences in the neural basis of emotional memories. *Proc Natl Acad Sci U S A, 99*(16), 10789-10794.

Canli, T., Desmond, J. E., Zhao, Z., Glover, G., & Gabrieli, J. D. (1998). Hemispheric asymmetry for emotional stimuli detected with fMRI. *Neuroreport, 9*(14), 3233-3239.

Canli, T., Zhao, Z., Brewer, J., Gabrieli, J. D. E., & Cahill, L. (2000). Event-related activation in the human amygdala associated with later memory for individual emotional experience. *J Neurosci, 20*(RC99), 1-5.

Christianson, S.-A. (1992). *The Handbook of Emotion and Memory: Research and Theory*: Lawrence Erlbaum Associates.

Cuthbert, B. N., Schupp, H. T., Bradley, M. M., Birbaumer, N., & Lang, P. J. (2000). Brain potentials in affective picture processing: Covariation with autonomic arousal and affective report. *Biological Psychology, 52*, 95-111.

D'Esposito, M., Postle, B. R., & Rypma, B. (2000). Prefrontal cortical contributions to working memory: Evidence from event-related fMRI studies. *Exp Brain Res, 133*(3–11).

Davidson, R. J. (1995). Cerebral asymmetry, emotion and affective style. In R. J. Davidson & K. Hugdahl (Eds.), *Brain Asymmetry* (pp. 361-387): MIT Press.

Davidson, R. J., & Irwin, W. (1999). The functional neuroanatomy of emotion and affective style. *Trends in Cognitive Sciences, 3*(1), 11-20.

Dolan, R. J., Lane, L., Chua, P., & Fletcher, P. (2000). Dissociable temporal lobe activations during emotional episodic memory retrieval. *NeuroImage, 11*, 203-209.

Dolcos, F., & Cabeza, R. (2002). Event-related potentials of emotional memory: Encoding pleasant, unpleasant, and neutral Pictures. *Cogn, Affect, & Behav Neurosci, 2*(3), 252-263.

Dolcos, F., LaBar, K. S., & Cabeza, R. (2004). Effect of emotion on successful encoding activity in the amygdala and the medial temporal lobe memory system: Evidence for the modulation hypothesis. *Neuron,42*, 855-863 .

Epstein, C. M., Sekino, M., Yamaguchi, K., Kamiya, S., & Ueno, S. (2002). Asymmetries of prefrontal cortex in human episodic memory: effects of transcranial magnetic stimulation on learning abstract patterns. *Neurosci Lett, 320*(1-2), 5-8.

Fletcher, P. C., Shallice, T., & Dolan, R. J. (1998). The functional roles of prefrontal cortex in episodic memory. I. Encoding. *Brain, 121*, 1239-1248.

Frijda, N. H. (1988). The laws of emotion. *Am Psychol, 43*(5), 349-358.

Frith, C. D., & Frith, U. (1999). Interacting minds--a biological basis. *Science, 286*(5445), 1692-1695.

George, M. S., Ketter, T. A., Parekh, P. I., Horwitz, B., Herscovitch, P., & Post, R. M. (1995). Brain activity during transient sadness and happiness in healthy women. *Am J Psychiatry, 152*(3), 341-351.

Goldman-Rakic, P. S. (1995). Architecture of the prefrontal cortex and the central executive. *Ann N Y Acad Sci., 769*, 71-83.

Grafman, J., & Wassermann, E. (1999). Transcranial magnetic stimulation can measure and modulate learning and memory. *Neuropsychologia, 37*, 159-167.

Gusnard, D. A., Akbudak, E., Shulman, G. L., & Raichle, M. E. (2001). Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proc Natl Acad Sci U S A, 98*(7), 4259-4264.

Hagemann, D., Naumann, E., Becker, G., Maier, S., & Bartussek, D. (1998). Frontal brain asymmetry and affective style: a conceptual replication. *Psychophysiology, 35*(4), 372-388.

Hamann, S. B., Ely, T. D., Grafton, S. T., & Kilts, C. D. (1999). Amygdala activity related to enhanced memory for pleasant and aversive stimuli. *Nat Neurosci, 2*(3), 289-293.

Hamann, S. B., Ely, T. D., Hoffman, J. M., & Kilts, C. D. (2002). Ecstasy and agony: Activation of the human amygdala in positive and negative emotion. *Psychol Sci, 13*(2), 135-141.

Kapur, S., Tulving, E., Cabeza, R., McIntosh, A. R., Houle, S., & Craik, F. I. (1996). The neural correlastes of intentional learning of verbal materials: A PET study in humans. *Conitive Brain Research, 4*, 243-249.

Kelley, W. M., Macrae, C. N., Wyland, C. L., Caglar, S., Inati, S., & Heatherton, T. F. (2002). Finding the self? An event-related fMRI study. *J Cogn Neurosci, 14*(5), 785-794.

Kensinger, E. A., Clarke, R. J., & Corkin, S. (2003). What neural correlates underlie successful encoding and retrieval? A functional magnetic resonance imaging study using a divided attention paradigm. *J Neurosci, 23*(6), 2407-2415.

Kirchhoff, B. A., Wagner, A. D., Maril, A., & Stern, C. E. (2000). Prefrontal-temporal circuitry for episodic encoding and subsequent memory. *J Neurosci, 20*(16), 6173-6180.

Koyoma, M., Hasegawa, I., Osada, T.; Adachi, Y., Nakahara, K., & Miyashita, Y. (2004). Functional magnetic resonance imaging of macaque monkeys performing visually guided saccade tasks: Comparison of cortical eye field with humans. *Neuron*, 41(5), 895-807.

Lane, D. R., & Nadel, L. (2000). *Cognitive Neuroscience of Emotion*. New York: Oxford University Press, Inc.

Lane, R. D., Chua, P. M., & Dolan, R. J. (1999). Common effects of emotional valence, arousal and attention on neural activation during visual processing of pictures. *Neuropsychologia, 37*(9), 989-997.

Lane, R. D., Fink, G. R., Chau, P. M., & Dolan, R. J. (1997). Neural activation during selective attention to subjective emotional responses. *Neuroreport, 8*(18), 3969-3972.

Lane, R. D., Reiman, E. M., Ahern, G. L., Schwartz, G. E., & Davidson, R. J. (1997). Neuroanatomical correlates of happiness, sadness, and disgust. *Am J Psychiatry, 154*(7), 926-933.

Lane, R. D., Reiman, E. M., Bradley, M. M., Lang, P. J., Ahern, G. L., Davidson, R. J., & Schwartz, G. E. (1997). Neuroanatomical correlates of pleasant and unpleasant emotion. *Neuropsychologia, 35*(11), 1437-1444.

Lang, P. J., Bradley, M. M., & Cuthberg, B. N. (1997). *International Affective Picture System* [Pictures]. Gainesville: NIMH Center for the Study of Emotion and Attention.

Lang, P. J., Greenwald, M. K., Bradley, M. M., & Hamm, A. O. (1993). Looking at pictures: Affective, facial, visceral, and behavioral reactions. *Psychophysiol, 30*(3), 261-273.

Liberzon, I., Taylor, S. F., Fig, L. M., Decker, L. R., Koeppe, R. A., & Minoshima, S. (2000). Limbic activation and psychophysiologic responses to aversive visual stimuli. Interaction with cognitive task. *Neuropsychopharmacology, 23*(5), 508-516.

McGaugh, J. L., McIntyre, C. K., & Power, A. E. (2002). Amygdala modulation of memory consolidation: Interaction with other brain systems. *Neurobiology of Learning and Memory, 78*(3), 539-552.

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience, 24*, 67-202.

Morris, P. L., Robinson, R. G., Raphael, B., & Hopwood, M. J. (1996). Lesion location and poststroke depression. *J Neuropsychiatry Clin Neurosci, 8*(4), 399-403.

Moscovitch, M. (1992). Memory and working-with-memory: A component process model based on modules and central systems. *Journal of Cognitive Neuroscience, 4*, 257-267.

Nakamura, K., Kawashima, R., Nagumo, S., Ito, K., Sugiura, M., Kato, T., Nakamura, A., Hatano, K., Kubota, K., Fukuda, H., & Kojima, S. (1998). Neuroanatomical correlates of the assessment of facial attractiveness. *Neuroreport*, 9(4), 753-757.

O'Doherty, J., Kringelbach, M. L., Rolls, E. T., Hornak, J., & Andrews, C. (2001). Abstract reward and punishment representations in the human orbitofrontal cortex. *Nat Neurosci, 4*(1), 95-102.

Owen, A. M., Herrod, N. J., Menon, D. K., Clark, J. C., Downey, S. P., Carpenter, T. A., Minhas, P. S., Turkheimer, F. E., Williams, E. J., Robbins, T. W., Sahakian, B. J., Petrides, M., & Pickard, J. D. (1999). Redefining the functional organization of working memory processes within human lateral prefrontal cortex. *Eur J Neurosci., 11*(2), 567-574.

Paller, K. A., & Wagner, A. D. (2002). Observing the transformation of experience into memory. *Trends Cogn Sci, 6*(2), 93-102.

Paradiso, S., Chemerinski, E., Yazici, K. M., Tartaro, A., & Robinson, R. G. (1999). Frontal lobe syndrome reassessed: comparison of patients with lateral or medial frontal brain damage. *J Neurol Neurosurg Psychiatry, 67*(5), 664-667.

Paradiso, S., Johnson, D. L., Andreasen, N. C., O'Leary, D. S., Watkins, G. L., Ponto, L. L., & Hichwa, R. D. (1999). Cerebral blood flow changes associated with attribution of emotional valence to pleasant, unpleasant, and neutral visual stimuli in a PET study of normal subjects. *Am J Psychiatry, 156*(10), 1618-1629.

Pardo, J. V., Pardo, P. J., & Raichle, M. E. (1993). Neural correlates of self-induced dysphoria. *Am J Psychiatry, 150*(5), 713-719.

Petrides, M. (1995). Functional organization of the human frontal cortex for mnemonic processing. Evidence from neuroimaging studies. *Ann N Y Acad Sci., 769*, 85-96.

Petrovic, P., Kalso, E., Petersson, K. M., & Ingvar, M. (2002). Placebo and opioid analgesia - Imaging a shared neuronal network. *Science*, 295, 1737-1740.

Phan, K. L., Wager, T., Taylor, S. F., & Liberzon, I. (2002). Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage, 16*(2), 331-348.

Phelps, E. A., & Anderson, A. K. (1997). Emotional memory: What does the amygdala do? *Current Biology: CB, 7*(5), R311-314.

Phelps, E. A., LaBar, K. S., Anderson, A. K., O'Connor, K. J., Fulbright, R. K., & Spencer, D. D. (1998). Specifying the contributions of the human amygdala to emotional memory: A case study. *Neurocase, 4*, 527-540.

Poldrack, R. A., Wagner, A. D., Prull, M. W., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (1999). Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. *NeuroImage, 10*, 15-35.

Reiman, E. M. (1997). The application of positron emission tomography to the study of normal and pathologic emotions. *J Clin Psychiatry, 58*(16), 4-12.

Reiman, E. M., Lane, R. D., Ahern, G. L., Schwartz, G. E., Davidson, R. J., Friston, K. J., Yun, L. S., & Chen, K. (1997). Neuroanatomical correlates of externally and internally generated human emotion. *Am J Psychiatry, 154*(7), 918-925.

Rolls, E. T. (2000). The orbitofrontal cortex and reward. *Cereb Cortex, 10*(3), 284-294.

Rossi, S., Cappa, S. F., Babiloni, C., Pasqualetti, P., Miniussi, C., Carducci, F., Babiloni, F., & Rossini, P. M. (2001). Prefrontal [correction of Prefontal] cortex in long-term memory: An "interference" approach using magnetic stimulation. *Nat Neurosci, 4*(9), 948-952.

Russell, J. (1980). A circumplex model of affect. *Journal of Personality and Social Psychology, 39*, 1161-1178.

Schneider, F., Gur, R. E., Mozley, L. H., Smith, R. J., Mozley, P. D., Censits, D. M., Alavi, A., & Gur, R. C. (1995). Mood effects on limbic blood flow correlate with emotional self-rating: a PET study with oxygen-15 labeled water. *Psychiatry Res, 61*(4), 265-283.

Shallice, T., Fletcher, P., Frith, C. D., Grasby, P., Frackowiak, R. S., & Dolan, R. J. (1994). Brain regions associated with aquisition and retrieval of verbal episodic memory. *Nature, 368*(633-35).

Shields, S. (1991). Gender in the psychology of emotion: A selective research review. In K. Strongman (Ed.), *International Review of Studies on Emotion* (pp. 227-245). New York: Wiley.

Simons, J. S., & Spiers, H. J. (2003). Prefrontal and medial temporal lobe interactions in long-term memory. *Nat Rev Neurosci, 4*(8), 637-648.

Smith, E., & Jonides, J. (1999). Storage and executive processes in the frontal lobes. *Science, 283*, 657-660.

Starkstein, S. E., Robinson, R. G., Honig, M. A., Parikh, R. M., Joselyn, J., & Price, T. R. (1989). Mood changes after right-hemisphere lesions. *Br J Psychiatry, 155*, 79-85.

Talairach, J., & Tournoux, P. (1988). *A Co-planar Sterotactic Atlas of the Human Brain.* Stuttgart, Germany: Thieme.

Talarico, J. T., LaBar, K. S., & Rubin, D. C. (2004). Emotional intensity predicts autobiographical memory experience. *Memory & Cognition, in press.*

Taylor, S. F., Liberzon, I., Fig, L. M., Decker, L. R., Minoshima, S., & Koeppe, R. A. (1998). The effect of emotional content on visual recognition memory: a PET activation study. *Neuroimage, 8*(2), 188-197.

Taylor, S. F., Liberzon, I., & Koeppe, R. A. (2000). The effect of graded aversive stimuli on limbic and visual activation. *Neuropsychologia, 38*(10), 1415-1425.

Teasdale, J. D., Howard, R. J., Cox, S. G., Ha, Y., Brammer, M. J., Williams, S. C., & Checkley, S. A. (1999). Functional MRI study of the cognitive generation of affect. *Am J Psychiatry, 156*(2), 209-215.

Tomarken, A. J., Davidson, R. J., Wheeler, R. E., & Doss, R. C. (1992). Individual differences in anterior brain asymmetry and fundamental dimensions of emotion. *J Pers Soc Psychol, 62*(4), 676-687.

Wager, T. D., Phan, K. L., Liberzon, I., & Taylor, S. F. (2003). Valence, gender, and lateralization of functional brain anatomy in emotion: a meta-analysis of findings from neuroimaging. *Neuroimage, 19*(3), 513-531.

