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THE NEURAL SUBSTRATES OF LEXICAL EMOTIONAL PROCESSING: AN fMRI STUDY

by

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A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

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This manuscript has been read and accepted for the Graduate Faculty in Psychology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

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Abstract

THE NEURAL CORRELATES OF LEXICAL EMOTIONAL PROCESSING:

AN fMRI STUDY

by

Matthias H. Tabert

Adviser: Professor Joan Borod

The amygdala has been implicated in the perception, evaluation, memory, and early visual processing of threat-related stimuli. The current study focused on elucidating the role of the amygdala in the processing of highly unpleasant words. This study also examined other regions of interest (ROIs), including the ventromedial prefrontal, insular, and right posterior cortices, and the anterior and retrosplenial cinguli.

Unpleasant and neutral trials were presented to nine healthy adult women. During the first scan, subjects viewed sets of unpleasant or neutral words while selecting the most unpleasant or neutral word, respectively. During the second scan, subjects identified words that were presented during the first scan. Images were detrended, filtered, and co-registered to standard brain coordinates. The Talairach coordinates for the center of the amygdala were chosen before analysis. Activations in the remaining ROIs were identified on a post-hoc basis from whole brain analyses.

The right amygdala, medial frontal gyrus (BA 9), and the right middle temporal gyrus revealed a greater response to unpleasant than neutral words during Scan 1, confirmed by Word Condition x Time Course ANOVAs. Only the ROI activation site in the right middle temporal gyrus demonstrated a lateralized response, as confirmed by a

Word Condition x Time Course x Hemisphere interaction. Correlational analyses further revealed a positive relationship between activation in this ROI and the right amygdala. While subjects recognized more of the unpleasant than neutral words, their memory performance was not correlated with the observed ROI activations. Finally, the selective response observed in the amygdala to unpleasant words was correlated with occipital activation to the unpleasant and neutral words.

Results agree with the view that the amygdala mediates the appraisal of threat-related stimuli, and modulates early processing of salient visual information in the occipital cortex. Activation in the medial frontal gyrus (BA 9) supports the notion that this region is involved in the conscious monitoring of one's emotional state while making personally relevant decisions. Finally, the right lateralized response in the middle temporal gyrus is consistent with the view that the right posterior cortex plays an important role in the perception of emotional stimuli.

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Table of Contents

Page

Page

List of Tables

List of Figures

General Introduction

Although emotions to a large extent define human experience, understanding the neuropsychological basis of emotion has proven to be a difficult task. Since Darwin's early behavioral observations on the expression and experience of emotion in human and nonhuman mammalian species (Darwin, 1998), modern psychology has attempted to integrate emotion into a theory of mind and behavior. After a century of research, however, psychologists still disagree on such basic issues as how best to define emotion, the relationship between cognition and emotion, and the degree to which different aspects of emotional processing are mediated by conscious processes (for in-depth discussions of these issues see: Borod, 2000; Damasio, 1995; Ekman, & Davidson, 1994; Lane & Nadel, 2000; LeDoux, 1989, 1996; Panksepp, 1998, 1999; Rolls, 1999). Despite this lack of consensus, however, researchers from different perspectives (e.g., cognitive, physiological, biological, and neuropsychological; see Borod, 1993a; Ekman & Davidson, 1994; Plutchik, 1980, 1984; Scherer, 2000) have generally acknowledged the existence of an array of components fundamental to any conceptualization of emotion. These components include perception/appraisal, subjective experience, autonomic arousal, expression, and goal-directed activity (approach vs. withdrawal). Hence, the term emotion is multicomponentially defined here as changes in the functioning of the above mentioned component processes in reaction to externally (e.g., novel stimulus) or internally (e.g., thoughts or memories) mediated events that are of biological or personal significance to the organism (Borod, 1992, 1996; Scherer, 2000).

An important element in this broad conceptualization of emotion is that emotional phenomena include both evaluative and response-related processes, and that these two

types of processes may be subserved by distinct yet overlapping neural substrates (Damasio, 1994, 1995; Ellsworth, 1991; Ledoux, 1995; Maddock, 1999). Emotional evaluative processes include the automatic recognition of the emotional salience of a stimulus via sensory/perceptual mechanisms and the subsequent preconscious and/or conscious appraisal of the personal or motivational significance of a stimulus set (e.g., perceiving a facial expression of fear). Emotional response processes, on the other hand, include both response tendencies/dispositions (i.e., covert preparation to respond) and overt responses to the emotional or motivational significance of a stimulus. In other words, when an organism is confronted with a salient (e.g., threatening or pleasurable) stimulus it must, at a conscious and/or preconscious level, evaluate the personal relevance of the presenting situation (i.e., perception/appraisal), prepare for (i.e., response disposition), and, if necessary, execute appropriate overt responses that maximize the likelihood of personal survival and well-being. Responses include changes in the autonomic, endocrine, neuromodulatory, and motor systems that typically lead to emotional arousal; postural, gestural, facial, vocal, and/or verbal expressions; goal-directed activity (e.g., approach vs. withdrawal); and emotional experiences or subjective feeling states. While some researchers consider the conscious subjective experience of emotion as a mere byproduct of higher order cognitive processes such as working memory (e.g., LeDoux, 1996) and, hence, not critical for the study of emotion, others argue that feeling states are a core response process of emotion, mediated by specialized brain mechanisms, and are critical for everyday decision-making, ultimately serving to direct future actions of the organism (e.g., Damasio, 1994, 1995; Panksepp, 1998, 1999).

The distinction between evaluative, response, and experiential emotional processes has had important implications for emotion research. For the most part, studies of emotion can be divided into those that examine the perception/appraisal of emotional information (i.e., evaluative processes) via distinct channels of communication (e.g., facial expressions, vocal intonations or prosody, and lexical (i.e., verbal) meaning or content) and those that investigate emotional response or expressive mechanisms including feelings or emotional experience (Borod, 1993b; Maddock, 1999). Studies of evaluative processes typically assess the effect of making an implicit or explicit decision about emotional versus nonemotional stimuli on a given dependent variable such as reaction time or response accuracy (e.g., identifying the word class [implicit task] or judging the emotional category [explicit task] of words [emotional and/or nonemotional] presented tachistoscopically to either hemisphere). Studies of expressive or experiential processes typically assess overtly posed and/or spontaneous expressions of emotion (e.g., via intensity or accuracy) and changes in covert mood states (e.g., via self-report or physiological measures). The focus of the current study was on the evaluative end of this continuum.

It is also important to distinguish emotions as defined above (i.e., componentially) from other affective phenomena, such as instinct, drive, motivation, preferences, mood, personality/temperament, and attitude, among others (see Benson, 1994, for detailed definitions of these terms). These affect-related concepts have been arranged into a variety of conceptual hierarchies and along a number of continua by different theorists (for reviews of theoretical conceptualizations of affective phenomena, see Borod, 2000; Cornelius, 1996; Ekman & Davidson, 1994; Griffiths, 1997; Oatley & Jenkins, 1996;

Rosenberg, 1998; Scherer & Ekman, 1984). While it is beyond the scope of this thesis to discuss the differing theoretical frameworks of affective phenomena, in a recent review of psychological models of emotion, Scherer (2000) distinguishes emotions from other affective phenomena in terms of a number of generally agreed upon dimensions (i.e., the degree to which changes have a clear onset and offset; are rapid, intense, and enduring; are triggered by a focused event; involve appraisal; result in a coordinated response across component processes; and significantly impact behavior). In general, emotions as defined above and when compared to other affective states, such as drives, moods, or attitudes, involve changes that have a relatively rapid onset and offset, are relatively intense, last for a relatively brief duration, are triggered by the conscious and/or unconscious evaluation of a specific stimulus, affect all or most of the component processes outlined above in a synchronized manner, and have an observable impact on behavior, even if this is measurable only at the physiological level (e.g., anger, sadness, and happiness) (see Scherer, 2000, for a comparison of different affective states along these dimensions).

Elucidating the neural basis of the different component processes of emotion and their interactions with one another continues to be a primary focus of current neurobiological and neuropsychological research efforts (Gainotti, 2000). In the following section, as background to the current study, a brief overview of different theories and approaches that have guided research on the neural correlates of emotional processing over the past century is presented. Both classical and more recent neuroscientific approaches/theories about the neural basis of emotion are summarized. Much of this research comes from ablation, electrical stimulation, pharmacological, and

electrophysiological recording experiments using animal models. These theories provide a general theoretical and empirical framework by which the neural basis of emotion can be understood. Furthermore, the brain areas implicated by these models of emotion provided a general backdrop for selecting brain structures/areas as regions of interest (ROIs) for the current functional neuroimaging study.

Next, the neuropsychological literature as it pertains to understanding hemispheric asymmetries in emotional processing is briefly summarized and discussed. This vast body of literature has largely come from studies examining affective changes following brain pathology (e.g., focal brain lesions) and from behavioral lateralization studies examining the performance of healthy adults on emotional and nonemotional tasks that use special presentation techniques (e.g., tachistoscopic, dichotic, and free-field viewing paradigms). The overall findings from these studies have led to a number of competing hypotheses concerning the hemispheric specialization of emotion (e.g., the right hemisphere and valence hypotheses). Findings from these studies and from recent neuroimaging data, which are also discussed in a subsequent section, form the basis for generating lateralization hypotheses relevant to the current study. Given the focus of the current study on the lexical perception/evaluation of emotion, a special emphasis is placed on studies of emotional perception/evaluation rather than expression.

Next, a brief overview of results from studies that use functional neuroimaging techniques (i.e., PET and fMRI) to further define the neuroanatomical systems underlying emotion is presented. The emphasis of this next section is on the extent to which recent neuroimaging findings corroborate the findings from lesion and behavioral neuropsychological data with regard to the processing of emotional information. This

section provides the backdrop for a more in-depth discussion of several neuroanatomical structures and areas (posterior parietal cortex) that have been implicated in the lesion and imaging literature as key players in the circuitry underlying emotional processing. These areas served as ROIs for the current study.

Neurobiological Theories of Emotion

Classical Theories

The James-Lange versus Canon-Bard Debate

At the turn of the century, the prevailing theory of emotion was the James-Lange peripheral feedback theory (1884, cited in Ledoux, 1996) that held that emotional experience is determined by feedback to the brain from bodily responses (i.e., autonomic and skeletal). According to James and Lange, the sequence of events leading to an emotional experience involves, first, the perception of a salient stimulus, which then leads directly to distinct bodily changes (i.e., physiological or visceral and skeletal musculature). It is only after these bodily changes have been registered by the sensory and motor areas of the neocortex that the organism becomes aware of the unfolding emotional experience. James and Lange emphasized that different emotions feel different from one another because they are accompanied by different bodily symptoms (for extensive reviews of this theory, see Cannon, 1927; Cornelius, 1996; Damasio, 1994; Ellsworth, 1994; James, 1994 (reprint); Lang, 1994; Ledoux, 1996; Panksepp, 1998).

In reaction to the peripheral theory of James and Lange, Canon (1929) and Bard (1929), proposed a centrally mediated or neural theory of emotion (AKA the Cannon-Bard theory). This theory, based on a systematic series of cortical and subcortical lesion studies in animals, held that emotional responses and experiences are the result of

processes completely contained within the brain and centered on the hypothalamus. When an organism is faced with a salient event, the nervous impulses travel directly to the thalamus where the message divides -- one part going to the somatosensory cortex where subjective emotional experiences like fear, rage, sadness, and happiness originate, while the other part goes directly to the hypothalamus which instigates physiological and muscular changes. While James and Lange believed that emotional experience originates from distinct bodily responses, Canon and Bard emphasized that bodily reactions and emotional experience occur simultaneously and are instigated by mechanisms contained within the brain (for a more extensive discussion of the James/Lange vs. Canon/Bard debate, see Cannon, 1927; Cornelius, 1996; Damasio, 1994; Lang, 1994; Ledoux, 1996; Panksepp, 1998).

Papez's Circuit

The next milestone in elucidating the neural substrates of emotion was reached when Papez (1937), expanding on the neurobiological theory of Cannon and Bard, proposed that emotional experience is not a function of any specific brain center but rather of several interconnected brain structures. According to Papez, sensory inputs are projected along two pathways. First, inputs can be routed through a neocortical or high-level pathway that projects from the thalamus to neocortical areas of the brain (lateral cortex), resulting in perceptions, thoughts, and memories (i.e., Stream of Thought). At the same time, sensory inputs can be relayed through a subcortical (low-level) pathway from the thalamus to the hypothalamus (mammillary bodies), back to the anterior thalamus, and then to the cingulate cortex (medial or older cortex formerly known as the limbic lobe and rhinencephalon). The cingulate, in turn, projects its outputs to the

hippocampus (a medial cortical structure), which in turn projects information back to the hypothalamus, thus completing the circuit. According to Papez, this subcortical pathway (AKA Papez's Circuit) is primarily responsible for the perception, experience, and expression of emotion. However, according to Papez, the neocortical pathway can also mediate emotional experience. This occurs when memories stored in the neocortex that are related to a stimulus event activate the low-level processing circuit via the cingulate cortex (for more extensive reviews of Papez's circuit, see Cornelius, 1996; Damasio, 1994; LeDoux, 1996; Mark, Daniels, Nadich, & Hendrix, 1995; Panksepp, 1998).

Kluver and Bucy's Observations

At the same time that Papez made public his neural theory of emotion, Kluver and Bucy (1937) reported on a collection of symptoms (Kluver-Bucy Syndrome) in animals that had their temporal lobes removed. Despite perfect visual acuity, these animals seemed blind to the psychological or emotional significance of stimuli (i.e., "psychic blindness"). They became tame, placid, visually agnosic, overly reactive to visual stimuli, hyperoral (involving the mouthing of inappropriate objects), and hypersexual (i.e., involving inappropriate partners and object choice). These observations pointed to the fact that temporal lobe structures play a critical role in the processing of emotional information. Subsequent animal and human research (see below for detailed discussion) has demonstrated that the amygdala, an anterior temporal lobe structure, is central to emotional processing (for more extensive discussion of Kluver and Bucy's observations, see Cornelius, 1996; Damasio, 1994; LeDoux, 1996; Panksepp, 1998).

MacLean's Triune Brain--The Limbic System

In 1949, based primarily on the neuroanatomical work of Canon, Bard, and Papez, and on the observations of Kluver and Bucy, Paul MacLean proposed an expanded emotional network, which he called the limbic system. MacLean emphasized the importance of brain areas that participate in emotional processing that went beyond Papez's circuit, such as the parahippocampal gyrus, amygdala, medial thalamic nucleus, septum, prosencephalic basal nuclei (most anterior area of the brain), and prefrontal (orbitofrontal and medialfrontal) cortex. MacLean also sought to clarify the role of emotional experience and expression in terms of a broader evolutionary context. In so doing, he proposed his theory of the "triune brain" (Maclean, 1990), which accounts for behaviors and mental functions at different levels of complexity (LeDoux, 1996). According to MacLean, the brain has gone through three stages of evolutionary development, ultimately resulting in three components that are distinct in anatomical structure, neurochemistry, and function. The oldest component, known as the archipallidum (AKA the primitive or reptilian brain), consists primarily of brain stem structures (i.e., medulla, pons, cerebellum, mesencephalon, globus pallidus, and olfactory bulbs); the next evolutionary component, known as the paleopallidum (AKA the intermediate or old mammalian brain), makes up the limbic system (see above); and the most recent one, known as the neopallidum (AKA superior, rational, or new mammalian brain), comprises the neocortex and some subcortical neuronal groups (e.g., striatum).

According to MacLean, all three of these components have been conserved over the course of animal evolution. This is seen in the fact that evolutionarily advanced mammals (e.g., primates) maintain all three components, while lower mammals lack the

neopallium, and all other vertebrates have only the archipallium. Moreover, although interconnected, MacLean argues that each component gives rise to its own brand of intelligence, memory, sense of time and space, and behavior. The primitive component ensures self preservation (e.g., aggression, instinctive reactions or reflex arcs, and visceral functions); the intermediate one mediates affective functions, such as the abilities to distinguish between and remember pleasant and unpleasant stimuli and to experience basic emotions (e.g., anger, fear, happiness); and the superior one has made possible higher cognitive functions as seen in the use of symbolic language and abstract thought (for more extensive discussion of MacLean's Triune Brain, see Cornelius, 1996; Damasio, 1994; LeDoux, 1996; Panksepp, 1998).

Recent Theories

Panksepp's Affective Neuroscience

Panksepp has extended MacLean's notion of the limbic system. Based on a wide array of behavioral and neurophysiological studies conducted over the past quarter of a century (see Panksepp, 1998, for a comprehensive review), Pansksepp has proposed a neuroscientific approach to understanding affect which he refers to as "Affective Neuroscience". Central to Panksepp's view is that MacLean's "intermediate" or "old mammalian" brain houses a variety of subcortical "affect generating emotional command systems." These command systems instigate and orchestrate the many diverse aspects of emotionality within the brain (Panksepp, 1999). According to Panksepp, there is solid evidence from neuroanatomical, neurophysiological, and neurochemical research for at least seven genetically ingrained emotional operating systems within the mammalian brain (Panksepp, 1998,1999; Panksepp & Miller, 1999). These distinct emotional

operating systems include what he calls the SEEKING (e.g., anticipation), the RAGE (e.g., anger and frustration), the FEAR (e.g., flight), the PANIC (e.g., separation distress), the LUST (e.g., sexual desire), the CARE (e.g., maternal nuturance and social attachment), and the PLAY (e.g., social engagement) systems. Each command system corresponds to distinct affective states, feelings, and action tendencies, and coordinates distinct emotional behavioral patterns. It should be noted that Panksepp uses uppercase letters when referring to these emotional systems to alert the reader that these everyday terms are used to denote specific neural systems that mediate specific archetypal behavioral patterns.

In addition, Panksepp postulates the existence of a "neurosymbolic" representation of the SELF (i.e., a virtual body) that is located within centromedial areas of the brainstem (i.e., McLean's Reptilian Brain), including the periaqueductal gray (PAG) and surrounding collicular and tegmental zones. In the mammalian brain, these brain circuits are interconnected with areas such as the prefrontal and sensory cortices via direct and indirect pathways. According to Panksepp, affective experiences (i.e., feelings) arise from interactions of the above-mentioned basic emotional operating systems and the neural substrates of the SELF, the outputs of which broadcast widely throughout the brain via general neurotransmitter systems (e.g., cholinergic and neuroadrenergic systems). Panksepp argues that through these projections to virtually all higher-order association areas, these integrated outputs ultimately are experienced as emotional feelings that provide a fundamental guiding influence on all cognitive functions (e.g., planning or selection of future actions). Emotional feelings in turn can be

extended, inhibited, and/or modified via sensory and associative/memory processes that are mediated by higher-order neocortical brain regions.

LeDoux's Dual Pathway Model

Although the amygdala has been implicated in emotional processing for sometime (i.e., since the observations of Kluver and Bucy and MacLean's inclusion of it in the limbic system), the central role played by this subcortical brain structure in emotional functions has only recently come to light (Amaral, Price, Pitkanen, & Carmichael, 1992; Davis, 1992a,b; Gray, 1987, 1994; Knapp, Whalen, Supple, & Pascoe, 1992; LeDoux, 1996; Panksepp, 1998; Rolls, 1999). In recent years (since the early 1980's), the work of Joseph LeDoux and that of other neuroscientists (Davis, 1992a,b; Rolls, 1999) has implicated the amygdala as a key subcortical player in the neural circuitry of emotion, particularly fear. By systematically placing lesions along brain pathways that transmit information from specific peripheral sensory systems to higher central processing areas of the brain, LeDoux and colleagues (for reviews of LeDoux's approach and findings, see Ledoux, 1986, 1990, 1991, 1992, 1995, 1996) have identified the existence of a subcortical thalamo-amygdala projection that, in the absence of the cortex, appears to mediate fear conditioning (e.g., freezing response to a tone after being paired with foot shock). These studies by LeDoux corroborated the much earlier findings by Cannon, Bard, and others, which demonstrated that both unconditioned and conditioned emotional reactions (e.g., sham rage) evoked by sensory stimuli survive massive decortication (Cannon, 1927, 1929). An important implication of LeDoux's findings with respect to the thalmo-amygdala pathway is that emotional processing, at least at a rudimentary level, can be directly mediated by subcortical circuitry. Efferent pathways from the

thalamus project to the lateral nucleus of the amygdala, which in turn project to the basolateral nucleus of the amygdala. The basolateral nucleus projects to the central nucleus, which in turn projects directly to a number of subcortical structures (e.g., lateral hypothalamus, bed nucleus of the stria terminalis, and PAG) that modulate various autonomic (e.g., arterial pressure response), neuroendocrine (e.g., release of stress hormones), and behavioral responses (e.g., freezing) related to fear conditioning.

The work of LeDoux and others have also revealed an important role for the cortex in fear conditioning. Romanski and LeDoux (1992, 1993) found that if the subcortical projections from the auditory thalamus to the amygdala are severed, projections from the thalamus to the amygdala via the temporal and perirhinal cortex are sufficient to establish a conditioned fear response. Hence in addition to a direct subcortical thalamo-amygdala pathway, the existence of a second more indirect thalamo-cortico-amygdala pathway that can also mediate fear conditioning has been identified. Together with the thalamo-amygdala route, these findings suggest that both the direct subcortical (i.e., thalamo-amygdala) and indirect cortical (i.e., thalamo-cortico-amygdala) pathways are sufficient, but not necessary, for the establishment of fear conditioning.

To clarify the different functions of these two processing pathways, LeDoux and colleagues (Bordi and LeDoux, 1994) conducted a series of single cell electrophysiological recording studies in which they recorded electrical activity from thalamic neurons that project to either the primary auditory cortex or to the amygdala. Results revealed that neurons in the auditory thalamus that project to the primary auditory cortex are "narrowly tuned" while those projecting directly to the lateral nucleus of the amygdala are "broadly tuned." In other words, a given thalamo-cortical neuron responds

only to a very narrow or specific range of acoustic frequencies while thalamo-amygdala neurons respond to a much wider range of frequencies. Hence, when an animal must discriminate between two similar acoustic frequencies in a conditioning experiment (i.e., where only one tone has been associated with the unconditioned stimulus [US]), the acoustic inputs of the two tones arriving via the thalamo-amygdala projection will appear identical to the amygdala. However, the same acoustic inputs sent via the thalamo-cortical-amygdala projection will be processed as two distinct sounds. If the cortex is damaged and only the direct thalamo-amygdala pathway is available, the amygdala will assign emotional significance to both stimuli each of which will elicit a conditioned fear response. These findings have led to the notion that the thalamo-cortico-amygdala projection transmits sharply tuned or highly specific, detailed, and accurate representations of the external world to the amygdala, whereas the thalmo-amygdala pathway is weakly tuned and thus provides the organism with a much cruder perception of peripheral stimuli.

Given this "tuning" discrepancy, one may wonder what role, in emotional processing, the thalamo-amygdala pathway could serve. LeDoux (1996) argues that this route offers several advantages over the cortical pathway. First and foremost, it offers the advantage of rapid transmission. While it takes about twelve milliseconds for an acoustic stimulus to reach the amygdala via the monosynaptic thalamo-amygdala path in a rat, it takes approximately twice as long via the thalamo-cortico-amygdala pathway, which involves at least three synapses (i.e., from auditory thalamus to primary sensory cortex, to adjacent association cortex, and finally to amygdaloid nuclei). Hence, although the subcortical pathway is incapable of accurately differentiating complex stimuli, it can

provide a fast signal to the organism that warns of possible impending danger. Although such a "quick and dirty" processing system may result in more false positive responses, such responses are less costly than are the consequences of postponing defensive action in the face of a real threat until the cortical system has had time to analyze the stimulus situation in more detail. Moreover, the rapid arrival of crude sensory/perceptual information from the thalamus prepares or primes the amygdala for the reception of more detailed information via the cortical projection and thus facilitates subsequent emotional processing. The lateral amygdala is also reciprocally connected to association cortex and, therefore, LeDoux suggests that the crude inputs from the thalamo-amygdala projection may act to modulate perceptual processing of inputs via sensory and association cortex by facilitating or inhibiting the processing of this information. The amygdala also projects to the entorhinal cortex, which is a major gateway to the hippocampus (Phillips and LeDoux, 1992). Thus, similar to its influence on perceptual processing in the cortex, LeDoux argues (1996) that the thalamo-amygdala pathway may also enhance or inhibit cognitive processing in the hippocampus. Through such a mechanism, the low level or unconscious subcortical processing of emotional information could modulate the formation (i.e., acquisition, consolidation, and recall) of conscious emotional memories (see discussion to follow on McGaugh's memory modulatory hypothesis). In sum, although these two emotional processing pathways can be dissociated, and thus are somewhat independent, LeDoux emphasizes that these pathways normally operate in parallel and are fully interactive via the direct and indirect reciprocal connections between the amygdala, hippocampus, and other cortical regions. The fast initial response of the subcortical route can bias the slower representational processing of the cortical

path, and conversely, the more elaborate processing of the cortical route can modulate the fast response of the subcortical path.

As recently pointed out by Buck (2000), LeDoux's elucidation of two emotional processing pathways has provided a resolution to the classic Zajonc-Lazarus debate concerning whether "emotion" precedes or follows "cognition." This debate began with findings by Zajonc (1980, 1984), suggesting that subjects respond preferentially (i.e., rate more positively) to stimuli (e.g., nonsense syllables and ideograms) that are previously presented for such brief time intervals that subjects are not able to consciously perceive them. Zajonc interpreted these findings to mean that emotional processing occurs prior to, and independent of, cognition. Lazarus (1984), on the other hand, argued that an essential component of emotion involves cognitive appraisal. LeDoux's discovery of a low-level, subcortical processing path that mediates fast, crude, and unconscious processing of emotional information corroborates Zajonc's discovery that the emotional salience of a stimulus is processed before we can become fully cognizant of the stimulus involved. On the other hand, LeDoux's articulation of a high-level, cortical processing route that mediates a slower, more elaborate, conscious processing agrees with Lazarus' notion of the need for conscious cognitive appraisal in emotion.

McGaugh's Memory Modulatory Theoretical Framework of Amygdala Function

While LeDoux's work has examined the role of the amygdala in emotional learning, McGaugh and colleagues have over the past few decades focused on the amygdala's role in modulating long-term consolidation of emotional memories (for recent reviews of this work, see Cahill, 1999; Cahill et al., 1996; Cahill & McGaugh, 1998; McGaugh, 2000; McGaugh, Cahill, & Roozendaal, 1996). Muller and Pilzecker

(1900, cited in McGaugh, 2000) first proposed the concept of memory consolidation. They noted that newly learned information could be easily disrupted if subjects were required to learn other information shortly after the original learning took place. Subsequent animal research has confirmed this observation, demonstrating that recently formed memories are highly susceptible to post-learning influences (e.g., drug injections and brain stimulation) for a limited time after they are formed (see McGaugh, 1966, for a review). These observations have lead to the notion that the processes underlying new memories (i.e., corresponding to short-term memory) initially persist in a fragile, tentative state. However, given enough time after initial learning, information can be consolidated and stored as long-term memories. McGaugh's work is largely based on the notion that this slow consolidation mechanism serves as an adaptive function, enabling endogenous processes, triggered by an experience perceived to be salient by the organism, to modulate memory strength or, in other words, to "weight" information storage in general proportion to the importance of the information being stored. On the basis of extensive animal and human studies that support this notion, McGaugh and colleagues have proposed the memory modulatory theoretical framework of amygdala function. This hypothesis postulates that hormones released during emotional arousal represents a (if not the) key influence by which memory storage is modulated, and that this "weighting" of memory storage is mediated by the amygdala for a limited time after acquisition or initial learning (i.e., in a time-limited manner) via neurotransmitter (e.g., largely noradrenergic and GABAergic; see Liang, Bennet, & McGaugh, 1986, and Brioni & McGaugh, 1988) and anatomical (e.g., via the stria terminalis; see Liang & McGaugh,

1983) links with other brain areas where the actual consolidation and/or storage of long-term memories occurs (McGaugh et al., 1996).

Considerable evidence has accrued to support this theoretical framework. First, a large body of behavioral research has demonstrated that emotionally arousing experiences are generally better remembered than nonemotional events (Christianson, 1992; Gabrielle, 1998). Drug studies in animals have demonstrated that endogenous stress hormones, such as epinephrine, norepinephrine, ACTH, and corticosterone, are released under the control of the hypothalamic-pituitary axis during emotionally arousing situations (Galvez, Mesches, & McGaugh, 1996; Levi, 1975). Once released, epinephrine activates [beta]-adrenergic receptors located peripherally on vagal afferents projecting to the nucleus of the solitary tract in the brainstem (McGaugh et al., 1996; Packard, Williams, Cahill, & McGaugh, 1995). Noradrenergic projections from the nucleus of the solitary tract then project to the other brain regions including the amygdala. On the other hand, glucocorticoids (e.g., corticosterone) released from the adrenal cortex readily enter the brain and activate intracellualar glucocorticoid receptors. A direct infusion of these substances (and their receptor agonists) into the amygdala, as well as systemic administration, within a limited time period after training, enhances memory for training related experiences (Liang, et al., 1985; Liang & McGaugh, 1983; Roozendaal & McGaugh, 1997). On the other hand, lesions of the amygdala or infusions of [beta]-adrenergic antagonists block the memory-enhancing effects of adrenergic or glucocorticoid agonists (Packard et al., 1995). Bianchin, Mello, Souza, Medina, & Izquierdo (1999) demonstrated the time-limited nature of these modulatory influences in a recent study. Here the administration of several drugs into the rat amygdala at the time

of training in a one-trial, step-down, inhibitory avoidance paradigm had no effect on either working memory (tested at 3 seconds post-training) or short-term memory (tested at 1.5 hours post-training). However, all these drugs had strong modulatory effects on long-term memory (tested at 24 hours post-training), some enhancing (i.e., norepinephrine and picrotoxin) and others (i.e., CNQX, AP5, scopolamine, Kn-62, and staurosporin) impairing performance. Together these findings provide strong evidence that the amygdala plays an important role, via the adrenergic system, in allowing an emotionally arousing experience to regulate the strength by which memories surrounding the event are consolidated and stored in long- but not short-term memory.