Wagner, A. D., Schacter, D. L., Rotte, M., Koutstaal, W., Maril, A., Dale, A. M., Rosen, B. R., & Buckner, R. L. (1998). Building memories: Remembering and forgetting of verbal experiences as predicted by brain activity. *Science, 281*, 1188-1191.

Wheeler, R. E., Davidson, R. J., & Tomarken, A. J. (1993). Frontal brain asymmetry and emotional reactivity: A biological substrate of affective style. *Psychophysiology, 30*, 82-89.

Yamasaki, H., LaBar, K. S., & McCarthy, G. (2002). Dissociable prefrontal brain systems for attention and emotion. *Proc Natl Acad Sci U S A, 99*(17), 11447-11451.

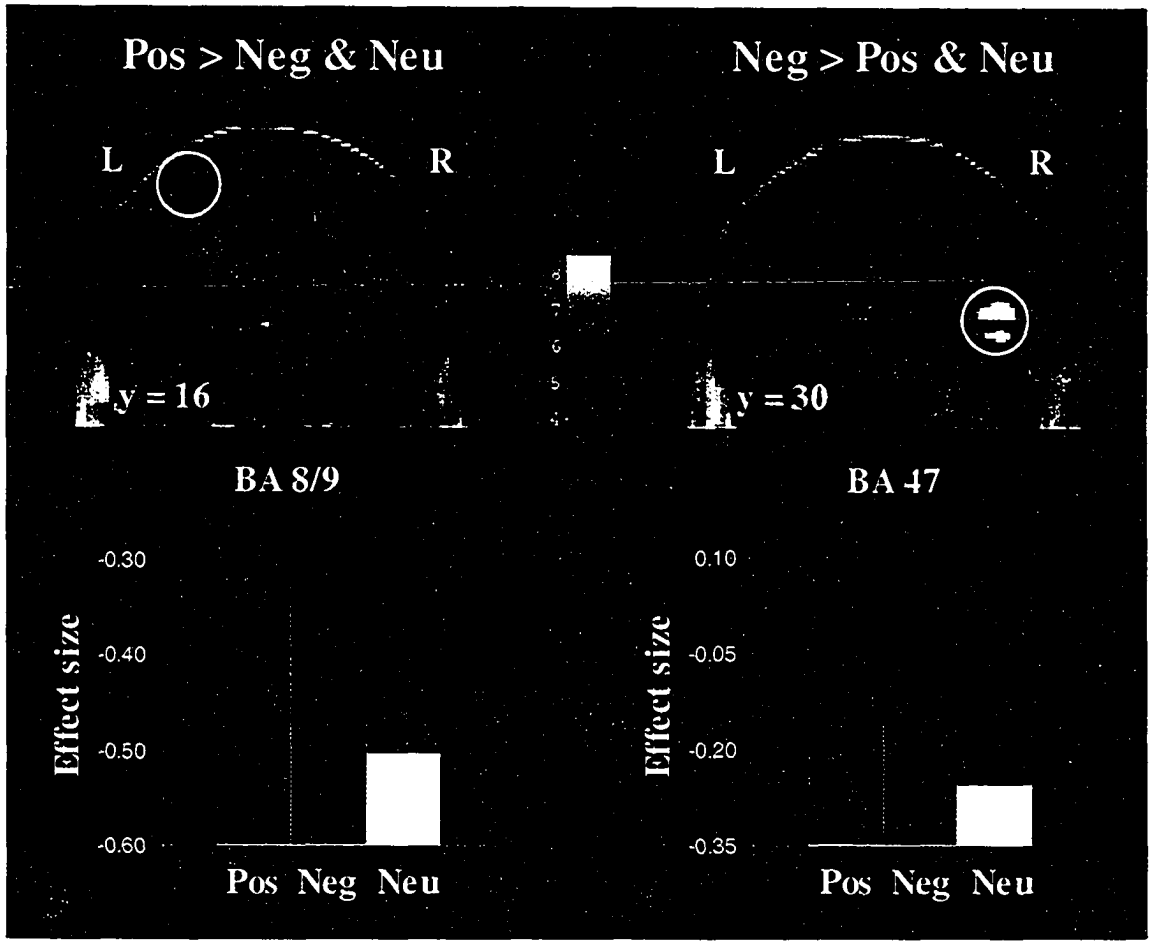

Figure 5-1. Activity in lateral PFC showed evidence for the valence hypothesis. In the left hemisphere, a dorsolateral PFC region (BA 8/9) was more activated during evaluation of positive pictures than during evaluation of negative pictures, whereas in the right hemisphere ventrolateral regions (BA 47) where more activated for negative than for positive pictures. The upper panels show the activation maps overlapped on high-resolution coronal anatomical images, and the bar graphs at the bottom show the effect size as extracted from the peak-voxels identified in the conjunction analyses (see Method section). The numbers at the left-bottom corner of the upper panels (e.g. y = 16) indicate the coordinate in MNI space. The color bar located between the upper panels indicates the conjunction T values. L = left, R = right; Pos = Positive, Neg = Negative, Neu = Neutral; BA = Brodmann Area.

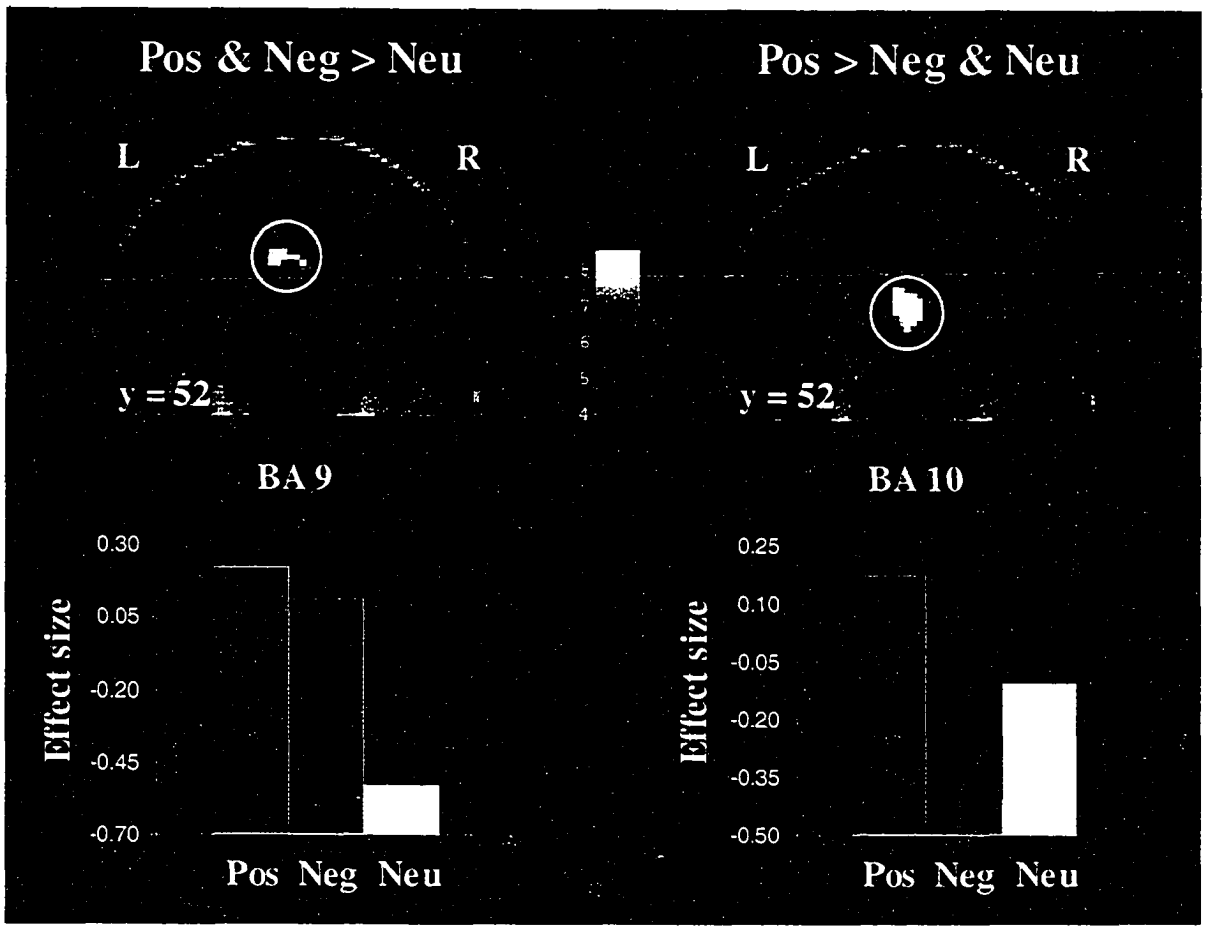

Figure 5-2. Activity in medial PFC identified dissociable regions associated with arousal and positive valence. Dorsomedial PFC (BA 9) activity was sensitive to arousal (Pos & Neg > Neu), whereas ventromedial PFC (BA 10) activity was sensitive to positive valence (Pos > Neg & Neu). L = left, R = right; Pos = Positive, Neg = Negative, Neu = Neutral; BA = Brodmann Area.

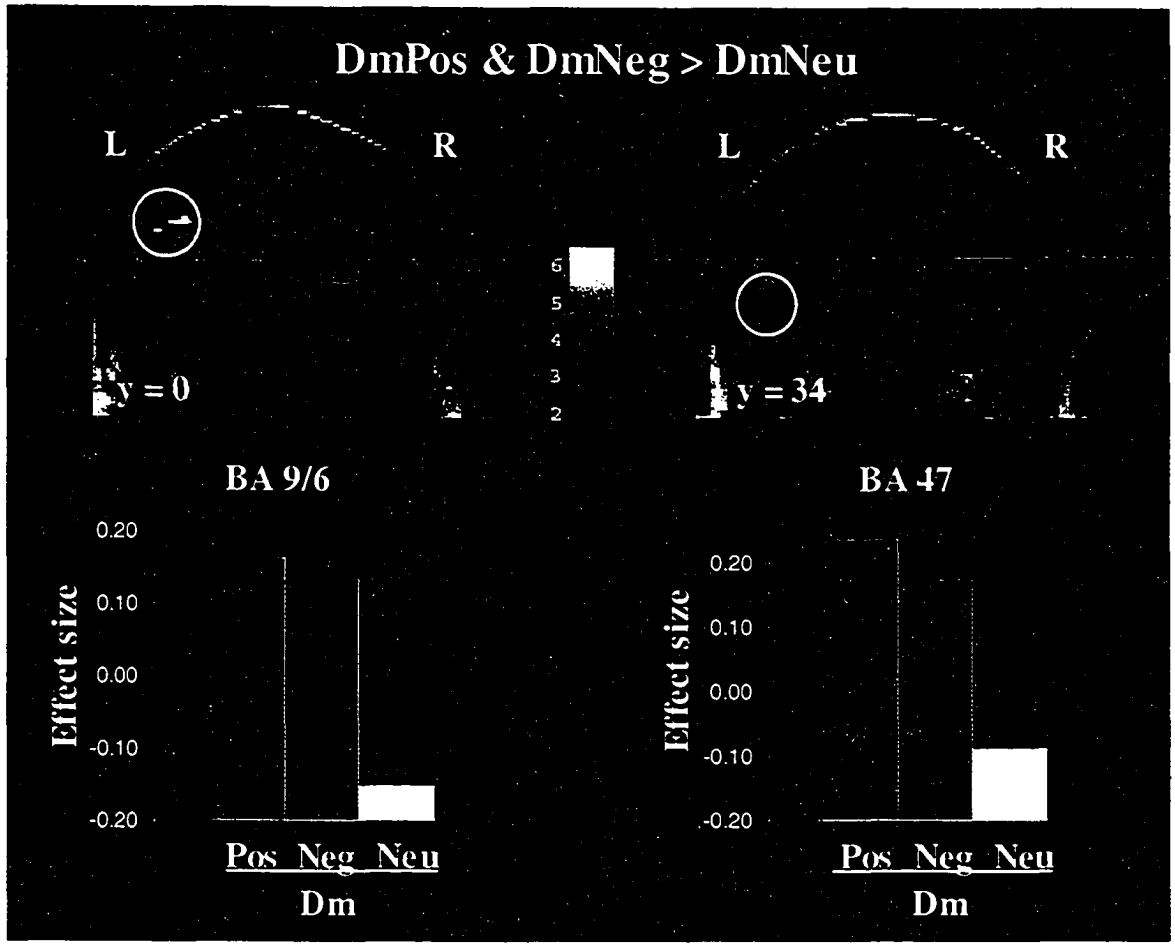

Figure 5-3. Arousal enhanced successful encoding activity (Dm) in left PFC. Compared to the Dm for neutral pictures, the Dm for arousing pictures (both positive and negative) was greater in left ventrolateral (BA 47) and dorsolateral (BA 9/6) PFC regions. L = left, R = right; Pos = Positive, Neg = Negative, Neu = Neutral. BA = Brodmann Area. Dm = Remembered – Forgotten.

CHAPTER 6

EFFECT OF EMOTION ON BRAIN ACTIVITY ASSOCIATED WITH EMOTIONAL MEMORY RETRIEVAL – FMRI EVIDENCE

Remembering One Year Later: Role of the Amygdala and Medial Temporal Lobe Memory System in Retrieving Emotional Memories

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Through evolution, the declarative memory system developed the ability to preferentially retain events that are relevant for survival, which are usually those associated with strong emotions and motivational goals (finding food, spotting a predator, etc.). Emotional arousal may enhance one or more of several memory stages, including the creation of new memory traces (encoding), the stabilization and persistence of these traces (consolidation and retention), and/or the final access to stored traces (retrieval). Yet, the vast majority of studies on the neural mechanisms of emotional memory have focused on early memory stages (encoding and consolidation), and very little information is available about retrieval. Neurobiological theories of emotional memory will not be complete without an account of retrieval mechanisms. This issue also has implications for understanding dysfunctional accessibility of traumatic memory traces in affective disorders. To fill this void, the present study used event-related functional magnetic resonance imaging (fMRI) to investigate the neural mechanisms underlying the long-term retrieval of emotional memories in healthy adults.