The hippocampus but not the amygdala has long been implicated as the key structure mediating long-term memory consolidation via extensive connections with other subcortical and cortical brain regions (Cahill, 1999; McGaugh, 2000). By what means then does the amygdala exert its modulatory influence on memory consolidation? Recent animal studies have examined this question and demonstrated that the amygdala modulates memory consolidation via its connections with the hippocampus and other brain regions (e.g., striatum). For example, in recent studies, Packard and colleagues (Packard, Cahill, & McGaugh, 1994; Packard & McGaugh, 1998) injected amphetamine into the hippocampus, caudate nucleus, or amygdala after training in either a "spatial" or "cued" water maze task. Previous lesion and injection studies had demonstrated that performance on these tasks was mediated by separate memory systems: the spatial task via the hippocampus (i.e., hippocampal-related memory process), and the cued task via the caudate nucleus (i.e., striatal-related memory process). As expected, results from these studies demonstrated that injections of amphetamine into the hippocampus resulted

in enhanced long-term retention (i.e., 24 hours later) of the spatial but not cued task, whereas caudate injections resulted in the opposite pattern. On the other hand, amygdala injections resulted in enhanced retention for both tasks. In the same study, inactivation of amygdala immediately before the retention test (via infusions of lidocaine) did not affect the memory enhancement produced by the post-training amphetamine injections. These findings suggest that while the amygdala is able to influence memory processes mediated by other brain regions (i.e., the hippocampus and caudate nucleus), it is not the locus where the memories are actually stored, nor is it involved in retrieval processes. In this vein, recent studies by Ikegaya and colleagues (Ikegaya, Saito, & Kazuho, 1995; Ikegaya, Saito, & Kazygi, 1994) have demonstrated that normal hippocampal long-term potentiation depends on influences from the amygdala. These investigators have reported that both reversible and permanent lesions of the basolateral nucleus of the amygdala attenuate the induction of long-term potentiation in the dentate gyrus *in vivo*. The Ikegaya et al. study demonstrates that cellular and molecular mechanisms of long-term potentiation, which are thought to underlie memory consolidation, are modulated by the basolateral nucleus of the amygdala.

Human studies also support McGaugh's memory modulatory hypothesis. For example, Soetens, Casaer, D'Hooge, Hueting et al. (1995) found that amphetamine administered to humans either immediately before or after learning of word lists significantly enhanced long-term free recall and recognition memory for the words when compared to placebo. A study by Cahill, Prins, Weber, & McGaugh (1994) administered [beta]-adrenergic receptor antagonists or placebo immediately before presenting a series of pictures accompanied by an emotionally arousing story. As expected, subjects in the

placebo condition remembered best the pictures presented during the most emotional part of the story. In contrast, subjects in the experimental condition show no memory enhancement for the emotional components of the story. Further evidence demonstrating that the effect of emotional arousal on conscious memory depends on the amygdala comes from human lesion studies. Several studies have reported that, in contrast to control subjects, patients with bilateral amygdala lesions do not demonstrate enhanced memory for emotionally arousing information (Adolphs, Cahill, Schul, Babinsky, 1997; Babinsky et al., 1993; Cahill, Babinsky, Markowitsch, & McGaugh, 1995; Markowitsch et al., 1994). On the other hand, amnesic subjects with intact amygdala show intact enhancement of memory for emotional material despite their overall impaired memory performance (Hamann, Cahill, & Squire, 1997).

Consistent with the memory modulatory model, recent brain imaging studies have also implicated the amygdala in modulating long-term memory. In a recent study, Mori, Ikeda, & Hirono (1999) correlated amygdala and hippocampal MRI volumes of Alzheimer's patients with their ability to remember a highly emotional event (i.e., a severe earthquake). Results revealed a highly significant correlation between amygdala, but not hippocampal, volumes and the emotionally salient personal events experienced during the earthquake. In contrast, general knowledge of the earthquake was not correlated with either hippocampal or amygdala volumes. Results from this study are consistent with the findings from a recent PET-O15 study by Hamann, Ely, Grafton, and Kilts (1999) using normal subjects which demonstrated that bilateral amygdala activity during memory encoding was correlated with enhanced long-term (4 weeks later) but not short-term (10 minutes following scan) recall for highly emotional pictures (e.g.,

mutilated and diseased bodies, frightening animals, or lethal violence) as compared to neutral control stimuli (e.g., pictures of chess players, plants, and animals or household scenes). Interestingly, enhanced recall for "interesting" pictures (i.e., ones that were highly memorable but not emotionally arousing, such as a chrome rhinoceros, surrealistic film, or an exotic parade) as compared to neutral control pictures was not correlated with amygdala activity during encoding. In contrast, hippocampal activity during encoding was correlated with enhanced recall for the interesting nonemotional and emotional stimuli. Cahill et al. (1996) also found a positive correlation between amygdala activity during the encoding of a story and enhanced recall performance for the emotional as compared to the nonemotional components of the story after three weeks. In a similar vein, another study found (Alkire, Haier, & Fallon, 1998) that while amygdala activity failed to correlate with long-term memory for a series of nonemotional words, hippocampal activity correlated very highly with memory in the same condition.

In summary, extensive animal and human studies using a number of different research modalities (e.g., lesion, drug, and brain imaging) have all converged to provide strong support for the theoretical framework proposed by McGaugh and colleagues. These studies have demonstrated that emotional arousal during encoding of information influences the strength with which this information will be consolidated and stored into long-term memory. Moreover, while the amygdala is not the locus where emotional memories are consolidated, stored, and/or retrieved, it acts as the remote "weigh station" that, via neurochemical (i.e., primarily adrenergic and GABAergic) and neuroanatomical (e.g., via the stria terminalis) links with other brain areas, especially the hippocampus,

determines the degree to which information, based on its biological and/or personal significance for the organism, will be remembered in the future.

Rolls' Reinforcement Theory of Emotion

Rolls' neurobiological reinforcement theory of emotion is based on extensive lesion, pharmacological, and electrophysiological recording studies with nonhuman primates (for comprehensive reviews of Rolls work and theory, see Rolls 1990, 1999, 2000). While he defines emotions in terms of behavioral states experienced by organisms in response to changing reinforcement contingencies, Rolls emphasizes the notion of cognitive appraisal since this perceptual/evaluative component of emotional processing allows the organism to assess whether an object or event in the environment is rewarding or punishing and hence should be worked for or avoided.

According to Rolls, there are two primary sets of brain mechanisms that mediate the encoding of emotional stimuli. The first set is involved in computing the reward of primary or unlearned reinforcers, such as taste, touch (pleasant versus pain), smell, or highly provocative auditory signals (e.g., vocalizations of distress), and visual signals that include facial expressions of emotion (e.g., fear or anger). When triggered, these mechanisms lead to instinctive, hardwired reactions that ensure the survival of the organism. The second set of brain mechanisms is concerned with learning associations between the above mentioned primary or unlearned reinforcers and neutral stimuli. It is through these associative mechanisms that the organism imbues emotional value or significance to everyday objects and events (higher-order reinforcers).

Rolls also proposes implicit and explicit processing routes by which behavioral responses to emotional stimuli are generated. However, unlike LeDoux (1996), Rolls

contends that both of these pathways necessarily involve cortical processing. Rolls argues that emotional stimuli are generally quite complex and, therefore, are automatically processed to the object-identification level via perceptual mechanisms involving primary and association cortices before emotional significance can be appraised. For example, before a visual object can elicit an emotional reaction it must be recognizable independent of its position in space, distance from the organism, apparent physical size, or angle at which it is viewed (i.e., as an invariant object with respect to physical transformations [Rolls, 1999]). Reaching this level of object recognition is important since it would be unadaptive for the organism if it did not have the same emotional response to a threatening object during a future encounter simply because it approached the object at a different angle or because the object appeared in a slightly different position. Once processed by the cortex, the perceptual information (i.e., invariant feature recognition) is passed to the amygdala and orbitofrontal cortex where the emotional significance of the object is added, after which a signal is passed from the amygdala and orbitofrontal cortex directly to one or more output regions that regulate autonomic, endocrine, and behavioral responses.

The implicit processing route largely corresponds to what has been described so far. Sensory inputs from one or more sensory modalities (e.g., visual) project to primary, secondary, and association cortices for perceptual/cognitive processing involved in object identification. The outputs of this object identification process are forwarded to the amygdala and orbital frontal cortex where the emotional significance of the object at hand is assessed and applied. Outputs from this evaluative stage are directed to the premotor cortex via the ventral striatum and thalamus where emotional responses are

generated. Rolls emphasizes that the outputs from this implicit system bypass the language system. Hence, verbal explanations given by subjects for actions stemming from this system generally involve confabulations, providing subjects with a consistent sense of self and spatial and temporal continuity.

There are several important functions of the implicit system. First, it allows the organism to rapidly assess the reward value (i.e., emotional/biological significance) of a stimulus in terms of such variables as personal reinforcement history, current motivational state, and the absolute value of the stimulus for the organism. It also allows the organism to generate an appropriate action tendency (i.e., approach towards versus withdrawal from the stimulus). Finally, this system mediates the execution of rapid automatic responses that ultimately allow for the most positive personal outcome (i.e., greatest immediate gain or gratification). Typically, this system is triggered during situations where the time constraints are such that the organism does not have the luxury of consciously evaluating all of the impending factors and possible courses of action that would need to be considered to allow for an optimal response.

In contrast, emotional processing via the explicit processing route occurs at a slower, more deliberate and conscious level. According to Rolls, conscious awareness of emotional processing occurs when the outputs of the amygdala and orbital frontal cortex are routed through the language centers and prefrontal areas of the brain. Ultimately, this allows for strategic planning that is based on past experiences before a behavioral response is executed.

There are several important functions of the explicit system. First, it allows for declarative processing associated with reasoning or making subtle judgements that allow

the organism to select from multiple courses of action. The final decision depends on the actual computation and outputs of the amygdala and/or orbital frontal cortex as to how rewarding a particular stimulus situation is or will be. These inputs are registered as emotional feelings that ultimately assist in the narrowing of possible response options. Second, this system allows the organism to delay gratification and to engage in long-term, multistep planning or strategizing as to the best way to accomplish its goals. Typically, this system is triggered when situations arise that cannot be resolved on an implicit basis. When dealing with complex situations that can only be resolved over extended periods of time, implicit emotional processes are more likely to lead to errors and inappropriate action and thus demand a consciously controlled evaluation. Like Ledoux (see above), Rolls emphasizes that these two systems are fully interactive, such that the explicit system can inhibit or facilitate the final behaviors produced by the implicit system and, conversely, the implicit system serves as a "biological highlighter," influencing the explicit system by enhancing certain stimuli in the environment that are more likely to lead to reward and thus ultimately direct attention towards them.

Damasio's Somatic Marker Hypothesis

Unlike the above neurobiological theories of emotion that are largely based on animal models (see above), Damasio's somatic marker hypothesis, largely an extension of the James-Lange theory, is based on neurological patients with focal brain damage (for comprehensive reviews of Damasio's work and theory, see Adolphs & Damasio, 2000; Damasio 1994, 1995; Damasio, Tranel, & Damasio, 1991; Damasio, Tranel, & Damasio, 1998). According to Damasio, James' primary premise that emotional feelings originate in the body rather than brain is basically correct. However, while James' theory

accurately describes the basis of "primary emotions" (i.e., emotions that rely on an innate and inflexible triggering mechanism which are mediated by limbic structures and that result in a preorganized and automatic response to specific features such as size, smell, motion, sounds, and sensations), Damasio argues that it fails to take into account the process by which organisms mentally evaluate the situation and context in which emotions are experienced (i.e., cognitive appraisal). According to Damasio, this evaluative component is critical for what he calls "secondary emotions" that involve forming systematic associations between categories of objects and situations, on the one hand, and emotional experiences on the other. This evaluative process allows for more variation in the extent and intensity of emotional responses and involves a broadened network of brain structures and mechanisms, which in addition to the classic limbic areas such as the amygdala and anterior cingulate, also involves the ventromedial prefrontal cortex and somatosensory cortex, particularly of the right hemisphere.

Damasio has outlined in detail the sequence of neural events leading up to the experience of a learned or secondary emotion. As an overview, the presence of a salient stimulus leads to a cognitive evaluation or appraisal of the triggering situation. Such appraisals are mediated by widely distributed, topographically organized, neural representations that are largely held in primary sensory cortices and limbic structures and are modulated or influenced by higher-order association cortices (i.e., ongoing thoughts and memories related to the stimulus situation). A record of this ongoing neural activity, occurring simultaneously in limbic, sensory cortical, and association cortical regions, is held in the ventromedial prefrontal cortex, which acts as a convergence zone. This internal record of the temporal conjunctions of neural activity occurring in various brain

areas defines the meaning of the current situation for the organism and forms the basis by which the organism can learn to associate certain situations with past and present emotional experiences.

Outputs from the ventromedial prefrontal convergence zone are directed to effector systems such as the amygdala and basal ganglia, which in turn activate body- and brain-state changes that are pertinent to the original instigating stimulus situation. These body- and brain-state changes are mediated by: 1) autonomic or visceral changes involving smooth muscle; 2) motor system changes involving striated muscle (facial expression and body posturing); and 3) endocrine, peptide, and widespread neurotransmitter system changes. Together, these body- and brain-state changes ultimately influence the cognitive processing style and behavioral efficiency of the organism. The newly enacted body- and brain-state changes are projected to somatosensory cortices (particularly those in the nondominant parietal region) where they are juxtaposed with the original instigating images held in the ventromedial prefrontal cortex. Damasio asserts that it is this juxtaposition, of body- and brain-state changes with the images of the original stimulus set, that forms the basis for the conscious experience of emotions.

To account for the fact that emotional experiences or "feelings" are not always predicated on body-state changes, Damasio has added hypothetical or "as-if" loops to his neuroanatomical model of emotion. Damasio proposes that after repeated reenactments of the above scenario, the brain can eventually create and hold in working memory an emotional experience without directly eliciting actual body state changes. In other words, the organism learns to concoct an emotional feeling within the brain alone, without

having to reenact it in the body-proper (i.e., allowing us to imagine what bodily feedback would feel like if it occurred). This neural system allows us to feel "as if" we were having an emotional state while at the same time bypassing the body and thus avoiding the energy-consuming processes involved in experiencing the "actual" emotion. Damasio suggests that such "as if" loops are acquired over the course of development as we learn to adapt to our environment. In other words, the creation of these bypass devices in the brain requires repeated first hand emotional experiences that are associated with actual body-state changes, in the face of triggering stimuli, over the course of development.

A fundamental premise of Damasio's Somatic-Marker Hypothesis is the notion that emotional experiences or "gut" feelings play a critical role in guiding general cognitive processes such as reasoning and decision making, particularly as they relate to personal needs and one's immediate social environment. For Damasio, feelings provide us with a glimpse of what goes on in our bodies, as momentary images of our body-state become juxtaposed to the mental images of stimulus objects and situations, and, in so doing, allow us to attribute a quality of goodness or badness, pleasure or pain to those objects and situations. By correlating somatic states with real-life encounters and behavioral situations, feelings allow us to make rapid decisions in the face of complex situations and thus ultimately guide ongoing behavior.

Summary

The classical and more recent conceptual frameworks for understanding the neural basis of emotion have, over the past century, consistently implicated a series of highly conserved structures (subcortical and cortical) that appear to lay the foundation for

an organism's specialized ability to evaluate emotional information, to process and modulate related emotional memories, and to generate appropriate and often highly automatic responses to salient stimuli. This network of structures is generally referred to as the "limbic system." The emotional experiences and related memories emerging from this system are thought, at least by some theorists, to provide a pervasive influence on higher-order cognitive abilities and act as a guiding influence on future actions of the organism. The processing structure that appears to be at the hub of this emotional processing system is the amygdala, which in close concert with the ventromedial sectors of the prefrontal cortex and other brain regions (e.g., somatosensory cortices) evaluates and attributes emotional significance to stimuli. The amygdala, in concert with a variety of subcortical structures (e.g., hypothalamus, PAG) and striatal projections to motor cortices, also coordinates and directs appropriate autonomic and behavioral emotional responses to salient stimuli. Relatively recent work has also provided strong evidence that the amygdala, via its connections to the hippocampus and other cortical areas, modulates long-term consolidation of emotional information, much like the hippocampus does for nonemotional information. The ventromedial prefrontal and somatosensory cortices have also been implicated in "as-if" loops that allow for emotional experience in the absence of full blown body- and brain-state changes that normally accompany such responses and experiences. A number of other brain regions have also been implicated in emotional processing such as the anterior cingulate cortex (see Papez circuit), the retrosplenial cingulate, and insula (see discussion below). The specific relevance of these areas for the current study will be discussed in subsequent sections of this literature review.

A consistent theme running throughout the classical and more recent theoretical frameworks outlined above is the fact that emotional information can be processed via two separate neuroanatomical pathways. Papez suggested the notion of two processing pathways, one a neocortical or high-level pathway, AKA the Stream of Thought, and a subcortical or low-level pathway, AKA Papez's Circuit. It is important to note that while Papez placed the primarily responsibility for the perception, expression, and experience of emotion in the subcortical path, he also believed that cortex (i.e., cingulate gyrus) can mediate emotion via connections with neocortical areas involved in cognitive functions such as thoughts and memories and with limbic structures. This notion of two emotional processing paths forms the basis of LeDoux's model in which he espouses a subcortical (thalamo-amygdala) processing route that rapidly provides crude information to the organism about salient environmental stimuli, and a neocortical (thalamo-cortico-amygdala) route that provides, albeit at a slower rate, high resolution information that ultimately modulates subcortical inputs and integrates them with past experience and preexisting knowledge. This model has provided new insights into the ongoing debate of the role of consciously versus preconsciously mediated cognitive appraisal in generating emotional responses. Rolls also emphasizes dual emotional processing routes, but places greater emphasizes on the involvement of the neocortex for both implicit and explicit processing of salient information.

Neuropsychological Theories of Emotional Processing

Overview

Over the past several decades, a number of neuropsychological theories/hypotheses concerning the neural substrates of emotion have been proposed.

Critical issues in this literature concern the degree to which different aspects (i.e., components addressed above) of emotion are mediated by separate and/or overlapping brain systems and to what degree these systems can be localized to either hemisphere. (For in depth discussions of these issues, see Borod, Pick et al., 2000; Gainotti, 2000.) To this end, studies using brain damaged individuals have examined the degree to which unilateral focal lesions result in deficits that affect a single versus multiple component(s) of emotion and whether such emotional processing deficits localize to one or the other hemisphere (Borod & Madigan, 2000; Borod, Pick et al., 2000). Studies with neurologically normal individuals have also been used to examined the degree to which performance on tasks specific to the different aspects of emotion are correlated and the extent to which performance on emotional versus nonemotional tasks are enhanced when the stimuli are preferentially presented to either hemisphere (Borod, Zalgardic, & Tabert, Koff, in press). In this vein, Borod has proposed a componential approach to the study of emotional processing (Borod, 1993a; Borod, Pick et al., 2000) that examines the neural mechanisms of four distinct hierarchically arranged components, namely, processing mode (i.e., perception/evaluation, expression, arousal, experience, and behavior); communication channel (i.e., facial, prosodic, lexical, gestural, and postural); emotional dimension (e.g., pleasantness/unpleasantness and approach/avoidance); and discrete emotions (e.g., happiness and fear). Each of these components has been extensively examined in terms of a number of competing lateralization hypotheses that have emerged from the neuropsychological literature (Borod, Tabert, Santschi, & Strauss, 2000).

Next, these competing hypotheses are examined. Findings from studies examining the perception of emotional facial, prosodic, and lexical stimuli in unilateral

brain-damaged patients and in normal individuals, using behavioral lateralization paradigms, are briefly summarized. This literature review serves as a background for understanding hemispheric lateralization of emotional functions and in generating lateralization hypotheses that pertain to the current brain imaging study.

Brain Asymmetries for General Cognitive Functions

In general, hemispheric mechanisms for emotion are less well understood than those for cognitive functions (Borod, Bloom, & Santschi-Haywood, 1998). A plethora of studies have conclusively demonstrated that, in right-handed individuals, verbal and linguistic functions, the numerical symbol system, and complex voluntary movements are primarily mediated by the left hemisphere, whereas nonverbal and spatial functions, attention, and melody are primarily mediated by the right hemisphere (Borod, 1992; Borod, Bloom et al., 1998; Lezak, 1995; Springer & Deutsch, 1997; Walsh & Darby, 1999). Borod (1992) has summarized pertinent literature that demonstrates differential left- versus right-hemisphere cognitive strategies and corresponding anatomical differences. According to Borod (1992), the respective strategies for the left- versus right-hemispheres are analytic versus synthetic, linear versus configurational, serial versus simultaneous, detailed versus holistic, and temporal versus spatial. The left-hemisphere is also involved in abstract, logical, and sequential reasoning, whereas the right-hemisphere is involved in concrete and perceptual insight. These functional dissociations seemingly correspond to anatomical differences between the two hemispheres.

On an anatomical level (for reviews, see Borod 1992; Borod, Bloom et al., 1998; Springer & Deutsch, 1997), it has been suggested that the right hemisphere is

predominately marked by overlapping horizontal axonal connections, whereas in the left hemisphere, nonoverlapping and highly coupled vertical axonal connections predominate. Consistent with these differences in neural circuitry, the right hemisphere, relative to the left, is thought to have a greater degree of multimodal integration, interconnectivity among regions, and more widespread stimulus-evoked physiological activity (Borod, Bloom et al., 1998).

Competing Lateralization Hypotheses of Emotion

Right Hemisphere Hypothesis

Of the various hypotheses that have been proposed to explain hemispheric differences in emotional processing, the "right hemisphere hypothesis" seems most consistent with the general pattern of cognitive and anatomical asymmetries just described (Borod & Madigan, 2000). The right hemisphere hypothesis maintains that the right cerebral hemisphere is specialized for all aspects of emotion (Borod, 1992). In terms of Borod's componential approach, this would include processing mode, communication channel, emotional dimension, and discrete emotion. Borod (1992) points out that, on a neuroanatomical level, this hypothesis receives support from the observation that emotional processing necessitates a neural circuitry that is congruent with that of the right hemisphere (see above discussion; i.e., one that fosters multimodal integration and widespread anatomical interconnectivity). Moreover, on a psychological level, it also receives support from the notion that emotional processing involves functions (e.g., nonverbal and visuospatial) and strategies (e.g., integrative and holistic) that are characteristic of the right hemisphere.

Another theoretical construct closely related to the right hemisphere hypothesis is arousal. Arousal has been shown to affect all aspects of emotion. Moreover, different levels of arousal are associated with specific emotional states and experiences. For example, Borod and Madigan (2000) point out that fear involves greater arousal than sadness (Mandal et al., 1986) and joy involves greater arousal than contentment (Fredrickson, 1998). In line with the right hemisphere hypothesis, Borod and Madigan (2000) also point out that research supports the notion that the right cerebral hemisphere, particularly the posterior parietal region (Eidelberg & Galaburda, 1984; Heilman, Schwartz, & Watson, 1978; Heller, 1993; Heller & Nitschke, 1997; Liotti & Tucker, 1992; Tucker & Williamson, 1984), mediates physiological arousal.

Valence Hypothesis

A competing hypothesis that has emerged in the neuropsychological literature is the valence hypothesis. There are two versions of this hypothesis (Borod 1992). One version postulates that the right hemisphere is specialized only for unpleasant/negative emotions, while the left hemisphere is specialized for pleasant/positive emotions, regardless of processing mode (e.g., perception and expression) (e.g., Sackeim, Greenberg, Weiman, Hungerbuhler, & Geschwind, 1982; Silberman & Weingartner, 1986). A revised version of this hypothesis contends that this pattern of differential hemispheric specialization occurs only for the expression and experience of emotion, whereas the right hemisphere is dominant for the perception of emotions of both valences (Davidson, 1984). On a theoretical level, according to Borod and colleagues (Borod, 1992; Borod, Cicero et al., 1998), it has been postulated that negative emotions are linked with survival (e.g., removing oneself from danger), and hence a system would be

required that is sensitive to multimodal inputs and able to quickly scan and evaluate the entire situation. Such behaviors seem more linked to Gestalt or synthetic processing typical of the right hemisphere (see above discussion). Positive emotions, on the other hand, may be more linguistic and communicative (Fredrickson, 1998) in nature than emotive and reactive and hence may be better suited to the discrete, focused analysis typical of the left hemisphere (see above discussion).

Motoric Direction Hypothesis

Finally, a hypothesis, that is closely related to the valence hypothesis, namely the motoric direction hypothesis, has also been proposed (Davidson, 1984; Kinsbourne, 1978). This hypothesis postulates that the left hemisphere is specialized for "approach" emotions and the right hemisphere for "avoidance" emotions. In a formulation about this hypothesis (Borod, 1996), avoidance/withdrawal emotions are linked with the right hemisphere's involvement in arousal, habituation, and undifferentiated automatic movements. Approach behaviors, on the other hand, are linked with the left hemisphere because of its specialization for activation and focal attention; further, the left hemisphere is considered superior for motor behavior, fine manual control, and sequentially executed movement, processes which would seem more critical in approach than avoidance behaviors (Borod, 1996; Davidson, 1993). Conceptual overlap clearly exists between the valence and approach/avoidance hypotheses, as most pleasant emotions (e.g., happiness) have an approach component, whereas most unpleasant emotions (e.g., disgust) have an avoidance component (Borod, Caron, & Koff, 1981; Fox, 1991; Gray, 1994; Sutton & Davidson, 1997; Watson, Wiese, Vaidya, & Tellegen., 1999). Anger may be an exception, being both negative and related to approach. Typically, the approach and

avoidance dimensions have been associated with frontal and anterior temporal structures (e.g., Davidson, 1993).

Studies Evaluating Lateralization Hypotheses for Emotion

An extensive body of literature has evaluated the merits of lateralization hypotheses as they relate to the various components of emotion using unilateral brain-damaged patients and neurologically healthy adults. Findings from these studies have been extensively reviewed by Borod (Borod, 1992; Borod, 1993b; Borod et al., in press; Borod, Koff, & Caron, 1983; Borod, Vingiano, & Cytryn, 1989) and others (e.g., Heilman, Blonder, Bowers, & Crucian, 2000; Heller, 1993; Ross, 1997). Next, the general findings from the facial, prosodic, and lexical channels (i.e., facial and prosodic) will be briefly summarized.

Facial and Prosodic Channels

With respect to brain-damaged patients, the majority of studies over the past two decades have demonstrated that patients with right-hemisphere damage have selective deficits in perceiving/evaluating facial and prosodic emotional stimuli relative to patients with left-hemisphere damage and/or healthy control subjects (e.g., Benowitz et al., 1983; Blonder, Bowers, & Heilman, 1991; Borod, Cicero, et al., 1998; Borod, et al., 1990; Schmitt, Hartje, & Willmes, 1997; Weddell, 1994). More specifically, while the posterior regions of the right hemisphere seem to be critical for perception in general (e.g., Feinberg & Farah, 1997; Heilman & Valenstein, 1995; Walsh & Darby, 1999), this region seems to play a special role in the perception of emotional facial and prosodic expressions (Adolphs, Damasio, Tranel, & Damasio, 1996; Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000; Borod, 1996; Heilman et al., 2000) and also appears to

mediate emotional arousal (e.g., Eidelberg & Galaburda, 1984; Heilman et al., 1978; Heilman et al., 2000; Heller, 1993; Liotti & Tucker, 1992; Nitschke, Heller, & Miller, 2000; Ross, 1997; Tucker & Williamson, 1984). With respect to the literature using perceptual lateralization paradiagms (e.g., dichotic listening and tachistoscopic viewing) with normal individuals, although somewhat more equivocal, recent reviews by Borod et al. (in press) reveal that the majority of studies investigating emotional facial and prosodic information also report left-sided/right-hemisphere asymmetries.

Lexical Channel

Much less research has been directed at the lexical channel of communication (Borod, 1996). While some argue that the right hemisphere mediates the emotional verbal content of language (Borod, 1996), others contend that, given its dependence on language in general, this channel is largely mediated by the dominant hemisphere (Bowers, Bauer, & Heilman, 1993; for review see Borod, Bloom et al., 1998; Heilman et al., 2000). Borod and colleagues (Borod, Bloom et al., 1998; Borod et al., in press) have recently conducted comprehensive reviews of the lexical emotion literature with respect to emotional processing (i.e., perception and expression) in unilateral brain-damaged individuals and perceptual lateralization studies in normal adults.

In terms of the brain-damaged literature, Borod, Bloom et al. (1998) recently reviewed studies that examined several aspects of lexical emotional processing, including perception, expression, and memory. For perception, seven studies were reviewed. Three of these studies found clear support for the right-hemisphere hypothesis of emotion (Borod, Andelman, Obler, Tweedy, & Welkowitz, 1992; Cicero et al., 1999; Semenza, Pasini, Zettin, Tonin, & Portolan, 1986) and four studies (Blonder et al., 1991; Cicone et

al., 1980; Etcoff, 1984; Lalande, Braun, Charlebois, & Whitaker, 1992) found no hemispheric effects for the perception of lexical emotion. However, as Borod, Bloom et al. (1998) point out, none of these latter three studies used a nonemotional control condition, and thus did not control for the linguistic aspects of lexical emotional stimuli. Further, it is interesting to note that while Blonder et al. (1991) did not report differences between the brain- damaged groups and normal controls on a lexical emotional processing task (i.e., evaluating the emotional content of sentences), she did find that right brain-damaged subjects were impaired relative to left brain-damage patients and normal controls in their ability to identify the emotion represented by sentences that depicted facial, prosodic, and gestural expressions (e.g., "He shook his fist").

With respect to studies investigating lexical emotional perception in normals, the majority showed a right visual-field/left-hemisphere processing advantage (Borod et al., in press). However, when valence was taken into account, this left-hemisphere propensity was only the case for positive emotions. For negative emotions, findings were more equivocal--some studies showing left-hemisphere superiority, others showing a right-hemisphere advantage, and others being consistent with hemispheric processing. Consistent with an earlier review of the lexical emotional perception literature in normal adults by Borod, Bloom et al. (1998), these findings provide some partial support for the valence hypothesis. Borod et al. speculate that the lack of a strong hemispheric asymmetry for negative lexical emotional stimuli might be accounted for by an interaction between two competing factors (e.g., see also Mandal et al., 1999). It is possible that the left hemisphere's special role in processing language may be suppressed

or countered by the right hemisphere's specialization for processing negative emotions, and vice versa.

Summary

Taken together, Borod, Bloom et al. (1998; in press) have concluded that studies of emotion involving individuals with unilateral focal brain lesions, including all three channels (i.e., facial, prosodic, and lexical), provide strong support for the right hemisphere hypothesis. However, while studies of facial and prosodic emotional processing in normal individuals also tend to support a right-hemisphere processing strategy, behavioral lateralization studies of lexical emotional processing remain equivocal. Borod, Bloom et al. (1998) have suggested that the discrepancy between the normal and lesion literature may be reconciled by the fact that neurological damage to the brain may cause a breakdown in selective aspects of lexical emotional processing such that dissociations among discrete emotional processing components between emotional and nonemotional processes are more readily observable. In normal individuals, it may be more difficult to dissociate the various emotional components and to separate nonemotional and emotional language functions, since the neural mechanisms mediating these functions, although lateralized, are highly integrated.