According to the modulation hypothesis, the memory-enhancing effect of emotion reflects the influence of the amygdala on the medial temporal lobe (MTL) memory system during encoding and consolidation (McGaugh, 2000, 2004). Although initially inspired by animal research (McGaugh, 2000, 2002), this hypothesis has recently received support from functional neuroimaging research in humans (Cahill et al., 1996; Canli, Desmond, Zhao, & Gabrieli, 2002; Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000; Dolcos, LaBar, & Cabeza, 2004a, 2004b; Hamann, Ely, Grafton, & Kilts, 1999; Kensinger & Corkin, 2004; Kilpatrick & Cahill, 2003; Phelps, 2004; Richardson, Strange, & Dolan, 2004). For instance, using event-related fMRI, Dolcos et al. (2004b) found that successful encoding activity (subsequently remembered vs. forgotten) in the amygdala and the MTL memory system (hippocampus and entorhinal cortex) was greater and more closely related for emotionally-arousing than for neutral pictures.

Although this evidence links the memory-enhancing effect of emotion to amygdalar modulation during encoding and early consolidation, it is not clear if a similar mechanism operates during retrieval. The animal literature suggests that the amygdala is involved in both emotional memory encoding (McGaugh, 2004) and retrieval (LeDoux, 2000), but the exact nature of its involvement during retrieval is a matter of current

debate (Nadel, 2000; Nader, 2003). The situation in the functional neuroimaging literature is very similar. Although a few studies have found amygdalar activity during retrieval (Dolan, Lane, Chua, & Fletcher, 2000; Fossati et al., 2004; Maratos, Dolan, Morris, Henson, & Rugg, 2001; Smith, Henson, Dolan, & Rugg, 2004), these studies have two main limitations. (i) They used short retention intervals (i.e., minutes), which do not allow a clear separation between the involvement of the amygdala in retrieval vs. consolidation processes. (ii) These studies did not demonstrate that the amygdala is differentially more involved in successful than in unsuccessful retrieval of emotional events relative to neutral events.

Thus, one goal of the present study was to investigate the effect of emotional arousal on retrieval activity while addressing these two limitations. (i) Retrieval processes were distinguished from consolidation processes by examining consolidated memories after a retention interval of one year. (ii) Activity of the amygdala and the MTL memory system was specifically measured using an event-related design that separated brain activity on a trial-by-trial basis, and hence isolated activity associated with retrieval success. Retrieval success activity was identified by comparing activity for old items classified as old (hits) to activity for old items classified as new (misses). This contrast is based on the same logic used by fMRI studies comparing subsequently remembered vs. forgotten items (Paller & Wagner, 2002) but applied to retrieval. An important advantage of this method for the present purposes is that it controls for perception-related emotional activity because in the emotional condition both hits and misses involve emotional stimuli but differ in terms of memory.

Another goal of the study was to disentangle the effects of emotional content on two different forms of episodic memory retrieval: recollection and familiarity (Yonelinas, 2002). *Recollection* refers to memory for an event (e.g., meeting someone) that is accompanied by the retrieval of contextual information and other associated elements (e.g., time, location, sensory details), whereas *familiarity* refers to the feeling that an event happened in the past but no associated information can be retrieved (e.g., knowing that a face was seen before but without remembering where or when). A popular method for distinguishing recollection and familiarity during recognition memory is to ask participants to decide, for each item classified as old, whether they can *remember* specific

details about the occurrence of the item in the study list (R response) and whether they *know* that the item was in the list but cannot retrieve any specific detail (K response) – Remember / Know task (Tulving, 1985). Distinguishing recollection and familiarity is critical because there is behavioral evidence that the memory-enhancing effect of emotion specifically modulates recollection rather than familiarity processes (Ochsner, 2000; Talarico, LaBar, & Rubin, in press). However, the neural correlates of this differential effect are unknown. Although a few fMRI studies have distinguished activity associated with recollection vs. familiarity (Dobbins, Rice, Wagner, & Schacter, 2003; Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Henson, Rugg, Shallice, Josephs, & Dolan, 1999), none of them investigated emotional memory. Thus, addressing this important issue was the second goal of the present study.

In the present study, participants encoded high-arousing emotional (pleasant and unpleasant) and low-arousing neutral pictures by rating their valence, and one year later, they were scanned while distinguishing between the pictures they previously saw and equivalent new pictures. For each picture, they made a Remember/Know/New decision. On the basis of behavioral evidence concerning the memory-enhancing effect of emotion (Bradley, Greenwald, Petry, & Lang, 1992; Christianson, 1992), the following prediction was made: (1) recognition would be better for emotional than for neutral pictures, and this effect would be driven by recollection (Ochsner, 2000; Talarico et al., in press). As concerning the neural basis of these effects, two additional predictions were made: (2) On the basis of the encoding results (Dolcos et al., 2004b), it was predicted that emotion would enhance retrieval success activity in the amygdala and the MTL memory system, specifically the hippocampus and the entorhinal cortex; (3) Finally, it was also predicted that recollection-based (R) responses would be associated with greater activity than familiarity-based (K) responses in the amygdala and the hippocampus but not in cortical MTL regions, such as the entorhinal cortex. The amygdala and the hippocampus were assumed to be the source of differential R vs. K effects because, as mentioned above, emotional arousal enhances recollective processes behaviorally, which have been more closely associated with hippocampal function than with other cortical MTL regions (Yonelinas, 2002).

Methods

Subjects. Nine young (20-35 yrs old; mean age = 26.8, SD = 4.6) right-handed female adults from Duke University community participated in the study. Due to high rates of false alarms, data from two subjects were excluded from analyses. Thus, in all analyses data from seven subjects (mean age = 26.0, SD = 4.8) were used. Subjects were healthy, with no self-reported history of neurological or psychiatric illness. Female participants were chosen because, compared to men, women are physiologically more reactive to emotional stimuli (Lang, Greenwald, Bradley, & Hamm, 1993), and are more likely to report intense emotional experiences (Shields, 1991). The protocol was approved for ethical treatment of human participants by the Institutional Review Board at Duke University Medical Center, and the experimental data were collected with the understanding and written consent of each participant. Subjects were paid $20/hr for their participation.

Stimuli. Stimuli consisted of 270 colored pictures selected from the International Affective Picture System (IAPS, Lang, Bradley, & Cuthberg, 1997), based on their standard scores for emotional arousal and valence. To equate the emotional and neutral pictures for complexity and human presence, the IAPS pictures were supplemented with neutral pictures from other sources (Yamasaki, LaBar, & McCarthy, 2002). Similar to the procedure employed in our previous ERP and fMRI studies of encoding (Dolcos & Cabeza, 2002; Dolcos et al., 2004b), pleasant and unpleasant pictures differed from each other only in terms of valence, whereas pleasant and unpleasant pictures differed from neutral pictures in terms of both arousal and valence. The mean arousal score was 6.0 for pleasant, 6.15 for unpleasant, and 3.15 for neutral pictures. The mean valence score was 7.1 for pleasant, 2.3 for unpleasant, and 5.0 for neutral pictures. The pictures were formatted so that on the screen they had a height between 14 and 18 cm and a width between 12.5 and 22.5 cm.

Procedure. Participants were scanned both during encoding and, one year later, during retrieval. During encoding, subjects were scanned while rating emotional and neutral pictures for pleasantness. Participants viewed 180 pictures (60 pleasant, 60 unpleasant, and 60 neutral), which were divided into 6 sets of 30 pictures (10 pleasant, 10 unpleasant,

and 10 neutral) and were randomly assigned to 6 study blocks. Functional MRI data were recorded while subjects viewed and rated the emotional and neutral pictures for pleasantness, using a 3-point scale (1 = unpleasant, 2 = neutral, 3 = pleasant). Subjects were instructed to make their responses as soon as possible, while the pictures were still on the screen. Nothing was mentioned about a possible subsequent memory test, before or during the encoding task (incidental learning). Forty-five minutes following the scanning session, subjects performed a cued-recall task, and memory performance was used to study the effect of emotion on brain activity associated with successful encoding, which we previously reported (Dolcos et al., 2004a, 2004b).

Ten to sixteen months later (average thirteen), the same participants were scanned again during a recognition task that included studied pictures mixed with new distracters. During retrieval, participants viewed 270 pictures (180 old pictures and 90 new distracters = 30 pleasant + 30 unpleasant + 30 neutral pictures), which were assigned to 9 blocks (30 pictures each: 10 pleasant, 10 unpleasant, and 10 neutral; 2/3 old and 1/3 new in each category). The IAPS scores for arousal and valence of the distracters did not significantly differ from those of the pictures used during encoding. Subjects were asked to perform the Remember-Know (R-K) recognition task (Tulving, 1985) using a 3-point scale (1 = Remember, 2 = Know, 3 = New). This paradigm was included to encourage subjects to use a recollection-based retrieval strategy. Subjects were instructed to press '1' if they remembered having seen the pictures during encoding session, along with other details from encoding episode (e.g., particular emotional reaction, thoughts, and/or sensorial details, etc. – Remember-R responses), to press '2' if they knew the pictures were in the encoding set but could not retrieve any specific details about their occurrence within the encoding set (Know-K responses), or to press '3' if they thought the pictures were not included in the encoding set (New responses).

The presentation timing, randomization scheme, and the MRI protocol used during retrieval were identical to those employed during encoding (Dolcos, Graham, LaBar, & Cabeza, 2003; Dolcos et al., 2004a, 2004b). The pictures were presented through an LCD projector to a screen located about 70 cm behind the subjects' crown, which subjects could see via an angled mirror attached to a pair of goggles that could also accommodate corrective lenses. Each picture was presented for 3 sec, followed by a 12-

sec fixation screen. Responses were recorded using a 3-button MR-compatible response box. Similar to the instructions employed during encoding task, participants were encouraged to make their responses as quickly and accurate as possible.

FMRI Methods

Anatomical scanning. A T1-weighted sagittal localizer series was first acquired. The anterior (AC) and posterior commissures (PC) were identified in the mid-sagittal slice, and 34 contiguous oblique slices were prescribed parallel to the AC-PC plane. High-resolution T1-weighted structural images were acquired with a 450-ms TR (repetition time), a 9-ms TE (echo time), a 24-cm FOV (field of view), a 256^2 matrix, and a slice thickness of 3.75-mm. A second series of 46 oblique T1-weighted images perpendicular to the AC-PC was then acquired using the same imaging parameters.

Functional scanning. Thirty-four contiguous gradient-echo echoplanar images (EPIs) sensitive to blood-oxygen level dependent (BOLD) contrast were acquired parallel to the AC-PC plane, using the same slice prescription described above for the near-axial structural images. The EPIs were acquired with a 3-s TR, 40-ms TE, one radio frequency excitation, 24-cm FOV, 64^2 image matrix, and a 90° flip angle. Slice thickness was 3.75-mm, resulting in cubic 3.75-mm^3 isotropic voxels.

Image preprocessing. Image preprocessing was performed with SPM99 [*http://www.fil.ion.ucl.ac.uk/spm/*]. Functional images were corrected for acquisition order, and realigned to correct for motion artifacts. Anatomical images were co-registered with the first functional images for each subject, and then both anatomical and functional images were spatially normalized to a standard stereotactic space, using the Montreal Neurological Institute (MNI) templates implemented in SPM99. Subsequently, the functional images were spatially smoothed using an 8-mm isotropic Gaussian kernel.

Statistical analyses. Analyses employed two levels: individual and group analyses. For individual analyses, the fMRI signal was selectively averaged in each subject as a function of stimulus condition (e.g., remembered – forgotten = retrieval success activity) and time point (one pre-stimulus and four post-stimulus onset time points were employed), using in-house software from Duke University's Brain Imaging and Analysis Center. No assumption was made about the shape of the hemodynamic response function.

These analyses produced whole-brain activation maps, which were used to calculate the percent signal change relative to stimulus onset corresponding to each condition of interest and time point. For group analyses, paired T tests were performed on a voxel-by-voxel basis, using the individual percent signal change maps for the conditions of interest and time points. Given the behavioral (Bradley et al., 1992) and neuroimaging (Anderson et al., 2003; Dolcos et al., 2004a, 2004b; Hamann, Ely, Hoffman, & Kilts, 2002) evidence that the emotional intensity rather than the emotional valence is the main factor determining long-term explicit memory for emotional stimuli, as well as successful encoding-related activity in the amygdala and the MTL memory system, the *emotional* category was formed by collapsing the pleasant and unpleasant pictures. This procedure was methodologically suitable since pleasant and unpleasant pictures were equated for emotional arousal, and memory performance did not differ for pleasant and unpleasant pictures.

Retrieval success activity was identified by comparing brain activity for successfully and non-successfully retrieved items (Hits vs. Misses). This comparison was employed, instead of a comparison between hits and correct rejections, because recent studies show that items correctly identified as novel can trigger encoding-related activity in the same MTL regions that are involved during retrieval (Stark & Okado, 2003). Thus, to avoid this possible confound retrieval, success activity was calculated by comparing brain activity for Hits vs. Misses. Similar to studies of encoding where such comparison allows the identification of brain regions associated with encoding success (Paller & Wagner, 2002), if employed during retrieval it allows the identification of brain regions associated with retrieval success (Prince, Daselaar, & Cabeza, submitted; Weis, Klaver, Reul, Elger, & Fernandez, 2004).

To identify the brain regions responsible for the memory-enhancing effect of emotion during retrieval, successful retrieval activity for the emotional pictures [Emotional Hits (R+K) – Emotional Misses = Emotional Retrieval Success] and for the neutral pictures [Neutral Hits (R+K) – Neutral Misses = Neutral Retrieval Success] was directly compared to each other. To make sure that the differences between Emotional and Neutral Retrieval Success activity occurred due to positive activations in the emotional condition rather than due to deactivations in the neutral condition, T maps

resulting from the above contrast were inclusively masked with the activation maps showing a significant Emotional RS effect at $p < 0.05$. To distinguish the effects of recollection- vs. familiarity-based retrieval, retrieval success activity for emotional items was separately calculated for the R responses [Emotional Hits (R) – Emotional Misses = Emotional Retrieval Success-R] and for the K responses [Emotional Hits (K) – Emotional Misses = Emotional Retrieval Success-K], which where then compared to each other. The voxels showing a significant Emotional R vs. K effect for successfully retrieved items were identified from those that showed greater overall retrieval success activity for emotional than for neutral pictures. Again, to make sure that the R vs. K differences for successfully retrieved emotional items occurred due to positive activations in the R condition rather than deactivations in the K condition, T maps identifying the voxels showing statistically significant R vs. K differences for successfully retrieved emotional items were inclusively masked with the activation maps showing a significant R effect for successfully retrieved emotional items at $p < 0.05$.