In summary, the above literature review suggests that emotional perceptual processing is largely mediated by the right hemisphere for all communication channels. Evidence for this comes primarily from studies of unilateral brain-damaged individuals, and is particularly true for the facial and prosodic channels and for the processing of negatively valenced information. Detecting hemispheric asymmetries (i.e., right-hemisphere advantage) for the emotional lexical channel is particularly difficult in

normals where adequate control tasks must be utilized to account for nonemotional language processing which is strongly lateralized to the left hemisphere and thus may suppress or obscure right-hemisphere superiority in processing the emotional content of speech. Using appropriate control tasks is also particularly relevant when conducting neuroimaging studies of emotion with healthy individuals.

Neuroimaging and Emotion

Background Considerations

Over the past several years an increasing number of functional neuroimaging studies (e.g., PET and fMRI) of emotional processing have emerged. These techniques allow one to probe the neural correlates of the various components of emotional processing *in vivo* in neurologically intact and impaired individuals with a relatively high degree of spatial (i.e., a few millimeters) and temporal (i.e., PET-O15: minutes; fMRI: seconds) resolution (see George et al., 2000, for a comparison of the technical features across a wide range of imaging techniques). An increasingly important role of imaging research is to assess the degree to which functional neuroanatomical data within specific ROIs is consistent with the neuroanatomical data that have emerged from animal and human lesion studies. This can easily be accomplished by examining whether or not specific brain structures or regions (e.g., amygdala, cingulate, gyrus, and prefrontal cortex) implicated in the animal and human emotion lesion literature are selectively activated when behavioral tasks, that isolate specific processing components of emotion, are presented to subjects while being scanned (e.g., see Brieter et al., 1996; Morris et al., 1996; Whalen, Rauch et al., 1998, for examples of imaging studies examining specific brain regions based on lesion data). Imaging data can also be used to assess the merits of

the competing hypotheses concerning the lateralization of emotional processes outlined above by assessing the degree to which either hemisphere is recruited while subjects engage in emotion specific tasks (for discussion, see below and Davidson & Irwin, 1999a,b).

Technical and Experimental Challenges

Although rapid progress is being made by functional imaging studies in elucidating emotional processing, a number of technical issues have posed specific challenges for the study of emotion (see Canli, Desmond, Zhao, Glover, & Gabrieli, 1998; Davidson & Irwin, 1999a,b; George et al., 2000, for comprehensive discussions of these issues). One important limitation of current functional imaging techniques for emotion research is that subjects are subjected to rigorous experimental demands that may interfere with their ability to realistically carry out the emotional processing tasks at hand. For example, subjects are required to perform cognitive/behavioral task while lying in a very confining tube with their motion severely restricted, often via some external restraint (i.e., bite bar, tape, face mask, etc.), and in the case of PET-O_{15}, while receiving an intravenous injection of a radioactive substance. These methodological constraints also place severe restrictions on the type of emotional processes that can be studied. For example, for the most part current brain imaging techniques (i.e., PET and fMRI) preclude the direct study of overt emotional expression since the muscle movements necessary for emotional speech, facial expressions, and gestures would introduce serious motion artifacts. In fact, to date there are few if any PET or fMRI studies that have used emotional expression paradigms similar to those used in traditional behavioral studies of emotion (see above). Furthermore, a number of studies have

revealed that normal nonclaustrophobic subjects experience a significant increase in state anxiety during the imaging procedure (Beauregard et al., 1997; Gur et al., 1987, 1988). Such increases in anxiety are likely to interfere with and differentially affect performance on control and emotion-related experimental tasks while in the scanner. These considerations impose even more severe restrictions on the study of emotional processing in pathological populations, since psychiatric patients may have even more extreme reactions (i.e., exacerbated or diminished responses) to the imaging protocol than normal subjects (Davidson & Irwin, 1999a).

Another important limitation, specific to fMRI studies of emotion, is that specific regions of the brain that interface with sinuses are extremely difficult to image with pulse sequences that are currently most commonly available to researchers due to susceptibility artifacts. One area that is particularly vulnerable to susceptibility artifacts is the ventromedial sector of the prefrontal cortex, an area that has been widely implicated via lesion studies to be critical for emotional processing (Borod, 1993b; Damasio, 1994).

A number of researchers have also emphasized the importance of carefully considering a number of experimental design and statistical issues when attempting to image affective phenomena (see Davidson & Irwin, 1999a,b; George et al., 2000; Papanicolaou, 1999, for extensive discussions of these issues). Key experimental design issues revolve around the selection of appropriate experimental and control tasks and presentation paradigms that allow one to isolate the neural correlates of the wide range of emotional components (e.g., perception of emotional information, mood states). An important statistical issue, particularly pertinent to the current study that has recently been raised by Davidson and Irwin (1999a,b) is the need for emotion researchers to use

appropriate analytic strategies before reporting hemispheric asymmetries related to emotional processing. A recent review of the imaging literature by Davidson revealed that imaging studies of emotion, for the most part, report hemispheric asymmetries on the basis of voxels in one hemisphere exceeding statistical threshold whereas homologous voxels in the opposite hemisphere did not. While such an analytic strategy tests for the main effect of condition, subject group, or hemisphere, it does not formally test the condition by hemisphere or group by hemisphere interaction. Davidson argued that if the interaction is not significant, it is not legitimate to claim that an asymmetric finding was observed, since this means that the changes found in one hemisphere are not significantly different from those observed in the other, even if the effects are independently significant in one hemisphere. In the current study, hemispheric asymmetries were directly assessed in ROIs by formally testing higher order interactions that included hemisphere as a within-subjects variable (see below for a description of the other within-subjects variables used in the current study).

Imaging Studies of Emotion

Over the past few years, an increasing number of PET and fMRI studies have examined the neural substrates of emotional processing. An important issue to be considered when reviewing this literature is the degree to which the functional data are consistent with results gleaned from lesion studies. Such converging evidence is critical for the ultimate elucidation of the neural circuitry mediating emotion, since damage to the brain can result in functional consequences that are far removed from the site of the actual lesion. In this vein, a number of recent reviews of the imaging and emotion literature have been conducted (e.g., Borod et al., in press; Davidson & Irwin, 1999a,b).

After reviewing studies of emotion that utilized a wide range of affective paradigms (e.g., studies of affective disorders, pharmacological manipulations, conditioning, pain, mood induction, and perception of emotional information), Davidson and Irwin (1999a,b) concluded that, in general, the imaging literature is consistent with the extensive body of lesion data that has implicated a number of brain regions, particularly the amygdala and orbitofrontal cortex.

In the following sections, the imaging and lesion literature are reviewed. The focus of this review is on a number of brain structures that have been implicated in emotional processing from the lesion and/or imaging literatures. A special emphasis is placed on the amygdala since recent research with animals and humans has placed this structure at the hub of the emotional processing circuitry (see discussion above). Recent lesion and imaging reports have implicated the amygdala in the perception/evaluation of negatively valenced emotional information and in modulating emotional memory systems. Imaging studies investigating these phenomena have primarily utilized facial and, to some extent, prosodic expressions of emotion. A primary focus of the current study was to evaluate the role of the amygdala in emotional processing using lexical stimuli. Although the prefrontal cortices, particularly the ventromedial sectors, are also thought to play a pervasive role in emotional processing, this area is difficult to image with fMRI due to susceptibility artifacts. Hence, while literature pertaining to this region is discussed, analyses for this ROI in the current study were not possible. Other brain regions highlighted in the next section include the cingulate gyrus, with an emphasis on the anterior and retrosplenial cingulate; the insular cortex; and the right posterior cortex.

Regions of Interest

The Amygdala

Studies of patients with bilateral amygdala lesions have provided evidence that the human amygdala plays a role in the evaluation of emotional facial expressions, particularly those related to fear and anger (Adolphs, Tranel, & Damasio, 1998; Adolphs, Tranel, Damasio, & Damasio, 1994; Adolphs, Tranel, Damasio, & Damasio, 1995; Broks et al., 1998; Calder et al., 1996; Young et al., 1995; Young, Hellawell, Van de Wal, & Johnson, 1996). Human bilateral lesion studies have also implicated the amygdala in the recognition of nonverbal threat-related sounds (e.g., screams and growling) (Scott et al., 1997) and in the evaluation of words (Scott et al., 1997) and sentences denoting negative emotions (Adolphs, Russell, & Tranel, 1999). These findings are consistent with a large body of animal literature that implicates the amygdala in the evaluation of cues that predict danger to the organism (Aggelton, 1992; Ledoux, 1995). These data also suggest that bilateral amygdala lesions in humans can result in a modality-independent impairment in the recognition of threat-related emotional expressions. Moreover, since the amygdala receives inputs from multiple sensory modalities (Amaral et al., 1992) and is capable of multimodal processing (Allman & Brothers, 1994), these data argue that the amygdala is part of an underlying processing mechanism geared to interpreting emotional signals of threat or danger regardless of their source.

However, it should be noted that not all patients with bilateral amygdala damage demonstrate selective emotional processing impairments. A number of studies have demonstrated that bilateral amygdala damage does not necessarily impair the ability to evaluate emotional facial (Adolphs, Tranel et al., 1999; Hamann & Adolphs, 1999;

Hamann et al., 1996, 1997) or prosodic (Adolphs & Tranel, 1999; Anderson & Phelps, 1998) expressions. Moreover, amygdala lesions do not appear to block normal autonomic (Bechara et al., 1995; Tranel & Damasio, 1993) or self-reported reactions (Adolphs et al., 1997; Cahill et al., 1995; Hamann et al., 1997) to salient emotional stimuli. While reasons for this discrepancy in the bilateral amygdala lesion literature are not fully understood (for possible explanations, see Adolphs 1999; Adolphs et al., 1998, 1999; Broks et al., 1998; Hamann et al., 1996; Hamann & Adolphs, 1999), there is overall convincing evidence from animal and human studies that the amygdala does play an important role in the evaluation of emotional, particularly threatening, information (Adolphs 1999; Adolphs, Russel et al., 1999; Allman & Brothers, 1994; Whalen 1998).

PET and fMRI studies investigating the perception and evaluation of prototypical emotional facial expressions (e.g., fear, anger, disgust, and happiness) in normal individuals have provided further evidence that the amygdala plays a role in the evaluation of emotional information. In a PET-O^{15} study, Morris and colleagues (Morris et al., 1996) observed increasing amygdala activation as a function of the intensity of fearful facial expressions. Interestingly, in a subsequent analysis of these data (Morris et al., 1998), Morris et al. found that amygdala activation in response to fearful expressions was strongly correlated with activity in the occipital cortex, suggesting that the amygdala can modulate early processing of visual information. In using fMRI, Breiter et al. (1996) also observed amygdala activation in response to fearful facial expressions. In the Morris et al. and Breiter et al. studies, subjects passively viewed facial expressions or made judgments as to the gender of the posers. Whalen, Rauch et al. (1998) presented fearful faces to subjects below the threshold of conscious awareness, using a backward masking

procedure, and also found that the amygdala revealed a significant increase in activation to masked fearful expressions. Phillips et al. (1997, 1998) and Baird et al. (1999) have also reported amygdala activation to facial expressions of fear.

Imaging studies have also investigated brain activation in response to emotionally intoned vocal expressions and to the emotional content of negatively valenced words. Phillips et al. (1998) reported right amygdala activation in response to vocal expressions of fear (e.g., screams) in normal subjects. Kiehl et al. (1998) reported right amygdala activation in response to viewing, rehearsing, and recalling negatively valenced emotional words. These studies provide further evidence that the amygdala is involved in processing negatively valenced stimuli, regardless of presentation modality.

A large body of behavioral, pharmacological, lesion, and imaging data also suggests that the amygdala plays an important role in memory processes related to emotion (Adolphs 1999; Phelps & Anderson, 1997). Normal subjects generally show superior memory for emotionally-arousing relative to emotionally-neutral stimuli (for review, see Gabrieli (1998). Lesion and functional neuroimaging findings have illuminated the importance of the amygdala in facilitating the acquisition of emotional memories (reviewed in Phelps & Anderson, 1997). Babinsky et al. (1993), Markowitsch et al. (1994), Cahill et al. (1995), and Adolphs et al. (1997), have all reported selective long-term memory impairment for emotional verbal and nonverbal material following bilateral amygdala lesions. Cahill et al. (1996) (using FDG-PET) and Hamann et al. (1999) (using PET-O^{15}) have also found that increases in amygdala activity while viewing emotional versus neutral stimuli are strongly correlated with performance on

long-term but not short-term free recall and recognition memory tasks for emotionally arousing as compared to neutral information.

Together, these findings support the memory modulatory theoretical framework, developed by McGaugh and colleagues (Cahill 1999; McGaugh 2000) via experimental animal data. This view suggests that when the human amygdala becomes active in the presence of emotionally arousing stimuli (i.e., during encoding), it enhances or weights conscious memory for the triggering stimuli in proportion to their salience by influencing or modulating long-term memory storage and consolidation via interactions with neurotransmitter systems, particularly the adrenergic system, and via anatomical connections to the hippocampus and other brain regions (McGaugh et al., 1996). An important aspect of this view is that the amygdala's role in declarative memory is unrelated to memory for nonemotional material. Moreover, with respect to emotional material, this view emphasizes that amygdala's involvement is time dependent in that its memory-enhancing effects only become apparent after enough time (i.e., several hours to days) has passed to allow for memory consolidation in remote brain regions to occur (Cahill 1999; McGaugh 2000; McGaugh et al., 1996). The amygdala itself is, therefore, not thought to be the site where actual emotional memories are stored and is not thought to participate in the retrieval or recall of emotional information (Packard et al., 1994). In this vein, a recent study by Bianchin et al. (1999) demonstrated that the administration of several drugs into the rat amygdala surrounding training in a one-trial, step-down, inhibitory avoidance paradigm had no effect on either working memory (tested at 3 seconds post-training) or short-term memory (tested 1.5 hours post-training). However, all drugs had strong modulatory effects on long-term memory (tested 24 hours post-

training), some enhancing (e.g., norepinephrine) while others (e.g., scopolamine) impairing performance.

In summary, neuroimaging studies corroborate human bilateral amygdala lesion and animal studies, implicating the amygdala in the processing of emotional stimuli. Aversive stimuli are particularly salient, evoking responses from the amygdala that can be independent of conscious awareness and that may rapidly attenuate across successive stimuli presentations. Further, the amygdala appears to have a special role in the perception of facial expression. Facial expressions of anger and fear are especially salient in that they provide potent, possibly hardwired cues, to the presence and source of personal danger (Davidson & Irwin, 1999b; Whalen 1998). There is, however, evidence from both lesion and imaging data that vocal expressions of fear (Phillips et al., 1998; Scott et al., 1997) and the evaluation of emotionally arousing negative lexical stimuli (e.g., words and sentences) (Adolphs, Russel et al., 1999; Kiehl et al., 1998; Scott et al., 1997) activate the amygdala. Finally, there is evidence that amygdala activity while viewing (encoding) stimuli is correlated with subsequently enhanced long-term recall of emotional as compared to neutral information (Cahill et al., 1996; Hamann et al., 1999).