Since the focus of the study was activity in the medial temporal lobe (i.e., the amygdala and the MTL memory structures), fMRI signal from the active MTL voxels as identified by the group analyses for the conditions of interest (e.g., Emotional Retrieval Success > Neutral Retrieval Success) was extracted using a medial temporal lobe (MTL) mask. This procedure involved two steps: first, the active voxels identified for a specific contrast on a time point-by-time point basis were clustered together across time points using the logical function *or*, then the averaged signal from this cluster (extent threshold = 4 contiguous voxels) was extracted using the MTL mask. The MTL mask was manually traced on a high-resolution anatomical image having the same resolution as those recorded for each subject and normalized to the same MNI template. The MTL mask was used for three purposes: (1) to separate the MTL activity from activity in other brain regions, (2) to more precisely localize the activity coming from various MTL subregions, and (3) to perform additional confirmatory quantitative analyses (i.e., T tests, ANOVAs) on the extracted data.

Similar to the procedure employed in our encoding study (Dolcos et al., 2004b), MTL tracing identified the amygdala, hippocampus, and entorhinal cortex using anatomic guidelines (Brierley, Shaw, & David, 2002; Duvernoy et al., 1999; Insausti et al., 1998;

Pruessner et al., 2002; Pruessner et al., 2000). ROI tracing first identified the main regions (i.e., the hippocampus and the parahippocampal gyrus), which were then further subdivided into their major subregions. Thus, following a rostro-caudal organization, the hippocampus was subdivided into head, body, and tail, and the parahippocampal gyrus was subdivided into anterior and posterior regions. The posterior region included the parahippocampal cortex, and the anterior region was subdivided into medial and lateral subregions corresponding to the entorhinal and perirhinal cortices, respectively. To further quantify activity in these regions and to reduce the probability of type I error, additional statistical analyses (i.e., T tests / ANOVAs) were performed on the average percent signal change data extracted using the MTL mask. Since the current approach involved *a priori* identified MTL ROIs, a threshold of $p < 0.05$ uncorrected was employed in all analyses. Finally, only the MTL subregions that showed at least five percent of active voxels in the contrasts of interest, and were confirmed by the subsequent statistics are reported.

Results

Behavioral Results. Confirming the first prediction, recognition was better for emotional than for neutral pictures, and this effect was driven by recollection. Hits for pleasant (0.54, SD = 0.12) and unpleasant (0.50, SD = 0.14) pictures were similar ($p > 0.05$) and were both greater ($p's < 0.05$) than hits for neutral pictures (0.33, SD = 0.10). Given that memory for pleasant and unpleasant pictures was similar, for the fMRI analyses these two conditions were combined into a single "emotional" category. To control for potential differences in guessing, corrected recognition scores were computed by subtracting false alarms from hits. Figure 6-1 displays corrected recognition scores for emotional and neutral pictures, and clearly indicates a difference between emotional and neutral items only for recollection (R responses) but not for familiarity (K responses). Confirming this impression, an ANOVA on these corrected recognition scores (hits – false alarms) yielded a significant memory (R vs. K) x picture type (emotional vs. neutral) interaction ($p < 0.05$), and pairwise contrasts revealed significant emotional-neutral differences for R responses ($p < 0.05$) but not for K responses ($T = 0$). In sum,

emotional content enhanced memory performance, and this effect was driven by recollective processes.

FMRI Results. Confirming the second prediction, retrieval success activity in the amygdala, hippocampus, and entorhinal cortex was greater for emotional than for neutral pictures (Figure 6-2). Retrieval success activity in other medial temporal lobe regions was not significantly different for emotional vs. neutral pictures. Paired T tests performed on retrieval success activity at the peak time point yielded significant differences as a function of emotion in the right amygdala, $T(6) = 2.56$, $p < 0.05$, right entorhinal cortex, $T(6) = 2.75$, $p < 0.04$, right hippocampus head, $T(6) = 2.98$, $p < 0.03$, and bilaterally in the hippocampus tail [left side: $T(6) = 2.48$, $p < 0.05$; right side: $T(6) = 2.62$, $p < 0.04$].

Confirming the third prediction, retrieval success activity for emotional pictures was greater for recollection-based (R) responses than for familiarity-based (K) responses in the amygdala and hippocampus but not in the entorhinal cortex (see Figure 6-3). Paired T tests revealed significant effects of recollection in the right amygdala, $T(6) = 2.89$, $p < 0.03$, right hippocampus head, $T(6) = 2.57$, $p < 0.05$, and bilaterally in the hippocampus tail [left side: $T(6) = 2.79$, $p < 0.04$; right side: $T(6) = 2.78$, $p < 0.04$], but not in the entorhinal cortex, $T(6) = 0.68$, $p > 0.5$. Further confirming this R vs. K difference, a two-way ANOVA (region: amygdala vs. hippocampus vs. EC) x (recollection: R vs. K), in which data from the three hippocampal regions (i.e., right hippocampal head and the hippocampal tail bilaterally) were considered separately, produced a significant region x recollection interaction. The most significant interaction was obtained when data from the hippocampal head was considered, $F(2, 12) = 8.16$, $p < 0.006$ (Figure 6-3).

Discussion

The present study yielded three main results relevant for understanding the psychological and neural mechanisms that mediate emotional memory retrieval. First, one year after their initial encoding, emotionally-arousing pictures were remembered better and elicited greater recollection than neutral pictures. Second, emotional content enhanced activity in the amygdala and the MTL memory system (hippocampus and entorhinal cortex) related to successful retrieval of individual items from long-term storage (hits vs. misses). Third, the emotion-enhancing effect during retrieval was greater

for recollection (R responses) than for familiarity (K responses) in the amygdala and the hippocampus but not in the entorhinal cortex. Collectively, the findings show that even after long retention intervals, emotionally-arousing events are preferentially retained in memory, their successful retrieval is associated with engagement of the amygdala and other MTL structures that also participate in their initial encoding, and they are more likely to be retrieved with a sense of recollection that is mediated by a subset of MTL regions. These findings are discussed, in turn, below.

Long-term retrieval of emotionally-arousing pictures is accompanied by a sense of recollection

The time course of the memory-enhancing effect of emotion has been characterized by laboratory studies that typically use delay intervals on the order of minutes to days. Early systematic investigations showed that paired associates to emotionally-arousing words exhibit a recall benefit as early as 20 min following encoding, which stabilizes for at least 1 week (Kleinsmith & Kaplan, 1963). This result is typically interpreted as an effect of emotionally-arousing context on memory consolidation. More recent studies have shown that emotional content yields retention advantages that increase from immediate to 1-hr delayed testing (LaBar & Phelps, 1998) and last as long as several weeks or months following encoding (Bradley et al., 1992; Cahill, Babinsky, Markowitsch, & McGaugh, 1995; Heuer & Reisberg, 1990). Here, consistent with Bradley et al. (1992), we show that memory-enhancing effect of emotion extends to delay intervals of one year. Also, we show that when arousal is equated, such long-term memory benefits are equivalent for negatively- and positively-valent material, consistent with previous studies using similar or shorter delays (Bradley et al., 1992; Dolcos et al., 2004b; Hamann et al., 1999).

One-year retention intervals may provide a limiting test case to observe such effects for laboratory-based models of memory, as longer intervals are likely to yield floor effects that mask the modulatory influence of emotion. Nonetheless, empirical studies of real-world events, including flashbulb and autobiographical memories, show emotional retention advantages that extend from years to decades (Maguire, 2001). It should be noted that although one year is 'remote' in terms of laboratory-based event

memory, it is usually considered 'recent' in terms of autobiographical memory. Thus, the present study provides an important bridge between retention intervals that are typically tested across these different episodic memory domains, and additional research is beginning to reveal brain regions common to retrieval of both laboratory-based and real-world events (Cabeza et al., 2004).

The results discussed above link emotional arousal to retention advantages as defined by accessibility of the memory trace (hits vs. misses). However, memory retrieval is associated with distinct mechanisms that can be dissociated behaviorally and which may be preferentially targeted by emotional processes. Specifically, recollection and familiarity are two types of memory retrieval that allow one to *remember* rich contextual details about the time and place episodic events took place (recollection), or only to *know* of their occurrence without retrieving specific contextual details (familiarity). These two types of retrieval have been found to be differentially affected by emotional arousal in both laboratory and autobiographical memory studies. Laboratory-based memory studies following short retention intervals (i.e., weeks) showed that recollection, but not familiarity, was increased by emotional arousal (Ochsner, 2000). As for autobiographical memories, there is evidence that emotional arousal also enhances more than just the accessibility of the memory trace – emotional autobiographical memories are retrieved with greater contextual detail (including visual imagery) and a sense of traveling back in time, which are core features of recollection (Reisberg, Heuer, McLean, & O'Shaughnessy, 1988; Talarico et al., in press). The present results extend the laboratory-based findings by showing that memory-enhancing effect of emotional arousal on recollection extends over a period of one year. This issue has not been explored by earlier laboratory-based studies of emotional memory retrieval following similar retention intervals (Bradley et al., 1992).

Emotional content enhanced retrieval success activity in the amygdala and the MTL memory system

As noted in the Introduction, the few functional neuroimaging studies that investigated emotional memory retrieval did not disentangle retrieval from consolidation and did not isolate the neural correlates of the difference between successfully

remembered and forgotten emotional items. To address these limitations, the present study investigated the retrieval of consolidated memories after a retention interval of one year and directly compared retrieval success activity (hits-misses) for emotional vs. neutral events. As a result, the present report provides strong evidence that successful retrieval of emotional memories involves MTL mechanisms similar to those identified during successful encoding (Cahill et al., 1996; Canli et al., 2002; Canli et al., 2000; Dolcos et al., 2004b; Hamann et al., 1999; Kensinger & Corkin, 2004; Kilpatrick & Cahill, 2003; Richardson et al., 2004). In a fMRI study of emotional encoding, Dolcos et al. (2004b) reported that emotion enhanced activity in the amygdala, the hippocampus, and the entorhinal cortex during successful encoding. In the present study, activity in the same set of regions was also modulated by emotion during successful retrieval of emotional stimuli.

Thus, the amygdala plays a role in emotional memory not only during successful encoding but also during successful retrieval. It is important to note that the amygdala activation in the present study cannot be attributed to the emotional nature of the stimuli used as retrieval cues (LaBar, 2003; Maratos et al., 2001; Smith et al., 2004). Specifically, amygdala activation was found as a difference between retrieval activity for emotional pictures correctly classified as old and activity for emotional pictures incorrectly classified as new (Emotional Hits > Emotional Misses). Moreover, this difference was also identified when successful retrieval activity for emotional pictures (Emotional Hits > Emotional Misses) was compared with successful retrieval activity for neutral pictures (Neutral Hits > Neutral Misses). Thus, activity related to perception of emotion is subtracted out, and the difference reflects the interaction between emotion and memory. This finding is consistent with evidence from animal research showing retrieval-related amygdalar involvement during fear conditioning (Nader, Schafe, & LeDoux, 2000).

The emotion effect was greater on recollection than familiarity in the amygdala and the hippocampus but not in the entorhinal cortex

Understanding the differences between recollection and familiarity and the factors that selectively enhance recollection are fundamental goals of memory research. Emotion

is assumed to be a critical factor, but the underlying neural mechanism is only partly understood. Behavioral studies have demonstrated that the ability to recollect past events is enhanced by emotional arousal (Ochsner, 2000; Talarico et al., in press), and functional neuroimaging studies have linked recollection of neutral events to activity in the hippocampus (Yonelinas, 2002). Thus, it was reasonable to predict that the recollection-enhancing effect of emotion was mediated by brain regions associated with arousal (i.e., the amygdala) and brain regions associated with recollection (i.e., the hippocampus). Yet, the connection between these two lines of evidence was lacking. Thus, the present study provides this critical missing link: emotion selectively enhanced recollection-based activity indexing retrieval success in both the amygdala and the hippocampus.

Given that the amygdala is a prototypical emotion region and the hippocampus is a prototypical memory region, one way of explaining their co-activation during emotional recollection is that emotion enhances recollection-related activity in the hippocampus while recollection enhances emotion-related activity in the amygdala. Emotion may enhance recollection because reinstating the affective context of the original episode is likely to facilitate the recovery of contextual details, such as where, when, and how the original events happened. Conversely, the recollection of the context surrounding an emotional effect is likely to augment the emotional arousal elicited by the event during retrieval. Thus, the amygdala and the hippocampus could be parts of a synergistic mechanism in which emotion enhances recollection and recollection enhances emotion. The clinical implication of this interpretation is that, in patients suffering from posttraumatic stress disorder, processing of emotional cues related to traumatic events may trigger recollection of traumatic memories, which is accompanied by hippocampal activity. This, in turn, may intensify amygdalar activity associated with emotional (e.g., fear-related) response (LeDoux, 2000).

In the entorhinal cortex, in contrast, emotion also enhanced familiarity-related activity (Figure 6-3). This may reflect the position of this region within the MTL memory system as a convergence point for information coming from unimodal and multi-modal association areas. As a result, this region may be sensitive to the reinstatement of sensory details that give rise to the experience of familiarity. On the other hand, the position of the hippocampus at the top of the MTL hierarchy may be critical for binding content and

context information required for the experience of recollection. In sum, the amygdala, hippocampus, and entorhinal cortex all contribute to the enhancing effect of emotion on retrieval processes, and the first two regions additionally differentiate between emotion effects on recollection and familiarity.

Conclusions

The present study provided behavioral and functional neuroimaging evidence concerning the effect of emotional arousal on memory retrieval processes following a long retention interval. Behavioral results showed that emotionally-arousing stimuli were remembered better than neutral ones, and this memory-enhancing effect affected recollection rather than familiarity. Functional neuroimaging results showed that emotion enhances successful retrieval activity in the amygdala and the MTL memory system, and that in the amygdala and the hippocampus (but not in the entorhinal cortex) the emotion effect is greater for recollection than for familiarity. Taken together, these results suggest that successful retrieval of remote emotional information involves MTL mechanisms similar to those identified during successful encoding, but different MTL subregions have dissociable contribution to successful retrieval of emotional memories based on recollection and familiarity.

References

Anderson, A. K., Christoff, K., Stappen, I., Panitz, D., Ghahremani, D. G., Glover, G., Gabrieli, J. D., & Sobel, N. (2003). Dissociated neural representations of intensity and valence in human olfaction. *Nat Neurosci, 6*(2), 196-202.

Bradley, M. M., Greenwald, M. K., Petry, M. C., & Lang, P. J. (1992). Remembering pictures: Pleasure and arousal in memory. *J Exp Psychol: Learn, Mem, & Cogn, 18*(2), 379-390.

Brierley, B., Shaw, P., & David, A. S. (2002). The human amygdala: A systematic review and meta-analysis of volumetric magnetic resonance imaging. *Brain Res Rev, 39*(1), 84-105.

Cabeza, R., Prince, S. E., Daselaar, S. M., Greenberg, D. L., Budde, M., Dolcos, F., LaBar, K. S., & Rubin, D. C. (2004). Brain activity during episodic retrieval of autobiographical and laboratory events: An fMRI study using a novel photo paradigm. *J Cogn Neurosci, in press*.

Cahill, L., Babinsky, R., Markowitsch, H., & McGaugh, J. L. (1995). The amygdala and emotional memory. *Nature, 377*, 295-296.

Cahill, L., Haier, R. J., Fallon, J., Alkire, M. T., Tang, C., Keator, D., Wu, J., & McGaugh, J. L. (1996). Amygdala activity at encoding correlated with long-term, free recall of emotional information. *Proc Natl Acad Sci U S A, 93*, 8016-8021.

Canli, T., Desmond, J. E., Zhao, Z., & Gabrieli, J. D. E. (2002). Sex differences in the neural basis of emotional memories. *Proc Natl Acad Sci U S A, 99*(16), 10789-10794.

Canli, T., Zhao, Z., Brewer, J., Gabrieli, J. D. E., & Cahill, L. (2000). Event-related activation in the human amygdala associated with later memory for individual emotional experience. *J Neurosci, 20*(RC99), 1-5.

Christianson, S.-A. (1992). *The Handbook of Emotion and Memory: Research and Theory*: Lawrence Erlbaum Associates.

Dobbins, I. G., Rice, H. J., Wagner, A. D., & Schacter, D. L. (2003). Memory orientation and success: Separable neurocognitive components underlying episodic recognition. *Neuropsychologia, 41*, 318-333.

Dolan, R. J., Lane, R., Chua, P., & Fletcher, P. (2000). Dissociable temporal lobe activations during emotional episodic memory retrieval. *Neuroimage, 11*(3), 203-209.

Dolcos, F., & Cabeza, R. (2002). Event-related potentials of emotional memory: Encoding pleasant, unpleasant, and neutral Pictures. *Cogn, Affect, & Behav Neurosci, 2*(3), 252-263.

Dolcos, F., Graham, R., LaBar, K., & Cabeza, R. (2003). Coactivation of the amygdala and hippocampus predicts better recall for emotional than for neutral pictures. *Brain and Cognition, 51*, 221-223.

Dolcos, F., LaBar, K. S., & Cabeza, R. (2004a). Dissociable effects of arousal and valence on prefrontal activity indexing emotional evaluation and subsequent memory: An event-related fMRI study. *NeuroImage, 23*(1), 64-74.

Dolcos, F., LaBar, K. S., & Cabeza, R. (2004b). Interaction between the amygdala and the medial temporal lobe memory system predicts better memory for emotional events. *Neuron, 42*, 855-863.

Duvernoy, H. M., Bourgouin, P., Cabanis, E. A., Cattin, F., Guyot, J., Iba-Zizen, M. T., Maeder, P., Parratte, B., Tatu, L., & Fuillier, F. (1999). *The Human Brain: Surface, Three-Dimensional Sectional Anatomy With Mri, and Blood Supply* (2nd Edition ed.). Wien: Springer-Verlag Wien New York.

Eldridge, L. L., Knowlton, B. J., Furmanski, C. S., Bookheimer, S. Y., & Engel, S. A. (2000). Remembering episodes: A selective role for the hippocampus during retrieval. *Nature Neuroscience, 3*(11), 1149-1152.

Fossati, P., Hevenor, S. J., Lepage, M., Graham, S. J., Grady, C., Keightley, M. L., Craik, F. I., & Mayberg, H. S. (2004). Distributed self in episodic memory: Neural correlates of successful retrieval of self-encoded positive and negative personality traits. *Neuroimage, 22*, 1596-1604.

Hamann, S. B., Ely, T. D., Grafton, S. T., & Kilts, C. D. (1999). Amygdala activity related to enhanced memory for pleasant and aversive stimuli. *Nat Neurosci, 2*(3), 289-293.

Hamann, S. B., Ely, T. D., Hoffman, J. M., & Kilts, C. D. (2002). Ecstasy and agony: Activation of the human amygdala in positive and negative emotion. *Psychol Sci, 13*(2), 135-141.

Henson, R. N. A., Rugg, M. D., Shallice, T., Josephs, O., & Dolan, R. J. (1999). Recollection and familiarity in recognition memory: An event-related functional magnetic resonance imaging study. *The Journal of Neuroscience, 19*(10), 3962-3972.

Heuer, F., & Reisberg, D. (1990). Vivid memories for emotional events: The accuracy of remembered minutiae. *Mem Cognit, 18*(5), 496-506.

Insausti, R., Juottonen, K., Soininen, H., Insausti, A. M., Partanen, K., Vainio, P., Laakso, M. P., & Pitkanen, A. (1998). MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. *Am J Neuroradiol, 19*(4), 659-671.

Kensinger, E. A., & Corkin, S. (2004). Two routes to emotional memory: Distinct neural processes for valence and arousal. *Proc Natl Acad Sci U S A, 101*(9), 3310-3315.

Kilpatrick, L., & Cahill, L. (2003). Amygdala modulation of parahippocampal and frontal regions during emotionally influenced memory storage. *NeuroImage, 20*(4), 2091-2099.

Kleinsmith, L. J., & Kaplan, S. (1963). Paired-associate learning as a function af arousal and interpolated interval. *J Exp Psychol, 65*, 190-193.

LaBar, K. S. (2003). Emotional memory functions of the human amygdala. *Curr Neurol Neurosci Rep, 3*(5), 363-364.

LaBar, K. S., & Phelps, E. A. (1998). Arousal-mediated memory consolidation: Role of the medial temporal lobe in humans. *Psychol Sci, 9*(6), 490-493.

Lang, P. J., Bradley, M. M., & Cuthberg, B. N. (1997). *International Affective Picture System* [Pictures]. Gainesville: NIMH Center for the Study of Emotion and Attention.

Lang, P. J., Greenwald, M. K., Bradley, M. M., & Hamm, A. O. (1993). Looking at pictures: Affective, facial, visceral, and behavioral reactions. *Psychophysiol, 30*(3), 261-273.

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annu. Rev. Neurosci., 23*, 155-184.

Maguire, E. A. (2001). Neuroimaging studies of autobiographical event memory. *Philos Trans R Soc Lond B Biol Sci, 356*(1413), 1441-1451.

Maratos, E. J., Dolan, R. J., Morris, J. S., Henson, R. N., & Rugg, M. D. (2001). Neural activity associated with episodic memory for emotional context. *Neuropsychologia, 39*(9), 910-920.

McGaugh, J. L. (2000). Memory-a century of consolidation. *Science, 287*(5451), 248-251.

McGaugh, J. L. (2002). Memory consolidation and the amygdala: A systems perspective. *Trends Neurosci, 25*(9), 456-461.

McGaugh, J. L. (2004). The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annu. Rev. Neurosci., 27*, 1-28.

Nadel, L. (2000). Memory traces revisited. *Nat Rev Neurosci, 1*(209-12).

Nader, K. (2003). Memory traces unbound. *Trend Neurosci, 26*(2), 65-72.

Nader, K., Schafe, G. E., & LeDoux, J. E. (2000). Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature, 406*, 722-726.

Ochsner, K. N. (2000). Are affective events richly recollected or simply familiar? The experience and process of recognizing feelings past. *J Exp Psychol Gen, 129*(2), 242-261.

Paller, K. A., & Wagner, A. D. (2002). Observing the transformation of experience into memory. *Trends Cogn Sci, 6*(2), 93-102.

Phelps, E. A. (2004). Human emoiton and memory: Interactions of the amygdala and hippocampal complex. *Curr Opin Neurobiol, 14*, 198-202.

Prince, S. E., Daselaar, S. M., & Cabeza, R. (submitted). Neural correlates of relational memory: Successful encoding and retrieval of semantic and perceptual associations. *Manuscript submitted for publication.*

Pruessner, J. C., Kohler, S., Crane, J., Pruessner, M., Lord, C., Byrne, A., Kabani, N., Collins, D. L., & Evans, A. C. (2002). Volumetry of temporopolar, perirhinal, entorhinal and parahippocampal cortex from high-resolution MR images: considering the variability of the collateral sulcus. *Cereb Cortex, 12*(12), 1342-1353.

Pruessner, J. C., Li, L. M., Serles, W., Pruessner, M., Collins, D. L., Kabani, N., Lupien, S., & Evans, A. C. (2000). Volumetry of hippocampus and amygdala with high-resolution MRI and three-dimensional analysis software: minimizing the discrepancies between laboratories. *Cereb Cortex, 10*(4), 433-442.

Reisberg, D., Heuer, F., McLean, J., & O'Shaughnessy, M. (1988). The quantity, not the quality, of affect predicts memory vividness. *Bulletin of the Psychonomic Society, 26*, 100-103.

Richardson, M. P., Strange, B. A., & Dolan, R. J. (2004). Encoding of emotional memories depends on amygdala and hippocampus and their interaction. *Nat Neurosci, 7*(3), 278-285.

Shields, S. (1991). Gender in the psychology of emotion: A selective research review. In K. Strongman (Ed.), *International Review of Studies on Emotion* (pp. 227-245). New York: Wiley.

Smith, A. P. R., Henson, R. N. A., Dolan, R. J., & Rugg, M. D. (2004). fMRI correlates of episodic retrieval of emotional contexts. *Neuroimage, 22*, 868-878.

Stark, E. L., & Okado, Y. (2003). Making memories without trying: Medial temporal lobe activity associated with incidental memory formation during retrieval. *J Neurosci, 23*(17), 6748-6753.

Talarico, J. T., LaBar, K. S., & Rubin, D. C. (in press). Emotional intensity predicts autobiographical memory experience. *Memory & Cognition.*

Tulving, E. (1985). Memory and consciousness. *Can. Psychol., 26*, 1-12.

Weis, S., Klaver, P., Reul, J., Elger, C. E., & Fernandez, G. (2004). Temporal and cerebellar brain regions that suppot both declarative memory formation and retrieval. *Cereb Cortex, 14*, 256-267.

Yamasaki, H., LaBar, K. S., & McCarthy, G. (2002). Dissociable prefrontal brain systems for attention and emotion. *Proc Natl Acad Sci U S A, 99*(17), 11447-11451.

Yonelinas, A. P. (2002). The nature of recollection and familiarity: A review of 30 years of research. *J. Mem. Language, 46*, 441-517.

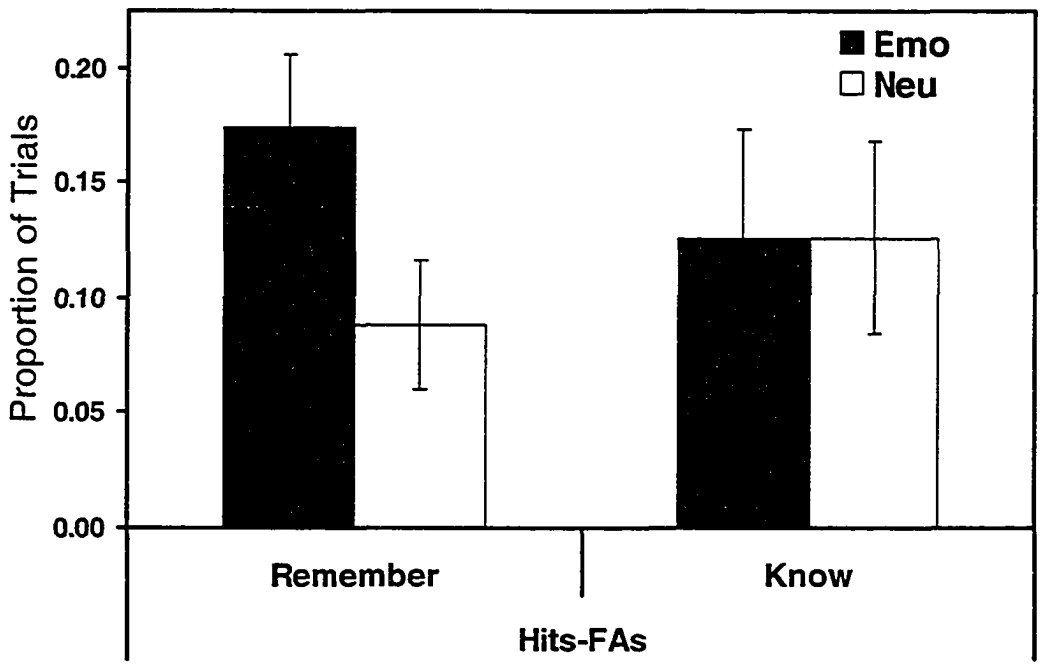

Figure 6-1. The memory-enhancing effect of emotion was driven by recollection. Corrected recognition scores (Hits – False Alarms) for emotional and neutral pictures are presented. Positive and negative pictures are collapsed into the emotional category. Emo = Emotional, Neu = Neutral; Remember = Recollection-based responses, Know = Familiarity-based responses; FAs = False alarms.