The Prefrontal Cortex

The prefrontal cortex has also long been thought to play a central role in the neural circuitry mediating emotional behavior. The central role attributed to the prefrontal cortex in emotion is largely premised on the fact that damage to the ventromedial or orbitofrontal sectors results in profound personality changes, first documented in the case of Phineas Gage. Over the past two decades, Damasio and colleagues have characterized the selective emotional dysregulation of frontal patients,

demonstrating that patients with lesions in the orbital frontal sectors are primarily characterized by an "acquired sociopathy" or the inability to anticipate one's own future and plan accordingly within the context of a complex social environment; the lack of a sense of personal and social responsibility; and the inability to direct personal survival, all in the face of a largely intact and, in many cases, superior intellectual profile (Damasio 1994, 1995; Damasio et al., 1991, 1998); also, see above summary of Damasio's theoretical view of emotion). Systematic neuropsychological evaluation of these patients by Damasio and colleagues has provided strong evidence that these patients cannot anticipate future positive or negative consequences of their actions, although they do respond to immediate rewards and punishments, along with concomitant failure in electrodermal autonomic reponses (Bechara et a.l, 1995). As discussed above, Damasio has constructed a theoretical framework of emotional processing in which the ventromedial sectors of the prefrontal cortex act as a convergence zone, holding a record of ongoing neural activity in limbic structures and in sensory and association cortices. This internal record of the temporal conjunctions of neural activity in these various brain areas defines the meaning of the current affective situation for the organism and forms the basis for the process by which an organism learns to associate certain types of situations with past and present emotional experiences.

In a recent series of PET-O15 studies, Lane, Reiman, and colleagues (Lane, Reiman, & Ahern et al. 1997; Lane, Reiman, & Bradley, 1997; Reiman et al., 1997) found that the medial prefrontal cortex (Brodmann's area 9) was consistently activated when subjects engaged in a variety of mood induction paradigms regardless of the emotion category, emotional valence, or the type of emotional stimulus (e.g., highly

emotional scenes or recall of recent emotional events). These authors postulate on the basis of their imaging findings and studies by other research teams (see Reiman, Lane, Ahern, Schwartz, & Davidson, 2000, for a review) that this region may participate in a number of functions, including the conscious experience of emotion, the inhibition of excessive expressions of emotion, and, as suggested by Damasio (see above), the monitoring of one's emotional state to make personally relevant decisions. Hence, this region will serve as a ROI for the current study.

The importance of the ventromedial sector of the prefrontal cortex for emotional processes is also underscored by the fact that this brain region receives projections from all sensory modalities (e.g., gustatory, somatosensory, olfactory, visual, and auditory), directly and/or indirectly, and in turn, is the only prefrontal region that has extensive bi-directional connections with limbic structures, particularly the amygdala. The orbitofrontal cortex also has outputs to the striatum and ventral striatum by which it can influence behavior; to the inferior temporal lobe, entorhinal cortex, and cingulate by which it can influence cognitive processes; and to the preoptic region and lateral hypothalamus by which it can influence autonomic responses (for reviews see Damasio et al., 1991; Price, 1999; Rolls & Treves, 1998).

The work of Rolls and colleagues using both primate and human lesion models has demonstrated that damage to the orbital frontal cortex not only results in disinhibited and socially inappropriate behavior, but also leads to a selective impairment in learning to correctly alter behavior in response to changing reinforcement (i.e., rewarding and punishing) contingencies in the environment (Rolls, 1999; Rolls & Treves,1998). This impairment in the ability to reverse stimulus-reinforcement associations closely agrees

with findings by LeDoux (1996), that animals with medial prefrontal lesions fail to extinguish their fear response to the CS and context long after the threatening properties of the stimulus situation (US) have been removed. According to Rolls and Treves (1998), the changes in emotional and social behavior typical of orbitofrontal patients can be accounted for at least, in part, by an inability to respond appropriately to stimuli on the basis of their previous and often rapidly changing association with positive or negative experiences. Interestingly, Rolls and colleagues found that some orbitofrontal patients are impaired at discriminating facial expressions without an impairment in facial recognition (Hornak, Rolls, and Wade, 1996), suggesting that the orbital frontal cortex is selectively attuned to the emotional content of faces (e.g., a smile) that act as reinforcers in social situations.

Davidson and colleagues have amassed considerable evidence over the past several years, using electrophysiological measures of regional activation in normal subjects, that the left and right prefrontal cortex as a whole are differentially involved in the expression and experience, but not perception, of positive versus negative emotion, respectively. These studies have found relative increased left anterior activation during positive affect and relative increased right-sided anterior activation during negative affect (see Davidson, 1993, 1995, for a reviews of this literature). These findings have been corroborated to some extent with PET and fMRI imaging modalities (Sutton & Davidson, 1997; see Davidson & Irwin, 1999a,b, for reviews).

In line with the focus of the current study, a recent PET-O15 study by Beauregard et al. (1997) found selective activation of the orbitofrontal cortex in response to passive viewing of highly unpleasant words as compared to linguistically matched neutral words.

This finding, along with that reported by Hornak et al. (1996) that the orbitofrontal cortex is selectively involved in processing emotional facial expressions, may suggest that this region of the prefrontal cortex may not only be involved in directing socially appropriate affective behavior, but also in the perception and evaluation of emotional information. However, an important technical caveat with respect to the ventromedial sectors of the orbitofrontal cortex is that this region is generally not visible when using fMRI due to susceptibility artifacts resulting in signal dropout (see above discussion). Hence, in the current fMRI study, activation in this region was not expected. The medial frontal gyrus (BA 9), identified by Reiman and others (see above) as important in emotional processing, extends dorsally beyond the ventromedial sectors that are vulnerable to susceptibility artifacts.

The Anterior Cingulate Gyrus

The anterior cingulate cortex has traditionally been viewed as a key limbic structure mediating emotional functions (MacLean, 1990; Papez, 1937; Vogt, Finch, & Olson, 1992; Vogt, Nimchinsky, Vogt, & Hof, 1995). It consists of a region around the rostrum of the corpus callosum and can be subdivided into affective and cognitive divisions (Devinsky, Morrell, & Vogt, 1995; Vogt et al., 1992, 1995). The affective division includes Brodmann areas 25, 33, and rostral area 24 (see Devinsky et al., 1995, for an extensive review of both divisions), and the cognitive division primarily includes caudal areas 24' and 32' (see Figure 4, in Devinsky et al., 1995).

The affective division of the anterior cingulate has extensive anatomical connections with the amygdala (see above), a structure thought to be at the hub of an extended emotional processing system (AKA the rostral limbic system) that includes the

septum, orbital frontal cortex, insula, anterior cingulate, ventral striatum (including the nucleus accumbens), periaqueductal gray, and several autonomic brainstem motor nuclei (Devinsky et al., 1995). The orbital frontal cortex and periaqueductal gray, two other principal structures of the extended limbic system, also form strong connections with the affective division of the anterior cingulate gyrus (see Devinsky et al., 1995). Lesion, electrical stimulation, and electrophysiological recording studies support the notion that the rostral portion of the anterior cingulate is involved in a wide variety of affective phenomena including conditioned emotional learning, vocalizations associated with expressing internal states, assessments of motivational content, maternal-infant interactions, and assigning emotional valence to internal and external stimuli (see Devinsky et al., 1995, for a review of this literature). The cognitive division, on the other hand, does not have substantial connections with the amygdala or other limbic regions and has not been implicated in emotional or autonomic functions. Rather, this division is thought to mediate skeletomotor control, response selection, and monitoring of interfering streams of cognitive information via connections with the spinal cord, brainstem nuclei, striatum, prefrontal, premotor, and supplementary motor areas (Devinsky et al., 1995). For the purposes of the current study, the affective division of the anterior cingulate is of particular interest.

Recent neuroimaging studies have reported selective activation in the affective division of the anterior cingulate cortex (see Whalen, Bush et al., 1998, for a review) to emotional stimuli. In a recent PET-O15 study, George et al. (1994) found that transient sadness and happiness were associated with elevated blood flow in the affective division of the anterior cingulate cortex, particularly area 25 (AKA as the "subgenual" region; see

Whalen, Bush et al., 1998). Interestingly, increased blood flow in the anterior cingulate during sadness was proportionately related to elevated blood flow in the amygdala and inversely related to amygdala activation during happiness. In another study by George and colleagues (1993), recognizing the emotional content of facial expressions resulted in the activation of area 24 (AKA "pregenual" region) of the anterior cingulate. Findings from these two studies suggest that the affective division of the anterior cingulate is involved in both the processing of internal states and externally presented emotional stimuli. In a similar vein, Lane et al. (Lane, Reiman, & Ahern et al. 1997; Reiman et al., 1997) exposed subjects to a series of emotional pictures under two conditions. During one condition, subjects attended to their subjective emotional responses and indicated whether a given picture evoked a pleasant, unpleasant, or neutral feeling. In another condition, the same subjects were asked to indicate whether a given picture depicted a scene that was indoors, outdoors, or either. Significant differential anterior cingulate activation was found to be specific to the condition in which subjects explicitly attended to the evoked internal emotional response versus attending to a nonemotional aspect of the scene.

A number of recent imaging studies have used variations of the standard and emotional Stroop paradigms to further dissociate the functions of the affective and cognitive divisions of the anterior cingulate. The classic color-word Stroop interference paradigm (Stroop, 1935) has extensively been used to study executive attentional processes thought to be mediated by the anterior cingulate (Posner & Petersen, 1990), such as how the brain focuses on and "chooses" from competing responses (i.e., response selection) while ignoring interfering stimuli and suppressing inappropriate responses

(George et al., 1994). To this end, the classic Stroop paradigm measures a subject's response latency to naming the color of ink used to print a list of stimuli (e.g., words and/or bars). In one condition, the incongruent condition, color-words (e.g., red, green, blue, or yellow) are used as the target stimuli. Here the color of the ink (e.g., blue) with which the words are printed is incongruent with the meaning of the color-word (e.g., "red"). In the control condition(s), the stimuli (e.g., words or bars) and the color of the ink with which they are printed do not interfere or compete with each other. The incongruent task, which represents the critical manipulation, requires subjects to provide the name of the ink color while ignoring or suppressing the incorrect, over-learned, and, hence, interfering response of reading the printed word. Behavioral studies have reliably demonstrated that the latency to name the color of the ink is significantly increased in the incongruent condition as compared to the control conditions (Bush et al., 1998). Moreover, recent PET-O15 studies using normal control subjects (Carter, Mintun, & Cohen, 1995; Pardo, Pardo, Janer, & Raichle, 1990) have demonstrated significantly greater activation in the cognitive division of the right anterior cingulate during the incongruent (e.g., word "red" printed in blue ink) versus the congruent (e.g., word "red" in red ink) condition.

In contrast to the standard Stroop task, the emotional Stroop paradigm requires subjects to name the color of the ink in which emotionally valenced (e.g., murder) versus neutral (e.g., cushion) words are printed. Although these words do not directly interfere with the appropriate response (i.e., naming the color of the ink), studies have consistently demonstrated that when subjects are presented with words relevant to their current concerns, automatic processing of word meaning delays naming of the word's color (see

Williams, Mathews, & MacLeod, 1996). This effect is particularly true for anxiety-related words across a number of patient groups (see Whalen, Bush et al., 1998). It is thought that the crucial interference in the emotional Stroop is provided by the emotional content or meaning (e.g., valence) of the words.

To examine anterior cingulate involvement in emotional Stroop performance, George et al. (1994) conducted a PET-O15 study in which normal subjects performed a version of the emotional Stroop called the "sad Stroop" (i.e., sad words are printed in different colors) versus a control task (i.e., colored bars are presented). For each condition, subjects were instructed to pronounce only the color of the stimulus. Results of this study demonstrated increased activation in the affective division of the anterior cingulate region while subjects named the printed color of sad words as compared to that of bars.

Using fMRI, Whalen and colleagues (Bush et al., 1998; Whalen, Bush et al., 1998) recently dissociated the cognitive and affective divisions of the anterior cingulate in a group of normal subjects using modified versions (particularly suited for fMRI) of the standard and emotional Stroop tasks. To avoid the usual head movements associated with making overt verbal responses (required by the standard Stroop task), which result in fMRI image artifacts, Whalen and colleagues (Bush et al., 1998) developed the counting Stroop (the cStroop). During the incongruent condition of the cStroop, sets of one to four identical number-words are presented on each trial, and subjects report via a button press the number of words presented (e.g., "four" written one to four times). During the control condition, response latencies are measured to similar presentations of non-number words (i.e., "bird" written one to four times). Behavioral validation studies

have shown that response latencies are significantly longer during the incongruent versus control conditions of the counting Stroop (Bush et al., 1998) task.

In a related fMRI study, Bush and colleagues (Bush et al., 1998) scanned the same normal subjects while engaged in the cStroop and an emotional version of the cStroop (Whalen, Bush et al., 1998), known as the emotional counting Stroop (ecStroop). In the ecStroop task, sets of one to four identical highly negative (e.g., "murder" written one to four times) versus neutral (e.g., "cushion") words are presented to subjects. Subjects reported the number of words presented on each trial via a button press. Similar to the Pardo et al. (1990) study, results from the cStroop imaging study revealed increased activation in the cognitive division of the anterior cingulate. In contrast, results from the ecStroop imaging study revealed increased activation in the affective division of the anterior cingulate. The authors argue that activation of the anterior cingulate to both the cStroop and ecStroop is consistent with the putative role of the anterior cingulate in reconciling competing information streams. Moreover, the different spatial locations of activation within the anterior cingulate to the cStroop versus ecStroop tasks suggests that recruitment of these distinct areas depends on the information content or meaning (i.e., cognitive vs. emotional) of the stimuli employed (i.e., names of numbers vs. highly negative words).

In summary, the imaging findings outlined above are consistent with the anatomical, pharmacological, electrophysiological and lesion data summarized by Vogt et al. (1992, 1995) and Devinsky et al. (1995), and together, support the notion of a cognitive and an affective division within the anterior cingulate that differentially monitor and reconcile interfering or conflicting streams of cognitive and emotional

information, respectively. This dissociation of activation areas within the anterior cingulate to cognitive versus emotional tasks will be examined further in the current study using a task in which subjects will be required to make subjective decisions about emotional versus neutral words (see below).

The Retrosplenial Cortex

While a variety of cognitive and affective functions have been associated with specific subregions of the anterior cingulate (see above), the functions associated with the posterior cingulated have been less well studied (Devinsky et al., 1995; Vogt et al., 1992). The posterior cingulate includes Brodmann's areas 23 and 31, along with the retrosplenial cortex comprising areas 29 (which lies within the callosal sulcus) and 30 (which extends from the callosal sulcus onto the convexity of the cingulate gyrus). See Maddock (1999) for a concise review of posterior and retrosplenial cingulate anatomy as delineated by the work of Vogt et al. (1995). While neuroanatomical, lesion, and imaging studies have implicated the posterior cingulate cortex, including the retrosplenial cingulate, in memory, visuospatial perception, and proprioceptive processing (see Maddock, 1999, for a review of this literature), it was not until a series of recent imaging studies by Maddock and colleagues (Maddock & Buonocore 1996,1997; Maddock, Buonocore, & Garrett, 1998) that the retrosplenial cortex was explicitly been implicated in emotional processing.

Maddock and colleagues scanned normal subjects (1997, 1998) and patients with panic disorder (1996) while the subjects were making judgements about the pleasantness of threat-related versus neutral spoken words in an effort to elucidate the neural substrates of lexical emotional processing. To their surprise, Maddock and colleagues

found that of all brain regions analyzed, the retrosplenial cortex was the region most consistently and robustly activated by the emotional stimuli. For example, in a study of threat-related words (i.e., terror, dangerous, and emergency) compared with matched neutrally spoken words (i.e., margin, pertinent, and translation), eight of ten normal volunteers showed highly significant selective activation of the retrosplenial cortex (Maddock & Buonocore, 1997). No other brain region showed this level of consistency across subjects. Subsequent studies demonstrated a similar activation pattern across normal subjects and patients with panic disorder to both intensely unpleasant and intensely pleasant words (Maddock & Buonocore, 1996; Maddock et al., 1998). These consistent findings prompted Maddock to review the functional neuroimaging literature in order to determine if the retrosplenial cortex is selectively activated to emotional manipulations as a rule or if these findings were anomalous.