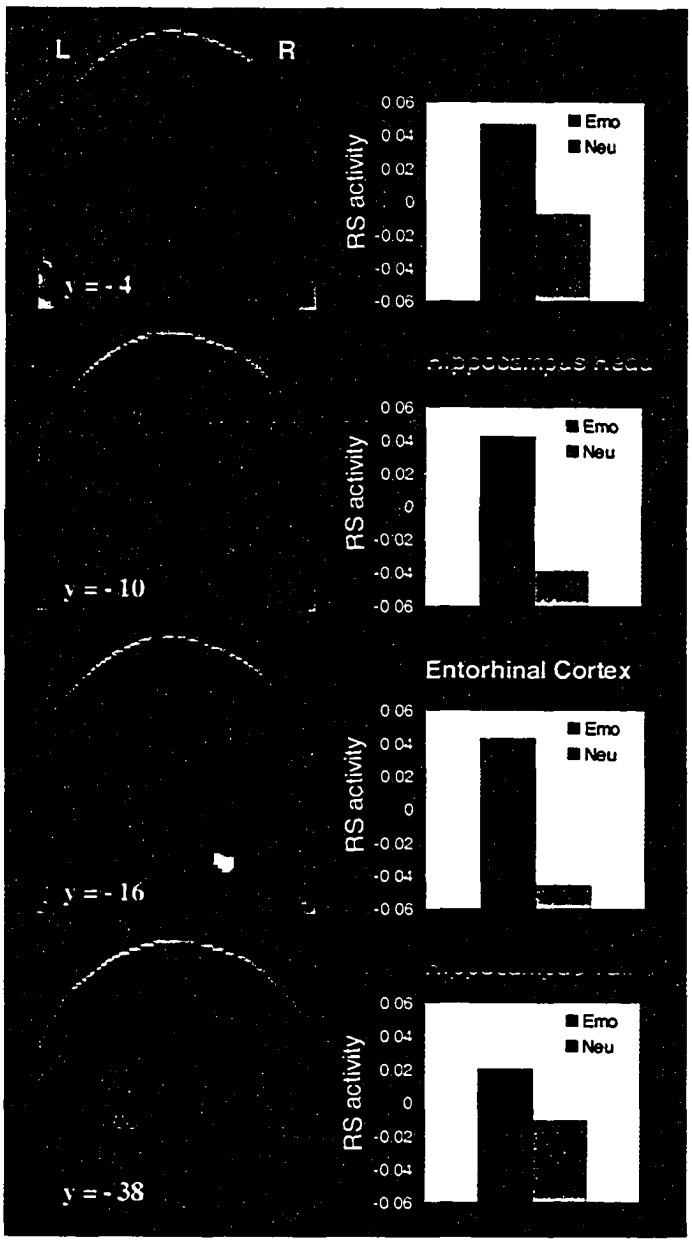

Figure 6-2. Greater retrieval success activity in the amygdala and MTL memory system for emotional than for neutral pictures. Compared to the neutral retrieval success (RS), the overall emotional RS was associated with greater activity in the right amygdala, entorhinal cortex, and hippocampus head, and bilaterally in hippocampus tail. On the left column are presented representative brain slices showing the active voxels as identified in the MTL regions by the random-effects group analysis for the comparison of interest (i.e., Emo RS > Neu RS). The active voxels (in color) are displayed on a high-resolution anatomical image normalized to the MNI (Montreal Neurological Institute) template. The numbers at the left bottom side of each brain slice (e.g., y = -4) represent the y values in MNI space. On the right column are presented graphs displaying the emotional and neutral RS expressed in percent signal change as extracted from the active voxels identified in the MTL regions (all bar graphs are based on data from right hemisphere). MTL = Medial Temporal Lobe; RS = retrieval success (Hits – Misses); Emo = Emotional, Neu = Neutral ; L = Left, R = Right.

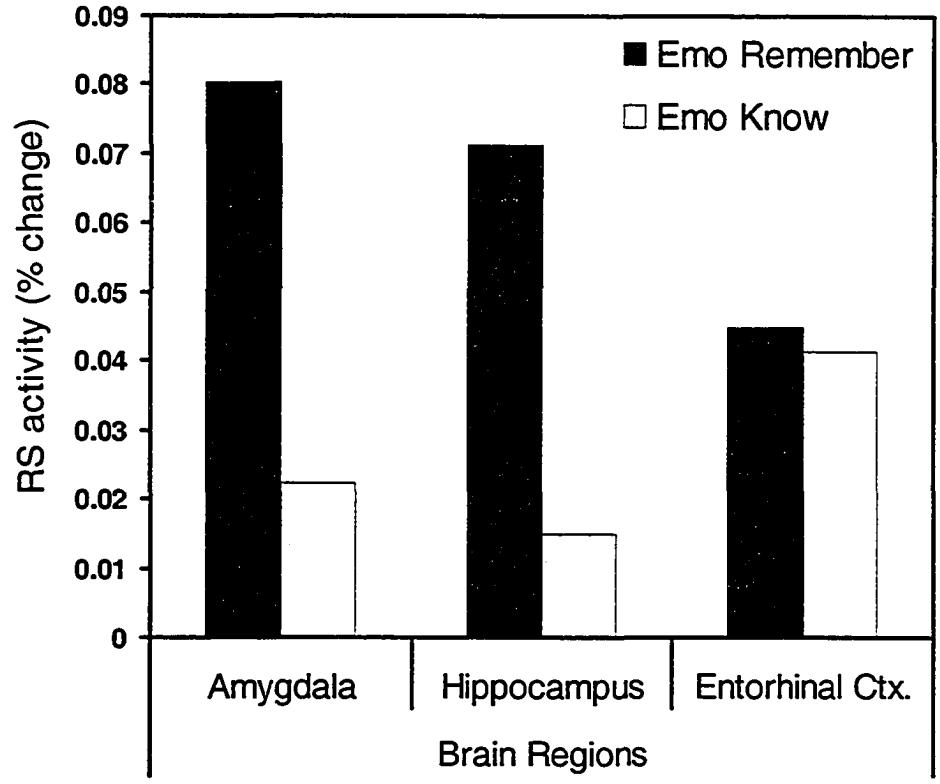

Figure 6-3. Dissociable effect of emotion on retrieval success activity in the amygdala and hippocampus vs. entorhinal cortex. In the right amygdala and hippocampus head, retrieval success (RS) activity for emotional pictures was greater for recollection than for familiarity, whereas in the entorhinal cortex it was similar for both recollection and familiarity. The bars for the amygdala and hippocampus head are based on the percent signal change extracted from the voxels showing the maximum recollection vs. familiarity difference. RS = retrieval success (Hits – Misses); Remember = Recollection-based RS (Hits-R > Misses); Know = Familiarity-based RS (Hits-K > Misses); Emo = Emotional, Neu = Neutral; Ctx. = Cortex.

CHAPTER 7
GENERAL DISCUSSION

Review of the main findings

The overarching goal of the present dissertation was to address critical issues concerning the effect of arousal and valence on the neural correlates underlying emotional evaluation and emotional episodic memory in neurologically intact human participants. Two complementary functional neuroimaging methods were used. One method (i.e., ERP) allowed highly accurate measurements of the temporal characteristics of the processing associated with the abovementioned phenomena, whereas the other (i.e., fMRI) allowed excellent spatial resolution in measuring the source of the effects of interest. The first two studies of the present dissertation, one using ERPs and the other using fMRI, focused on processing associated with emotional evaluation and successful encoding of emotional memories. The third study used fMRI and focused on processing associated with successful retrieval of emotional memories. The main findings of these studies were that, while neural correlates of emotional evaluation were sensitive to both arousal and valence, neural mechanisms of emotional memory (during both encoding and retrieval) were mainly sensitive to arousal. Below, I will briefly discuss the findings for each of the issues highlighted in the introductory section and addressed in the body of the present work.

Study I. Effect of emotion on brain activity associated with emotional evaluation and emotional memory encoding – ERPs evidence

The ERP study yielded two main results (Chapter 2, Dolcos & Cabeza, 2002). First, there was a clear topographical difference between arousal- and valence-related components of the emotion effect: at parietal electrodes the emotion effect was sensitive to arousal, whereas at frontocentral electrodes the emotion effect was sensitive to both arousal and valence. Second, there was a difference between the subsequent memory effect for emotional and neutral pictures: the subsequent memory effect at central electrodes was faster for high-arousing stimuli than for low-arousing neutral stimuli.

I.1. Effect of arousal and valence on ERP correlates of emotional evaluation. The parieto-frontal dissociation concerning the effect of arousal and valence on the neural correlates of emotional evaluation is consistent with evidence involving parietal regions in the processing of arousal (Heilman, 2000; LaBar et al., 1999), as well as with evidence

involving the frontal regions in the processing of emotional valence (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Davidson, 1995; Diedrich, Naumann, Maier, & Becker, 1997). These findings are also consistent with Heller's model (Heller, 1993; Heller & Nitschke, 1998), which proposes the existence of two distinct neural systems involved in the processing of emotional information: one involved in the processing of emotional arousal located in the parietal lobes, and the other involved in the processing of emotional valence located in the frontal lobes.

Interestingly, the valence-related difference in the emotion effect at the frontocentral electrodes occurred because the emotion effect started earlier for pleasant than for unpleasant pictures (Figure 2.2): there was a faster effect of positive valence (positive > negative = neutral), and a delayed effect of arousal (positive = negative > neutral). Given the evidence that positive stimuli typically trigger "approach" reactions, and given the suggestion that emotion effect in the 400-600 ms epoch reflects the processing of the emotional qualities of the stimuli, depending on the amount of attention paid to the emotional content (Diedrich et al., 1997), faster emotion effect for pleasant valence could reflect a preference toward detecting and processing pleasant pictures. This interpretation has ecological validity in the sense that, typically, people are more likely to show a preference for pleasant than for unpleasant stimuli (Pollyanna effect, Matlin & Stang, 1978).

The neural generators of the ERP differences reported are unclear, but one may speculate that arousal-related differences in the emotion effect primarily reflected the contribution of amygdala-cortical interactions (Amaral, Price, Pitkanen, & Carmichael, 1992), whereas valence-related differences primarily reflected the contribution of the prefrontal cortex (Davidson, 1995; Dolcos, LaBar, & Cabeza, 2004a). Interestingly, as discussed later, valence-related difference in timing at middle frontal electrodes may be connected to the valence-related differences in location identified in the medial prefrontal regions (Dolcos et al., 2004a). At any rate, these results are consistent with previous ERP evidence (Cuthbert et al., 2000; Diedrich et al., 1997), and with evidence supporting the general notion that parietal areas are involved in the processing of emotional arousal (Heilman, 2000; LaBar et al., 1999), whereas prefrontal areas are involved in the

evaluation of the emotional valence of stimuli (Davidson, 1995; Davidson & Irwin, 1999).

I.2. ERP correlates of the modulatory effect of emotion on memory formation. The main finding concerning this issue was that there was a faster subsequent memory effect for emotional than for the neutral items. In other words, successful encoding of emotional items occurred earlier than for the neutral items. Assuming that shorter ERP latencies reflect privileged access to processing resources (Ganis, Kutas, & Sereno, 1996), the present finding of an earlier subsequent memory effect for emotional pictures could be one of the mechanisms underlying better memory for emotional than neutral events.

The neocortical generators of the emotional modulation of the subsequent memory effect are unclear, but they may involve medial-temporal, prefrontal, and parietal regions generally associated with emotional processing (Barbas, 2000; Davidson & Irwin, 1999; LaBar et al., 1999; R.D Lane et al., 1997; Lang et al., 1998), associated with mnemonic functions (Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Paller & Wagner, 2002; Wagner et al., 1998), and/or sensitive to the modulatory effect of emotion on memory formation (Cahill et al., 1996; Canli, Desmond, Zhao, & Gabrieli, 2002; Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000; Dolcos, Graham, LaBar, & Cabeza, 2003; Dolcos et al., 2004a; Dolcos, LaBar, & Cabeza, 2004b; Hamann, Ely, Grafton, & Kilts, 1999; Kensinger & Corkin, 2004; Kilpatrick & Cahill, 2003; Richardson, Strange, & Dolan, 2004). The fMRI findings concerning the effect of arousal on MTL and PFC activity associated with encoding success, as shown in Chapters 3-5 of the present dissertadtion (Dolcos et al., 2003; Dolcos et al., 2004a, 2004b) support this interpretation.

In sum, these results are compatible with evidence about the role of different brain areas in the processing of emotional information, and with evidence concerning the memory-enhancing effect of emotion. The present study also provides the first available evidence of a link between two seemingly unrelated ERP phenomena: the *emotion effect* and the *subsequent memory effect*.

Study II. Effect of emotion on brain activity associated with emotional evaluation and emotional memory encoding – fMRI evidence

II.1. Role of the amygdala during emotional evaluation. The finding concerning this issue was that, while the amygdala was involved in the processing of both positive and negative emotions, this region was more involved in the processing of unpleasant stimuli. This finding provides new insight into the role of this region during emotional evaluation. Although much research supports amygdalar involvement in the evaluation of negative emotions (Adolphs & Tranel, 1999), its role in positive emotions continues to be debated. Previous functional studies that found amygdalar activity for appetitive cues (e.g., food, sex) did not determine whether this involvement was stimulus-specific or reflect sustained changes in motivational or attentional states (Beauregard, Levesque, & Bourgouin, 2001; Hamann, Ely, Hoffman, & Kilts, 2002; LaBar et al., 2001). In contrast, the present study demonstrated amygdalar activity for both pleasant and unpleasant stimuli in conditions in which arousal was matched and stimuli were randomized during scanning (see also, Anderson et al., 2003).

Although activity in the amygdala was sensitive to both positive and negative emotions, it was greater during processing of negative pictures. These finding suggests that the amygdala is generally involved in the processing of emotional arousal, regardless of valence, while showing particular preference for unpleasant stimuli. The suggested role of the amygdala in processing of emotional arousal seems in disagreement with evidence suggesting that the amygdala is important in arousal-mediated memory effects, rather than in arousal *per se* (e.g., Cahill et al., 1995; LaBar & Phelps, 1998). That is, it has been shown that amygdala patients did not show enhanced memory to emotional items despite normal skin conductance responses to emotional words (LaBar & Phelps, 1998) or normal arousal ratings of emotional scenes of a narrated slide show (Cahill et al., 1995). One possible explanation is that the amygdala is involved in emotional arousal but is not necessary for it. Thus, damage to the amygdala may not impair emotional arousal even though this region participates in the processing of emotional arousal in the neurologically intact brain, as clearly shown by the present results (Dolcos, et al, 2003).

It has been proposed that the amygdala is involved in processing that goes beyond its function in the processing of emotional arousal. More specifically, it has been proposed that one role of the amygdala is to increase the *vigilance* or response readiness of other systems (Whalen, 1998). For instance, in the case of visual stimuli, the amygdala may signal the presence of stimuli with emotional significance via back projection to the visual cortical areas. Consequently, more resources will be allocated to the processing of emotional compared to non-emotional stimuli (Lang et al., 1998). Consistent with this idea, compared to neutral pictures, evaluation of emotional pictures in the present study was associated with greater activity in both the amygdala and the parietooccipital extrastriate cortices (Figures 3.1 and 3.2). Activity in the amygdala, however, may not always be associated with an emotional response. Interestingly, in the present study activity in the amygdala was not totally insensitive to the presence of neutral stimuli (see Figure 3.2). Thus, it may be possible that the amygdala responds whenever the likelihood of emotional stimuli increases (in the present study, emotional and neutral stimuli where randomly presented, so that any novel stimulus could potentially be emotional). Thus, the amygdala may function as an "emotional detector", which triggers subsequent processing in other response systems if emotion is detected, or it does not trigger further processing if no emotional content is detected. This interpretation is consistent with the idea that amygdala is associated with *vigilance* (see also, Anderson & Phelps, 2001).

II.2. Role of the prefrontal cortex during emotional evaluation. As presented in Chapter 5 (Dolcos et al., 2004a), the fMRI study of encoding generated two main findings concerning the PFC role during emotional evaluation. First, consistent with the valence hypothesis, there was a valence-related hemispheric asymmetry in the lateral PFC: specific areas in the left hemisphere showed greater activity for positive than for negative pictures whereas areas in right hemisphere showed the converse pattern. Second, there was a dorsoventral dissociation in the medial PFC: activity in dorsomedial PFC was sensitive to arousal (positive = negative > neutral), whereas ventromedial PFC activity was sensitive to positive valence (positive > negative = neutral).