In his review of the neuroimaging literature, Maddock (1999) included 25 publications that reported the results of 51 experimental comparisons in which normal subjects performed the following tasks: 1) they evaluated emotional versus nonemotional stimuli matched for perceptual and task-related characteristics (e.g., fearful versus neutral faces); 2) they evaluated two different categories of emotional stimuli (e.g., happy versus sad faces); or 3) they were exposed to emotionally salient stimuli as part of a mood induction paradigm (e.g., scenes or memories) compared to a resting baseline. Maddock identified 20 experiments from the 11 studies that had well-matched emotional and nonemotional conditions and thus could be used to evaluate selective retrosplenial involvement to emotional manipulations. Of the regional activations associated specifically with the emotional salience of stimuli in these 20 experiments, the

retrosplenial cortex was indeed the region most frequently activated. The regions of activation included Brodmann areas 29 (within the cingulate sulcus) and 30, and 23 and 31 (parasplenial and adjacent isocortex posterior to the splenium). A further analysis of these studies found suggestive evidence of lateralized activation in the retrosplenial cortex as a function of the emotional task. Only one of the experiments that activated the retrosplenial-cortex used verbal stimuli (i.e., single words), and only this study demonstrated greater left- than right-sided retrosplenial activation. All of the other experiments used nonverbal, pictorial stimuli (e.g., faces and scenes), and these activated greater right- than left-sided retrosplenial activation. Moreover, although Maddock (1999) found a greater association between retrosplenial activation and negatively valenced stimuli, some preliminary evidence (Maddock et al., 1998) exists that this region also responds to highly pleasant words. Further, the majority of studies that activated the retrosplenial cortex involved the evaluation of emotionally salient stimuli without mood induction manipulations, suggesting that the emotion-related function of the retrosplenial cortex might be more closely associated with emotional perception and evaluation processes than with the generation of emotional responses or feelings. Also, the retrosplenial cortex was activated both by studies that used auditory and visual stimuli, suggesting that this region is not restricted to a single sensory modality. Maddock's review of the literature (1999) also found little to no evidence that the retrosplenial cortex is activated during cognitive tasks in general. Rather, Maddock suggests that it is more typical for this region to show decreases in activation to nonemotional conditions (e.g., active visual tasks versus passive viewing of the same

visual tasks), further supporting the selective sensitivity of this region to emotional material.

Maddock further points out that while this region has no connections to the amygdala (Amaral et al., 1992) it does receive strong afferent inputs from the anterior cingulate, the orbital frontal cortex, and the anterior dorsal bank of the superior temporal sulcus, all of which receive significant input from the amygdaloid complex. Maddock suggests that all of these inputs are a potential source of information about the emotional and motivational significance of ongoing stimuli and events that could be integrated in the retrosplenial cortex. Similar to the modulatory effects of the amygdala on declarative memory (see above), the strong efferent connections from the retrosplenial cortex to the parahippocampal and entorhinal cortices provide another means by which the retrosplenial cortex can influence episodic memory processes to reflect emotional and motivational priorities. In turn, the entorhinal cortex provides strong afferent inputs to the retrosplenial cortex, which then projects to the anterior cingulate, dorsal lateral prefrontal cortex, superior temporal sulcus, and precuneus. Together, this system of afferent and efferent projections places the retrosplenial cortex in position to influence emotional memory. Evidence for such a role comes from the Maddock & Buonocore (1997) study in which a significant correlation was observed between retrosplenial activation in response to threat related words and an enhancement in memory (measured by immediate free recall) for the same words as compared to neutral words. In summary, although the exact emotion-related function of this region is not clear, Maddock, on the basis of his experimental findings and metaanalysis, concludes that the extant literature

does support the hypothesis of retrosplenial involvement in the evaluation and memory of emotionally salient stimuli.

The Insular Cortex

The insular cortex, also known as the fifth lobe of the brain, is buried in the lateral sulcus and is covered by the opercular parts of the frontal, parietal, and temporal lobes (AKA the operculum) (see Augustine [1985, 1996] for reviews of the neuroanatomy and functions of the insula). It consists of four to six gyri that are divided into an anterior and posterior division by the central insular sulcus, and includes Brodmann areas 13 through 16.

The insular lobe in primates including humans has reciprocal connections with widespread cortical and subcortical areas that include regions critical to emotion such as the orbital frontal cortex, the temporal pole, the anterior cingulate, prepyriform olfactory cortex, the amygdala, the basal ganglia, and thalamus (Augustine, 1985, 1996). A plethora of studies in primates have also documented a wide array of sensory, perceptual, and cognitive functions in which the insular cortex plays an important role (see Augustine, 1996 for review), a number of which are closely related to emotional processing. For example, the anterior insular cortex contains neurons that respond selectively to pleasant and unpleasant tastes (for reviews of this literature, see Augustine, 1996; Davidson & Irwin, 1999a; Phillips et al., 1997) and thus serves in primates as a sensory area for taste (i.e., the primary sensory gustatory area).

Lesion studies have also revealed that the insular cortex stands as a gateway between somatosensory areas S1 and S2 and limbic structures in the temporal lobe, such as the amygdala, and thus plays an important role in relaying somatosensory information

to limbic structures. Damage to the insular cortex can result in a syndrome known as asymbolia for pain in which patients recognize pain but lack appropriate motor and emotional responses to painful stimuli applied anywhere on the body surface. Interestingly, these patients are also unresponsive to offensive visual and auditory threats (for a review of this literature, see Augustine, 1996). This syndrome is best explained in terms of a sensory-limbic disconnection in which damage to the insula interrupts the connections between somatosensory areas S1 and S2 and limbic structures, such as the amygdala. Electrical stimulation of the insula and studies of patients with insular seizures have also revealed that the insular cortex plays an important role in regulating visceral motor or autonomic functions (e.g., vomiting, defecation, and cardiovascular functions) that closely accompany emotional phenomena. This is consistent with the fact that insular cortex receives afferents from several major autonomic regions and sends efferents to a number of brain regions that play a critical role in regulating autonomic responses such as the amygdala and lateral hypothalamus.

Recent neuroimaging studies that have manipulated emotion have also reported selective activation of the insula. Of particular interest for the current study is the observation made by Phillips et al. (1997) in which an increasingly robust response from the right anterior insular cortex was elicited to increasingly intense facial expressions of disgust as compared to neutral faces, but not to facial expressions of fear. This finding suggests that the anterior insula is not only involved in the actual perception of aversive stimuli (e.g., tastes and smells) but also in the perception and evaluation of abstract information related to the experience of disgust in others (visual stimuli depicting another's disgust). The study by Phillips et al. (1997) also demonstrated selective

activation in the ventromedial prefrontal cortex and in the right putamen and thalamus. The authors argue that this pattern of activation may reflect an extended neural network that mediates emotional responses to actual visceral, offensive stimuli or to information pertaining to such responses. This network closely overlaps with a cortico-striatal-thalamic circuit (i.e., connecting the orbitofrontal cortex with the ventral striatum and mediodorsal thalamic nucleus) thought to mediate responses to emotional stimuli (Alexander, DeLong, & Strick, 1986).

In a series of PET-O15 studies, Lane, Reiman, and colleagues (Lane, Reiman, & Ahern et al. 1997; Lane, Reiman, & Bradley, 1997; Reiman et al., 1997) found that the anterior insular region is preferentially involved when subjects are required to attend to their internal emotional experience while viewing highly emotional scenes versus attending to specific features of the externally presented stimuli, or when subjects are required to recall recent negative events (i.e., sad) as opposed to viewing similar emotional scenes. Anterior insular activation has also been observed in response to a wide variety of emotion-related manipulations (for review of this literature, see Lane & Nadel, 2000), including normal anticipatory anxiety, lactate-induced panic, and the perception of temperature and pain, while tasting salt. In light of these neuroimaging findings, Reiman et al. (2000) postulate that the anterior insular region participates in an evaluation procedure that alarms the organism to the aversive emotional significance of potentially distressing bodily sensations and thoughts (i.e., internally generated perceptual or cognitive stimuli).

In summary, while both lesion and imaging studies have implicated the insular cortex in the processing of a wide variety of emotional stimuli, this region seems

particularly involved in processing aversive stimuli that evoke a sense of disgust. In the current study, subjects are required to evaluate a variety of highly unpleasant words in terms of their personal experience. While some of these words may evoke a sense of disgust, the words used here were not selected to represent any one discrete emotional category. Nonetheless, activation in this region was examined since the insular cortex has been implicated in the processing of aversive emotional experience.

The Posterior Right Hemisphere

As discussed above, the posterior regions of the right hemisphere (i.e., parietal and temporal lobes) appear to play a special role in the perception of negatively valenced facial and prosodic information (Adolphs et al., 1996; Adolphs et al., 2000; Borod, 1996; Heilman et al., 2000), and in emotional arousal (e.g., Eidelberg & Galaburda, 1984; Heilman et al. 1978; Heilman et al., 2000; Heller, 1993; Liotti & Tucker, 1992; Nitschke et al., 2000; Tucker & Williamson, 1984; Ross, 1997). While some evidence exists to suggest that the emotional content of words is also selectively processed by the right hemisphere, lesion findings with respect to the lexical channel remain equivocal (see above discussion).

In a recent studies, Adolphs et al. (1996, 2000) evaluated the hypothesis (see above discussion) that the right posterior cortex, including the somatosensory cortex, plays a special role in the perception and recognition of facial emotions. In these studies the relationship between performance on a facial expression recognition task involving a wide range of emotions, both positive and negative, and lesion location and extent was examined in 108 patients with focal left, right, and bilateral hemisphere lesions. Results demonstrated that when lesions occurred in somatosensory-related cortices of the

posterior right hemisphere, including S-I, S-II, anterior supramarginal gyrus, and to a lesser extent the insula, selective deficits in recognizing and retrieving conceptual knowledge about emotions from human facial expressions occurred.

In a recent review of the literature, Borod et al. (in press) reviewed neuroimaging studies that used the facial, prosodic, and/or lexical channel to investigate the neural substrates of emotional perception. The focus of this review was limited to the posterior cortex (i.e., parietal and temporal lobes) with the goal of ascertaining the degree to which recent imaging data corroborate the general findings from human lesion studies that this brain region plays a critical role in the perception/evaluation of emotional information.

Overall, this review (Borod et al., in press) found that when collapsing across the parietal and temporal lobes, there were more instances of right-hemisphere activation (55%) than there were of bilateral (12%) or left-hemisphere (33%) activation. When communication channel was considered, the distributions were relatively similar for facial and prosodic channels. In the facial and prosodic channel, overall, there were more instances of right-hemisphere activation (58% and 56% respectively) than bilateral (6.5% and 22% respectively) or left-hemisphere (35.5% and 22% respectively) activation. In contrast, for the lexical channel, the distribution was relatively equivalent across the three categories: right-hemisphere (44.4%), bilateral (22.2%), and left-hemisphere (33.3%). In terms of valence, because almost all of the imaging studies reviewed by Borod et al. (in press) were limited to negative emotions, it was not possible to evaluate the valence hypothesis in terms of the imaging literature.

A recent fMRI study by Crosson et al. (1999), which set out to identify brain areas that are involved in the retrieval of words with emotional versus neutral

connotations using a word generation task, found that the generation of emotional versus neutral words engaged brain regions in the frontal and temporal poles that are strongly connected to limbic structures. However, the authors limited their analyses to the left hemisphere and therefore could not speak to the selective involvement of the right posterior cortex in the processing of emotional words.

The overall findings from the imaging literature reviewed here are largely consistent with findings from the lesion literature reviewed above. In general, they support the notion that the right posterior cortex is more involved than the left in the perception of emotional information via the facial and prosodic channels. Moreover, with respect to the lexical channel, the imaging data similar to the lesion data remains equivocal. On a cautionary note, however, it is important to view the review of the imaging data by Borod et al. (in press) as preliminary and merely suggestive, since all of the studies reviewed reported activation changes in either hemisphere without using appropriate analytic strategies to directly test for hemispheric asymmetries (i.e., assessing the interaction of condition or subject group with hemisphere) (see above discussion).

The Ventral Striatum

The ventral striatum includes the caudate nucleus, putamen, and nucleus accumbens (Groenewegen, 1997). In primates, the ventral striatum receives major projections from a number of prominent limbic structures, including the medial orbitofrontal cortex, amygdala, anterior cingulate, hippocampus, and temporal association cortex. The ventral striatum, in turn, projects back to the orbitofrontal and anterior cingulate cortices via the ventral pallidum and mediodorsal thalamic nucleus. These projections form a "limbic" basal ganglia-thalamocortical circuit, first defined by

Alexander and colleagues (1986), which is thought to selectively mediate emotional processes and to interact with a number of other parallel basal ganglia-thalamocortical circuits that mediate motor and higher-order association/cognitive processes, respectively. A large amount of nonhuman data has demonstrated that the ventral striatum, and particularly the nucleus accumbens which is a part of the mesolimbic dopaminergic pathway, plays a critical role in addictive behaviors and in positive emotion related to reward processes (see Rolls, 1999, for an extensive review of this literature).

Recent neuroimaging studies have confirmed these findings. Breiter et al. (1997) demonstrated strong activation in the nucleus accumbens in response to an infusion of cocaine in cocaine addicts. Davidson and colleagues, using PET-O15, have found increased activation in the nucleus accumbens during picture-induced positive but not negative affect (for review, see Davidson & Irwin, 1999b). Although the above mentioned evidence strongly suggests an important role for the ventral striatum, and particularly the nucleus accumbens, in emotion-related functions, given that the focus of the current study was on the perception and evaluation of negatively valenced information, which does not involve reward processes, this brain area did not serve as a ROI here.

The Anterior and Dorsal Medial Thalamus

The anterior thalamic nucleus (Mark et al., 1995; Papez, 1937) and the dorsal medial thalamus (Alexander et al., 1986; Price, 1999) are part of a complex system of connections, known as the limbic system (see discussion above), that mediate emotional processes. Neuroimaging data have demonstrated that selective thalamic activation to

emotional manipulations appear to be unrelated to the discrete type of emotion, the emotional valence, or the nature of the emotional stimulus and task involved (Reiman et al., 2000). However, as pointed out by Reiman et al. (2000), the limits in anatomical localization and spatial resolution make it difficult to localize activation in specific thalamic nuclei. Hence, while selective thalamic activation to the emotional manipulation used in the current study will be explored as part of the whole brain analyses, the anterior and dorsal medial thalamic nuclei was not specified as a ROI.

Objectives

The purpose of the current study was to examine brain activation as measured by the fMRI BOLD signal in response to the evaluation and immediate memory of unpleasant and neutral words. Analyses focused on brain regions thought to be part of a neural network specialized for the processing of emotional information (see review above). These areas included the amygdala, ventromedial sectors of the prefrontal cortex, affective division of the anterior cingulate, retrosplenial cingulate, insular cortex, and the right posterior cortex. To establish specificity of the findings in these ROIs, and facilitate comparisions with other research teams, whole brain activation is presented on an exploratory basis. Correlational analyses were also conducted in order to investigate relationships between those ROIs that revealed selective activation during the emotional conditions of the decision and/or immediate recognition memory tasks. Further, these activated ROIs were correlated with memory performance data obtained from the immediate recognition memory task. Finally, the influence of anxiety created by the scanning procedure on activated ROIs was also explored.