The finding concerning the valence hypothesis extends the existing evidence in two ways. First, this finding demonstrates hemispheric asymmetry effects predicted by

the valence hypothesis under conditions in which positive and negative stimuli were matched for arousal and visual properties, and in which the effects of valence could be distinguished from the effects of arousal on a trial-by-trial basis. Second, the present results not only demonstrated a valence-related hemispheric asymmetry but also identified the specific left and right PFC regions associated with positive (left dorsolateral PFC) and negative valence (right ventrolateral PFC).

Given the evidence that dorsolateral PFC regions are typically associated with working memory tasks (see Cabeza & Nyberg, 2000, for a review), one interpretation of the left dorsolateral PFC involvement in processing of positive valence could be that it reflects the maintenance and manipulation of positive information in working memory during the valence-rating task. As concerning the findings for the right ventrolateral PFC involvement during processing of negative valence, given the putative role of these regions in the inhibition of negative emotions (Petrovic, Kalso, Petersson, & Ingvar, 2002), one can speculate that it reflects the inhibition (avoidance) of negative information.

Turning to the dorsoventral dissociation in the medial PFC, although previous findings are consistent with the idea of possible segregation among medial PFC regions with respect to their involvement in emotional processing, it is not clear whether the role of these regions is related to arousal or to valence. Thus, by identifying specific medial PFC regions sensitive to arousal and positive valence, these findings complement and reconcile previous functional neuroimaging evidence suggesting non-specific (Lane, Fink, Chau, & Dolan, 1997; Lane, Reiman, Ahern, Schwartz, & Davidson, 1997; R. D. Lane, E. M. Reiman, M. M. Bradley et al., 1997; Reiman, 1997; Reiman et al., 1997; Teasdale et al., 1999) vs. valence-specific involvement of medial PFC during emotional processing (George et al., 1995; Paradiso et al., 1997; Paradiso et al., 1999).

As mentioned earlier, this finding is also consistent with the results of the ERP study presented in Chapter 2 (Dolcos & Cabeza, 2002) where arousal vs. valence dissociations were found at midline frontal electrodes: there was a faster effect of positive valence (positive > negative = neutral), and a delayed effect of arousal (positive = negative > neutral). Although spatial resolution of ERP did not allow to separate these

effects topographically, assuming that ERPs recorded at the middle frontal electrodes reflects activity in the medial PFC regions, it is reasonable to imagine that there is a relationship between the dissociation in timing identified in the ERP study and the dissociation in location identified in the fMRI study. At any rate, the faster ERP effect and overall greater medial PFC activity for positive stimuli are compatible with the interpretation that these findings may reflect bias towards detecting and processing positive stimuli.

II.3. Role of the amygdala and the MTL memory regions during emotional memory formation. As presented in Chapters 3 & 4 (Dolcos et al., 2003; Dolcos et al., 2004b), the following findings are relevant to this issue. (1) Analysis of behavioral data showed that memory performance was better for emotional than for neutral items, with no significant difference between positive and negative items. Analysis of the fMRI data produced the following results, three (2-4) of which are consistent with the modulation hypothesis: (2) compared to remembered neutral items, remembered emotional items were associated with greater activity in the amygdala and the MTL memory system, (3) emotional Dm was greater than the neutral Dm in both the amygdala and the MTL memory system, and (4) more strongly correlated for emotional than for the neutral items. (5) Finally, there was a dissociation along the longitudinal axis of the MTL memory regions: anterior regions showed a greater emotional Dm, whereas posterior regions showed a greater neutral Dm. Below, I will briefly summarize the significance of these findings.

Evidence for the modulation hypothesis. By addressing the shortcomings of previous functional neuroimaging studies, the present fMRI study of emotional encoding provides strong evidence supporting the modulation hypothesis in neurologically intact humans. These results were possible as a result of combining two important features: (1) the use of the subsequent memory paradigm to identify the MTL regions associated with successful encoding activity for emotional items, and (2) the use of anatomically defined ROIs to parcel out the contribution of each MTL region during successful encoding of emotional items. Moreover, this combination allowed correlational analyses that provided strong evidence supporting the notion that emotional arousal exerts its beneficial effect

on explicit memory through interactions between the amygdala and memory-related MTL regions.

The study also allowed the identification of specific contribution from amygdalar and parahippocampal subregions (i.e., basolateral amygdala and entorhinal cortex, respectively) during the formation of emotional memory. Given that basolateral amygdala has been identified by animal research on emotional memory as the main site through which the amygdala modulates memory-related activity in other brain regions (Cahill, 1998; McGaugh, 2000, 2002, 2004; McGaugh, McIntyre, & Power, 2002), and given the evidence that places the entorhinal cortex in a key position within the MTL memory system (Eichenbaum, 2000; Squire & Zola-Morgan, 1991), it is not surprising that these two regions showed the greatest effects consistent with the modulation hypothesis.

Dissociation along the longitudinal axis of the MTL. The dissociation along the longitudinal axis of the parahippocampal gyrus is the first evidence that anterior vs. posterior regions of the MTL memory system are differently involved in the formation of emotional vs. neutral information. Although future research is needed to clarify the specific mechanism involved, this finding is consistent with the models concerning possible rostrocaudal segregations of MTL function. As mentioned in Chapter 4, one possibility is that the greater emotional Dm in the anterior MTL memory regions reflects enhanced semantic and relational processing for emotional stimuli, whereas the greater neutral Dm in the posterior MTL reflects enhanced perceptual processing for neutral stimuli (Cabeza, Rao, Wagner, Mayer, & Schacter, 2001). At any rate, this finding clearly indicates that different MTL sectors are specialized to encode emotional and neutral information into long-term memory.

In sum, the findings concerning the role of MTL regions during emotional memory formation provided novel insights into the neural mechanisms associated with the formation of explicit emotional memories in the intact human brain. These findings clearly show that the ability to subsequently remember emotionally-arousing events relies on concomitant activity in an amygdala-based emotional processing system and in MTL memory regions during the initial encounter and encoding of stimuli. Moreover, the

present results also reveal a functional specialization within the MTL regarding the effects of emotion on memory formation.

II.4. Role of the PFC regions during emotional memory formation. As described in Chapter 5 (Dolcos et al., 2004a), emotional arousal enhanced successful encoding (Dm) activity in specific regions of the lateral PFC (i.e., left ventrolateral and dorsolateral regions). Research on the neural bases of the memory-enhancing effect of emotion has mainly emphasized the role of the amygdala and its interactions with MTL memory regions (Cahill et al., 1996; Canli et al., 2002; Dolcos et al., 2003; Dolcos et al., 2004b; Hamann et al., 1999; Kilpatrick & Cahill, 2003; McGaugh et al., 2002), and very little is known about the role of the PFC regions during emotional memory formation. Thus, the present PFC results expand this line of research by showing that the memory-enhancing effect of emotion during memory formation is also mediated by changes in PFC activity (see also, Canli et al., 2002; Kensinger & Corkin, 2004).

The specific PFC regions where the Dm was increased by arousal suggest that arousing events are better remembered because they receive deeper semantic processing and working memory resources during encoding. That is, given the role of left ventrolateral PFC regions in semantic processing (Kapur et al., 1996; Poldrack et al., 1999; Shallice et al., 1994), the present finding suggests that arousal facilitated successful encoding by increasing semantic processing of the information in the emotional items. As concerning the involvement of the dorsolateral PFC regions, given that activity in these regions has been typically associated with working memory processes (D'Esposito, Postle, & Rypma, 2000; Owen et al., 1999; Petrides, 1995), the effect of arousal on left dorsolateral PFC is likely to reflect the augmentation of working memory. Thus, it is possible that the contents of arousing events not only receive deeper semantic processing but are also maintained longer or manipulated more intensely in working memory, leading to better retention.

An important aspect of the present findings is that the enhancing effect of emotion on memory formation is primarily related to arousal rather than to valence. Similar to the PFC results discussed above, the MTL results presented in Chapters 3 & 4 (Dolcos et al., 2003; Dolcos et al., 2004b) also showed that the Dm increase was related to arousal

rather than to valence. Thus, it seems fair to conclude that arousal is the main factor modulating the neural mechanisms of emotional memory formation. This conclusion is consistent with the behavioral results, which showed that compared to non-arousing neutral events, memory was better for arousing positive and arousing negative pictures, with no significant difference between these two conditions. Thus, from the point of view of memory, a negative event can be as "good" as a positive event (see also Talarico, LaBar, & Rubin, 2004).

Taken together the findings concerning the role of the MTL and PFC mechanisms during emotional memory encoding, it can be concluded that the enhancing effect of emotion on memory formation (i) is mainly related to arousal, (ii) is mediated by changes in both MTL and PFC activity; and (iii) may involve an enhancement of storage and consolidation processes (MTL), as well as an amplification of semantic and working memory processes (PFC). In sum, the present fMRI study of emotional encoding provides novel evidence concerning the effect of arousal and valence on the neural correlates of emotional evaluation and emotional memory encoding. It also identifies the role of specific MTL and PFC regions in the processing underlying these phenomena.

Study III. Effect of emotion on brain activity associated with emotional memory retrieval – fMRI evidence

As presented in Chapter 6 (Dolcos, LaBar, & Cabeza, submitted), the fMRI study of retrieval yielded two main results concerning the neural mechanisms underlying the successful retrieval of emotional memory. First, emotional arousal enhanced retrieval success (RS) activity in the amygdala and the MTL memory system (hippocampus and entorhinal cortex). Second, this effect was greater for recollection-based (R responses) than for familiarity-based (K responses) responses in the amygdala and the hippocampus but not in EC.

III.1. Role of the amygdala and the MTL memory regions during retrieval of emotional memory. A number of functional neuroimaging studies investigating the neural mechanisms underlying the memory-enhancing effect of emotion are now available (for a review, see Phelps, 2004). Most of these studies, including those reported in the Chapters 2-5 (Dolcos & Cabeza, 2002; Dolcos et al., 2003; Dolcos et al., 2004a, 2004b), have

focused on encoding, and hence very little is known about the retrieval mechanisms of emotional memory in humans. One possibility is that retrieval of emotional memories depends on MTL mechanisms similar to those identified during encoding. Although a few studies have found amygdalar activity during retrieval (Dolan, Lane, Chua, & Fletcher, 2000; Fossati et al., 2004; Maratos, Dolan, Morris, Henson, & Rugg, 2001; Smith, Henson, Dolan, & Rugg, 2004), as mentioned in Chapter 6, these studies have two main limitations. (i) They used short retention intervals (i.e., minutes), which do not allow a clear separation between the involvement of the amygdala in retrieval vs. consolidation processes. (ii) These studies did not demonstrate that the amygdala is differentially more involved in successful than in unsuccessful retrieval of emotional events relative to neutral events.

By addressing these limitations, the fMRI study described in Chapter 6 (Dolcos et al., submitted) provides strong evidence that successful retrieval of emotional memories involves MTL mechanisms similar to those identified during successful encoding. That is, activity in the amygdala, hippocampus, and entorhinal cortex (Dolcos et al., 2004b) was also modulated during emotional memory retrieval. It is important to note that the amygdala activation we found cannot be attributed to the *perception* of emotional pictures, since this activation was found as a difference between activity for emotional pictures correctly classified as old and activity for emotional pictures incorrectly classified as new. Thus, this study provides the first clear functional neuroimaging evidence that the amygdala plays a critical role in emotional memory not only during successful encoding but also during successful retrieval.

III.2. Effect of emotion on retrieval activity associated with recollection and familiarity. As highlighted in the Introduction, understanding the differences between recollection and familiarity and the factors that enhance recollection are fundamental goals of memory research. Emotion is assumed to be a critical factor, but the underlying neural mechanism has been uncertain. Behavioral studies have demonstrated that the ability to recollect past events is enhanced by emotional arousal (Ochsner, 2000; Talarico, LaBar, & Rubin, in press), and functional neuroimaging studies have linked recollection of neutral events to activity in the hippocampus (Yonelinas, 2002). Thus, it

was reasonable to predict that the recollection-enhancing effect of emotion was mediated by brain regions associated with arousal (i.e., the amygdala) and brain regions associated with recollection (i.e., the hippocampus). Yet, the connection between these two lines of evidence was lacking. The present study provides this critical missing link: emotional arousal selectively enhanced recollection and this behavioral effect was associated with increased recollection-based activity indexing retrieval success in both the amygdala and the hippocampus. In contrast, the effect of arousal on the entorhinal cortex did not differ between recollection and familiarity. Thus, the amygdala, hippocampus, and entorhinal cortex all contribute to the enhancing effect of emotion on retrieval processes, but only the first two regions differentiate between emotion effects on recollection and familiarity.

Taken together, the results of the present fMRI study of emotional memory retrieval suggest that successful retrieval of emotional information involves MTL mechanisms similar to those identified during encoding, and that different MTL regions have dissimilar contribution to successful retrieval of emotional memories based on recollection and familiarity.

Summary and Conclusions

The present research brings novel insight concerning the effect of arousal and valence on the neural correlates of emotional processing, from initial perception and evaluation to successful encoding and, later, successful retrieval of consolidated emotional memories. The main findings of these studies were that, while neural correlates of emotional evaluation were sensitive to both arousal and valence, neural mechanisms of emotional memory were mainly sensitive to arousal.

The present research also identified the contribution of specific brain regions during emotional evaluation and emotional memory encoding and retrieval. As concerning emotional evaluation, the main findings were that (1) the amygdala was mainly sensitive to arousal, while showing preference for negative emotions, (2) medial PFC dissociates arousal and positive valence topographically and possibly temporally, and (3) specific left PFC regions are sensitive to positive emotions, while right PFC regions are sensitive to negative valence. As concerning the neural mechanisms of

emotional memory, the main findings were that (1) interaction between the amygdala and MTL memory regions predicts better memory for emotional than for neutral stimuli, (2) retrieval of emotional memory involves MTL mechanisms similar to those involved during encoding, and (3) compared to neutral memories, successful retrieval of emotional memories is accompanied by a sense of recollection, and this phenomenon is mediated by activity in the amygdala and hippocampus.

While these findings are basic in nature, better delineation of the role of specific brain regions during emotional evaluation and emotional memory could aid understanding the neural mechanisms of clinical conditions, such as depression and post traumatic stress disorder (PTSD). For instance, it is known that people who suffer from depression ruminate obsessively on negative or unpleasant memories, and PTSD patients suffer from intrusive traumatic memories. These problems could reflect a pathology in how their memory systems have processed emotional memories. Thus, the present findings on neurologically intact population could provide hints to future studies investigating the alterations associated with such clinical conditions.

References

Adolphs, R., & Tranel, D. (1999). Preferences for visual stimuli following amygdala damage. *J Cogn Neurosci, 11*(6), 610-616.

Amaral, D. G., Price, J. L., Pitkanen, A., & Carmichael, S. T. (1992). Anatomical organization of the primate amygdaloid complex. In J. P. Aggleton (Ed.), *The Amygdala, Neurobiological Aspects of Emotion, Memory and Mental Dysfunction* (pp. 1-66). New York: Wiley-Liss.

Anderson, A. K., Christoff, K., Stappen, I., Panitz, D., Ghahremani, D. G., Glover, G., Gabrieli, J. D., & Sobel, N. (2003). Dissociated neural representations of intensity and valence in human olfaction. *Nat Neurosci, 6*(2), 196-202.

Anderson, A. K., & Phelps, E. A. (2001). Lesions of the human amygdala impair enhanced perception of emotionally salient events. *Nature, 411*, 305-309.

Barbas, H. (2000). Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices. *Brain Research Bulletin, 52*(5), 319-330.

Beauregard, M., Levesque, J., & Bourgouin, P. (2001). Neural correlates of conscious self-regulation of emotion. *J Neurosci, 21*(18), RC165.

Brewer, J. B., Zhao, Z., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (1998). Making memories: Brain activity that predicts how well visual experience will be remembered. *Science, 281*, 1185-1187.

Cabeza, R., Rao, S. M., Wagner, A. D., Mayer, A. R., & Schacter, D. L. (2001). Can medial temporal lobe regions distinguish true from false? An event- related functional MRI study of veridical and illusory recognition memory. *Proc Natl Acad Sci U S A, 98*(8), 4805-4810.

Cahill, L. (1998). Interactions between Catecholamines and the Amygdala in Emotional Memory: Subclinical and Clinical Evidence. *Advances in Pharmacology, 42*, 964-967.

Cahill, L., Haier, R. J., Fallon, J., Alkire, M. T., Tang, C., Keator, D., Wu, J., & McGaugh, J. L. (1996). Amygdala activity at encoding correlated with long-term, free recall of emotional information. *Proc Natl Acad Sci U S A, 93*, 8016-8021.

Canli, T., Desmond, J. E., Zhao, Z., & Gabrieli, J. D. E. (2002). Sex differences in the neural basis of emotional memories. *Proc Natl Acad Sci U S A, 99*(16), 10789-10794.

Canli, T., Zhao, Z., Brewer, J., Gabrieli, J. D. E., & Cahill, L. (2000). Event-related activation in the human amygdala associated with later memory for individual emotional experience. *J Neurosci, 20*(RC99), 1-5.

Cuthbert, B. N., Schupp, H. T., Bradley, M. M., Birbaumer, N., & Lang, P. J. (2000). Brain potentials in affective picture processing: Covariation with autonomic arousal and affective report. *Biological Psychology, 52*, 95-111.

D'Esposito, M., Postle, B. R., & Rypma, B. (2000). Prefrontal cortical contributions to working memory:

Evidence from event-related fMRI studies. *Exp Brain Res, 133*(3–11).

Davidson, R. J. (1995). Cerebral asymmetry, emotion and affective style. In R. J. Davidson & K. Hugdahl (Eds.), *Brain Asymmetry* (pp. 361-387): MIT Press.

Davidson, R. J., & Irwin, W. (1999). The functional neuroanatomy of emotion and affective style. *Trends in Cognitive Sciences, 3*(1), 11-20.

Diedrich, O., Naumann, E., Maier, S., & Becker, G. (1997). A frontal positive slow wave in the ERP associated with emotional slides. *Journal of Psychophysiology, 11*(1), 71-84.

Dolan, R. J., Lane, R., Chua, P., & Fletcher, P. (2000). Dissociable temporal lobe activations during emotional episodic memory retrieval. *Neuroimage, 11*(3), 203-209.

Dolcos, F., & Cabeza, R. (2002). Event-related potentials of emotional memory: Encoding pleasant, unpleasant, and neutral Pictures. *Cogn, Affect, & Behav Neurosci, 2*(3), 252-263.

Dolcos, F., Graham, R., LaBar, K., & Cabeza, R. (2003). Coactivation of the amygdala and hippocampus predicts better recall for emotional than for neutral pictures. *Brain and Cognition, 51*, 221-223.

Dolcos, F., LaBar, K. S., & Cabeza, R. (2004a). Dissociable effects of arousal and valence on prefrontal activity indexing emotional evaluation and subsequent memory: An event-related fMRI study. *NeuroImage, 23*(1), 64-74.

Dolcos, F., LaBar, K. S., & Cabeza, R. (2004b). Interaction between the amygdala and the medial temporal lobe memory system predicts better memory for emotional events. *Neuron, 42*, 855-863.

Dolcos, F., LaBar, K. S., & Cabeza, R. (submitted). Remembering One Year Later: Role of the Amygdala and Medial Temporal Lobe Memory System in Retrieving Emotional Memories. *Manuscript submitted for publication.*

Eichenbaum, H. (2000). A cortical-hippocampal system for declarative memory. *Nat Rev Neurosci, 1*(1), 41-50.

Fossati, P., Hevenor, S. J., Lepage, M., Graham, S. J., Grady, C., Keightley, M. L., Craik, F. I., & Mayberg, H. S. (2004). Distributed self in episodic memory: Neural correlates of successful retrieval of self-encoded positive and negative personality traits. *Neuroimage, 22*, 1596-1604.

Ganis, G., Kutas, M., & Sereno, M. I. (1996). The search for 'common sense': An electrophysiological study of the comprehension of words and pictures in reading. *Journal of Cognitive Neuroscience, 8*(2), 89-106.

George, M. S., Ketter, T. A., Parekh, P. I., Horwitz, B., Herscovitch, P., & Post, R. M. (1995). Brain activity during transient sadness and happiness in healthy women. *Am J Psychiatry, 152*(3), 341-351.

Hamann, S. B., Ely, T. D., Grafton, S. T., & Kilts, C. D. (1999). Amygdala activity related to enhanced memory for pleasant and aversive stimuli. *Nat Neurosci, 2*(3), 289-293.

Hamann, S. B., Ely, T. D., Hoffman, J. M., & Kilts, C. D. (2002). Ecstasy and agony: Activation of the human amygdala in positive and negative emotion. *Psychol Sci, 13*(2), 135-141.

Heilman, K. M. (2000). Emotional experience: A neurological model. In D. R. Lane & L. Nadel (Eds.), *Cognitive Neuroscience of Emotion.* (pp. 328-344). New York: Oxford University Press, Inc.

Heller, W. (1993). Neuropsychological mechanisms of individual differences in emotion, personality, and arousal. *Neuropsychology, 7*(4), 476-489.

Heller, W., & Nitschke, J. B. (1998). The puzzle of regional brain activity in depression and anxiety: The importance of subtypes and comorbidity. *Cognition and Emotion, 12*(3), 421-447.

Kapur, S., Tulving, E., Cabeza, R., McIntosh, A. R., Houle, S., & Craik, F. I. (1996). The neural correlastes of intentional learning of verbal materials: A PET study in humans. *Conitive Brain Research, 4*, 243-249.

Kensinger, E. A., & Corkin, S. (2004). Two routes to emotional memory: Distinct neural processes for valence and arousal. *Proc Natl Acad Sci U S A, 101*(9), 3310-3315.

Kilpatrick, L., & Cahill, L. (2003). Amygdala modulation of parahippocampal and frontal regions during emotionally influenced memory storage. *NeuroImage, 20*(4), 2091-2099.

LaBar, K. S., Gitelman, D. R., Parrish, T. B., Kim, Y. H., Nobre, A. C., & Mesulam, M. M. (2001). Hunger selectively modulates corticolimbic activation to food stimuli in humans. *Behav Neurosci, 115*(2), 493-500.

LaBar, K. S., Rabinovici, G. D., Ranganath, C., Gitelman, D. R., Parish, T. B., Paller, K. A., & Mesulam, M.-M. (1999). *Spatiotemporal dynamics of a neural network for emotional picture encoding revealed by parallel evoked potential and fMRI measurements.* Paper presented at the Society for Neuroscience Annual Meeting.

Lane, R. D., Fink, G. R., Chau, P. M., & Dolan, R. J. (1997). Neural activation during selective attention to subjective emotional responses. *Neuroreport, 8*(18), 3969-3972.

Lane, R. D., Reiman, E. M., Ahern, G. L., Schwartz, G. E., & Davidson, R. J. (1997). Neuroanatomical correlates of happiness, sadness, and disgust. *Am J Psychiatry, 154*(7), 926-933.

Lane, R. D., Reiman, E. M., Bradley, M. M., Lang, P. J., Ahern, G. L., Davidson, R. J., & Schwartz, G. E. (1997). Neuroanatomical correlates of pleasant and unpleasant emotion. *Neuropsychologia, 35*(11), 1437-1444.

Lane, R. D., Reiman, E. M., Bradley, M. M., Lang, P. J., Ahern, G. L., Davidson, R. J., & Schwartz, G. E. (1997). Neuroanatomical correlates of pleasant and unpleasant emotion. *Neuropsychologia, 35*(11), 1437-1444.

Lang, P. J., Bradley, M. M., Fitzsimmons, J. R., Cuthbert, B. N., Scott, J. D., Moulder, B., & Nangia, V. (1998). Emotional arousal and activation of the visual cortex: An fMRI analysis. *Psychophysiology, 35*, 199-210.

Maratos, E. J., Dolan, R. J., Morris, J. S., Henson, R. N., & Rugg, M. D. (2001). Neural activity associated with episodic memory for emotional context. *Neuropsychologia, 39*(9), 910-920.

Matlin, M. W., & Stang, D. J. (1978). *The Pollyanna principle: Selectivity in language, memory, and thought.* Cambridge, MA: Shenkman.

McGaugh, J. L. (2000). Memory-a century of consolidation. *Science, 287*(5451), 248-251.

McGaugh, J. L. (2002). Memory consolidation and the amygdala: A systems perspective. *Trends Neurosci, 25*(9), 456-461.

McGaugh, J. L. (2004). The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annu. Rev. Neurosci., 27*, 1-28.

McGaugh, J. L., McIntyre, C. K., & Power, A. E. (2002). Amygdala modulation of memory consolidation: Interaction with other brain systems. *Neurobiology of Learning and Memory, 78*(3), 539-552.

Ochsner, K. N. (2000). Are affective events richly recollected or simply familiar? The experience and process of recognizing feelings past. *J Exp Psychol Gen, 129*(2), 242-261.

Owen, A. M., Herrod, N. J., Menon, D. K., Clark, J. C., Downey, S. P., Carpenter, T. A., Minhas, P. S., Turkheimer, F. E., Williams, E. J., Robbins, T. W., Sahakian, B. J., Petrides, M., & Pickard, J. D. (1999). Redefining the functional organization of working memory processes within human lateral prefrontal cortex. *Eur J Neurosci., 11*(2), 567-574.

Paller, K. A., & Wagner, A. D. (2002). Observing the transformation of experience into memory. *Trends Cogn Sci, 6*(2), 93-102.

Paradiso, S., Johnson, D. L., Andreasen, N. C., O'Leary, D. S., Arndt, S., Cizadlo, T., Ponto, L. L. B., Watkins, G. L., & Hichwa, R. D. (1997). Left amygdala and prefrontal activation during conscious evaluation of emotional valence of visual stimuli. *NeuroImage, 5*, S116.

Paradiso, S., Johnson, D. L., Andreasen, N. C., O'Leary, D. S., Watkins, G. L., Ponto, L. L., & Hichwa, R. D. (1999). Cerebral blood flow changes associated with attribution of emotional valence to pleasant, unpleasant, and neutral visual stimuli in a PET study of normal subjects. *Am J Psychiatry, 156*(10), 1618-1629.

Petrides, M. (1995). Functional organization of the human frontal cortex for mnemonic processing. Evidence from neuroimaging studies. *Ann N Y Acad Sci., 769*, 85-96.

Phelps, E. A. (2004). Human emotion and memory: Interactions of the amygdala and hippocampal complex. *Curr Opin Neurobiol, 14*, 198-202.

Poldrack, R. A., Wagner, A. D., Prull, M. W., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (1999). Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. *NeuroImage, 10*, 15-35.

Reiman, E. M. (1997). The application of positron emission tomography to the study of normal and pathologic emotions. *J Clin Psychiatry, 58*(16), 4-12.

Reiman, E. M., Lane, R. D., Ahern, G. L., Schwartz, G. E., Davidson, R. J., Friston, K. J., Yun, L. S., & Chen, K. (1997). Neuroanatomical correlates of externally and internally generated human emotion. *Am J Psychiatry, 154*(7), 918-925.

Richardson, M. P., Strange, B. A., & Dolan, R. J. (2004). Encoding of emotional memories depends on amygdala and hippocampus and their interaction. *Nat Neurosci, 7*(3), 278-285.

Shallice, T., Fletcher, P., Frith, C. D., Grasby, P., Frackowiak, R. S., & Dolan, R. J. (1994). Brain regions associated with aquisition and retrieval of verbal episodic memory. *Nature, 368*(633-35).

Smith, A. P. R., Henson, R. N. A., Dolan, R. J., & Rugg, M. D. (2004). fMRI correlates of episodic retrieval of emotional contexts. *Neuroimage, 22*, 868-878.

Squire, L. R., & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science, 253*(5026), 1380-1386.

Talarico, J. T., LaBar, K. S., & Rubin, D. C. (in press). Emotional intensity predicts autobiographical memory experience. *Memory & Cognition*.

Teasdale, J. D., Howard, R. J., Cox, S. G., Ha, Y., Brammer, M. J., Williams, S. C., & Checkley, S. A. (1999). Functional MRI study of the cognitive generation of affect. *Am J Psychiatry, 156*(2), 209-215.

Wagner, A. D., Schacter, D. L., Rotte, M., Koutstaal, W., Maril, A., Dale, A. M., Rosen, B. R., & Buckner, R. L. (1998). Building memories: Remembering and forgetting of verbal experiences as predicted by brain activity. *Science, 281*, 1188-1191.

Whalen, P. J. (1998). Fear, vigilance, and ambiguity: Initial neuroimaging studies of the amygdala. *Curr. Direct. Psychol. Sci., 7*(177:188).

Yonelinas, A. P. (2002). The nature of recollection and familiarity: A review of 30 years of research. *J. Mem. Language, 46*, 441-517.