Hypotheses

Hypotheses articulated here specify selective increases, and not decreases, in activation to emotional stimuli. Although it has long been known that the cerebral cortex serves to inhibit the unbridled expression of emotion (see Ledoux, 1989, 1996), it remains to be determined which cortical structures participate in emotional inhibition, or in other words, which structures need to be "turned off" for the disinihibition of emotion, and what effects such deactivations have on other brain structures (Reiman et al., 2000). Given this limitation in the current ability to predict and interpret reductions in cerebral activity, selective increases in activation to emotional stimuli will be interpreted.

General Hypotheses Pertaining to all ROIs

The following hypotheses guided analyses in the current study for all ROIs.

1) The lesion and imaging studies reviewed above have to varying degrees demonstrated that the selected ROIs (i.e., amygdala, orbitofrontal cortex, anterior cingulated, retrosplenial cingulate, insular cortex, and right posterior cortex), for the current study are involved in the perception/evaluation, encoding, and/or recognition of emotional information. In so far as this is true, it was hypothesized that each of these respective areas would show a greater (i.e., magnitude of amplitude) time-locked activation pattern in response to the evaluation of highly unpleasant than neutral words during the emotional decision and recognition memory scans of the current study (see Methods section below for a detailed description of these tasks).

2) In so far as the ROIs for the current study function as an emotional processing network or system, it was hypothesized that BOLD response to the unpleasant but not

neutral words will be significantly correlated. Only those ROIs which demonstrated a selective time-locked response to the emotional condition will be part of this analysis.

3) With respect to hemispheric lateralization, asymmetries in the perception, expression, and experience of emotional stimuli have been well documented in patients with focal unilateral cortical lesions (Adolphs et al., 1996, 2000; Borod, 1992; Gainotti, Caltagirone, & Zoccolotti, 1993; Heilman et al., 2000; Ross, 1997). In general, lesion studies support the notion that the right cerebral hemisphere is specialized for the processing of emotional information (i.e., right-hemisphere hypothesis) (see above). However, for the most part, imaging studies investigating the same experimental conditions have reported left-sided bilateral in addition to right-sided, activation (see Davidson & Irwin, 1999a,b). Moreover, Davidson and Irwin (1999a,b) have recently pointed out that although many imaging studies have reported asymmetric changes associated with emotion, the data by and large have not been analyzed with specific right-left laterality-focused contrasts. In light of these considerations, although one might expect, on the basis of the right- hemisphere hypothesis, greater right- than left-sided involvement, predictions about the laterality of activation to emotional information in specific brain regions cannot easily be made from the current imaging literature. Hence, with the exception of the right posterior cortex (see next section for specific hypotheses with respect to this ROI), predictions about hemispheric lateralization for the ROIs were not made. The observed activation sites in each area of interest were however analyzed for asymmetries using a 3-way Word Condition by Time Course by Hemisphere (right versus left) ANOVA (see Statistical Analysis section below).

4) Normal subjects generally show superior (immediate and long-term) memory for emotional as compared to neutral lexical stimuli (for review, see Gabrieli, 1998). Hence, it was hypothesized that subjects would recall more emotional as compared to neutral words immediately following the first scan (i.e., evaluation and encoding). Moreover, correlational analyses were conducted on an exploratory basis to examine the relationship between the memory performance data and the observed activation from each ROI during the emotional decision and recognition memory scans. It was predicted that activation in those brain regions that facilitate (e.g., encoding or retrieval) immediate recognition memory for emotional versus neutral words would be correlated with memory performance for emotional but not neutral words. Specific hypotheses involving the emotional memory data are articulated in the next section for ROIs thought to play a special role in emotional memory (e.g., amygdala and retrosplenial cortex).

5) A further goal of this study was to investigate the influence of anxiety created by the scanning procedure on amygdala activation. Based on our own pilot work and reports from previous studies (Gur et al., 1987, 1988), we predicted a significant increase in self-reported state anxiety (STAI; Speilberger, Gorsuch, & Lushene, 1970) in comparisons of subjects' scores immediately before entering the scanner to scores reflecting their anxiety level during the scanning session (measured immediately after the scan). Correlational analyses were conducted on an exploratory basis to examine the relationship between changes in state anxiety due to the scanning procedure and the observed activation in ROIs. No a priori hypotheses were made with respect to these correlational analyses (see above discussion).

Specific Hypotheses Pertaining to Several ROIs

In this section, specific hypotheses are proposed for a number of ROIs.

Amygdala Hypotheses

As pointed out above, a vast number of recent lesion and imaging studies have focused on the amygdala's role in the perception of emotional information, particularly as it relates to aversive threat-related stimuli. While a great many of these studies have used facial and, in some cases, prosodic emotional expressions as stimuli, only a few studies have examined the role of the amygdala in the perception/evaluation of verbal emotional expressions (see literature reviewed above). Hence, a major focus of the current study was to further investigate the degree to which the amygdala is involved in the processing (i.e., perception, evaluation, encoding, and recognition memory) of emotional information communicated via the lexical channel. Here, a number of specific hypotheses are proposed and discussed with respect to amygdala activation in response to the presentation of unpleasant versus neutral words.

1) Normal subjects generally show superior (immediate and long-term) memory for emotional as compared to neutral lexical stimuli (see above discussion). However, recent imaging (Cahill et al., 1996; Hamann et al., 1999) and animal studies (Bianchin et al., 1999) have demonstrated that amygdala activity during encoding (Scan 1) is correlated with long-term (e.g., three weeks later) but not short-term memory. This finding is consistent with the memory modulatory model of amygdala functioning (for extended discussion, see above) that suggests that amygdala activation during encoding facilitates long-term consolidation of emotional information by modulating the declarative memory system elsewhere in the brain. It is thought that at shorter delays

little consolidation will have taken place, and hence the amygdala's activity during encoding will not be correlated with immediate memory performance. Moreover, although the amygdala is involved in modulating storage processes in other brain regions, it is not thought to be involved in the retrieval of emotional material (Cahill, 1999). Hence, it was hypothesized that while subjects would recall more emotional words as compared to neutral words (see general hypotheses) immediately following the first scan (i.e., evaluation and encoding), this short-term memory enhancement would not be related to amygdala activity during Scan 1 (i.e., encoding) or during Scan 2 (i.e., while subjects engage in a recognition memory task).

2) In contrast to the amygdala, we hypothesized that the occipital or visual cortex would show an increase in activation to the presentation of words irrespective of word type (i.e., an averaged time-locked response across unpleasant and neutral trials). We also hypothesized that this overall response in the occipital cortex to words (i.e., unpleasant and neutral) would be positively correlated with the selective amygdala response to the unpleasant words. This hypothesis was based on recent studies by Morris et al. (1997, 1998) which demonstrated that while occipital activity increased to facial expressions irrespective of emotional valence, the overall occipital response to faces was positively correlated with amygdala activation to threat-related (i.e., fear), but not non-threatening (i.e., neutral and happy), facial expressions. These findings are consistent with the notion that amygdala activation in response to visually presented aversive stimuli can influence, in a category- specific way, early visual processing in the occipital cortex.

Anterior Cingulate Hypotheses

Based on a number of recent studies that have all demonstrated selective activation of the affective division of the anterior cingulate while attending to a variety of affective stimuli (Whalen, Bush et al., 1998), including emotional words, it was hypothesized that the emotional, but not the neutral, lexical stimuli presented in the current study would selectively activate the affective division of the anterior cingulate (i.e., BA 24 and 32). It should be noted that, similar to the ventromedial prefrontal cortex, the "subgenual" region of the anterior cingulate (BA 25), also a part of the affective division, is extremely vulnerable to signal dropout associated with susceptibility from sinus space, and hence functional data from this region was not expected.

Retrosplenial Cortex Hypotheses

Based largely on studies by and the extensive literature review by Maddock (see Maddock, 1999), the retrosplenial cortex has been implicated in the selective perception/evaluation of negatively valenced emotional words. In addition, Maddock's review of the literature suggests a special role of this area in facilitating emotional memory processes, including immediate recall of emotional versus neutral words (Maddock & Buonocore, 1997). Hence, it was hypothesized that in addition to demonstrating increased activation to the unpleasant versus neutral words used in the current paradigm, the retrosplenial response would also be positively correlated with immediate recognition memory performance for the emotional but not neutral words.

Right Posterior Cortex Hypotheses

Based primarily on the unilateral brain-damaged literature reviewed above which suggests that the right posterior cortex (i.e., temporal and parietal lobes) is specialized for

the perception of emotional information, we hypothesized that selective activations in this ROI to the emotional condition would demonstrate greater right- than left-hemisphere activation as confirmed by a higher order interaction involving both word condition (unpleasant vs. neutral) and hemisphere (right vs. left) (see Statistical Analysis section below).

Methods

Subjects

Nine women (mean age, 28.2 years; s.d., 4.7 years; range, 23 – 38 years) participated in this study. All were right-handed, native English-speakers with an estimated verbal IQ in the average or above average range (Mill Hill vocabulary test [Raven, 1982]: mean verbal IQ estimate [Peck, 1970] = 111; SD = 7.5). Handedness was determined using the Coren, Porac, and Duncan (1979) inventory. Subjects had no history of psychiatric, neurological, or other major medical illness, and never were treated with psychotropic medications. Written informed consent was obtained from all subjects, and each subject was paid for participation. To eliminate sex differences and improve statistical power, only females were scanned in the current study.

Procedures

Measure of State Anxiety

State anxiety was measured with the State Trait Anxiety Inventory (STAI; Spielberger et al., 1970; range of possible scores: 20 to 80) both immediately before and immediately after scanning. During the second administration, subjects were instructed to complete the STAI in terms of their experience inside the scanner. These measures

were used to examine changes in subject's state anxiety with respect to the scanning procedure.

Emotional Decision Scan

The words used in the current study were selected from the database of Toglia and Battig (1978) (see Table 1a), which include 2,854 words that have been rated on 7-point scales for concreteness (from 1 [low concreteness] to 7 [high concreteness]), imagery (from 1 [low imagery] to 7 [high imagery]), and pleasantness (from 1 [unpleasant] to 7 [pleasant], with 4 as the neutral midpoint). For the current study, 30 highly unpleasant words and 30 neutral words (mean pleasantness ratings = 2.1 vs. 4.0 on a 7-point scale) that do not differ significantly on word length (mean word length = 5.4 letters [range: 3-9] vs. 5.7 [range: 3-11], $P = 0.509$), word frequency (Francis & Kucera, 1986; mean frequency of occurrence = 62.1 vs. 61.8 per million, $P = 0.989$), concreteness (mean concreteness ratings = 4.4 vs. 4.7 on a 7-point scale; $P = 0.289$), and imagery (mean imagery ratings = 5.0 vs. 4.7 on a 7-point scale; $P = 0.152$) were selected. Although words were not specifically matched for part of speech, both lists contained nouns, verbs, adjectives, and adverbs.

The selected words were used to generate unpleasant and neutral word sets, such that each word set comprised a unique combination of three words. Word sets were presented in eight alternating unpleasant and neutral blocks (4 cycles; see Figs. 1a & b). A 2- to 3-min. break occurred halfway through the scan to allow acquired data to be transferred to a remote computer workstation for storage and analysis. Each block began with a 2-s cue indicating whether the block consisted of unpleasant or neutral trials (see Fig. 1b). Five word set trials were presented during each block, each appearing for 4 s

with a 2-s inter-stimulus interval (ISI). During each ISI, a centrally placed fixation-cross replaced the word set. During each ISI, a centrally placed fixation-cross will replace the word set. The total duration of each block of trials including the cue was 32 s. Thus, the BOLD response will be recorded to four blocks of unpleasant words and four blocks of neutral words. A 20-s resting baseline preceded the first block of trials, and a 24-s resting period separated all subsequent blocks of trials, during which subjects viewed a central fixation cross. During each trial, a word set was projected to the center of the subject's field of view via an SVGA computer-controlled projection system that presented stimuli to a rear-projection screen located at the entrance of the magnet bore. Subjects viewed stimuli projected to the screen via a 1.5-inch x 3-inch mirror attached to the head coil and positioned approximately 6 inches from and directly above the subject's eyes. Each word appeared twice over the course of the scan (i.e., first presentation occured during the first two blocks, and the second presentation during the last two blocks of each stimulus type) within unique word sets. Word sets were presented in a fixed pseudo-randomized order across the blocks with the condition that a word did not reappear until all words had been presented once. The position of a word within a word set was counterbalanced across presentations of that word. The sequence in which blocks of unpleasant and neutral trials were presented was counterbalanced across subjects by reversing the trial order for four of the nine subjects.

Immediately before scanning began, subjects were given 10 practice trials (5 unpleasant and 5 neutral). The negative and neutral words presented during practice did not overlap with the experimental words and were selected from the list of Brown and

Ure (1969), which includes 650 words that were also rated for pleasantness using a 7-point scale.

During unpleasant blocks, subjects were instructed to select the most unpleasant or most threatening word from the three negatively valenced words (word set) presented on each trial. Subjects were instructed to base their decision on their personal knowledge of and experience with the concepts and connotations conveyed by the words. Similarly, during neutral blocks, subjects selected the word they deemed to be the most neutral (e.g., nonemotional or non-threatening) word from each word set. Subjects indicated their response for each trial by pressing one of three buttons on a response pad.

Recognition Memory Scan

Immediately following the first scan (described above), a second scan was performed to assess recognition memory for the words presented (targets) during the emotional decision task. Sixty additional new words were selected from Toglia and Battig (1978) to serve as foils in the memory scan (30 highly unpleasant and 30 neutral). Given the limited number of words available, particularly for the unpleasant category, the foils were matched to the targets (see Table 1b) on word length only (mean word length of unpleasant targets = 5.4 letters [range: 3-9] vs. unpleasant foils 5.7 [range: 3-10], P = 0.506; mean word length of neutral targets = 5.7 letters [range: 3-11] vs. neutral foils 5.7 [range: 3-10], $P = 1.00$).

Together, 120 words (60 previously seen and 60 not previously seen) were presented one at a time in the center of the subject's field of view in 12 alternating unpleasant and neutral blocks (6 cycles; see Fig. 2a). Each block consisted of a fixed random sequence of 10 words, with a 0.50 probability of being a previously seen word

(see Fig. 2b). Each word was presented for 2 s and was immediately followed by the next word. Hence, the total duration of each block of trials was 20 s. A 20-s resting period preceded the first block of trials and separated successive blocks, during which time subjects viewed a central fixation cross. The sequence in which blocks of unpleasant and neutral trials was presented was counterbalanced across subjects by reversing the trial order for four of the nine subjects. Subjects were instructed to press a key with their index finger whenever they recognized a word from the previous scan.

Image Acquisition and Postprocessing

An initial T1-weighted sagittal localizer (spoiled gradient recall acquisition in a steady state [SPGR]) sequence was acquired using a 1.5 Tesla GE Horizon LX scanner (General Electric, Milwaukee, WI). Subsequently, 14 axial spin-echo T1-weighted images were acquired, encompassing the whole brain (TE/TR = 18/600 ms, FOV = 23 mm^2, slice thickness = 5 mm, skip = 2.5).

Echoplanar magnetic resonance brain images were acquired with a multi-slice 2D EPI sequence (64 x 64 matrix, 23 cm^2 FOV, TE = 40 ms, TR = 2000 ms, 5-mm thickness, 2.5-mm gap) every 2 s over the course of the scan. For the first (emotional decision) scan, 244 T2*-weighted images depicting BOLD contrast (Ogawa, Lee, Nyak, & Glynn., 1990) were acquired over 8 min and 8 s (488 s). For the second (recognition memory) scan, 260 images were acquired over 8 min and 40 s (520 s). Each image consists of 14 near-axial, non-contiguous slices, providing whole-brain coverage.

Preprocessing of the raw fMRI signal for each scan involved the removal of the mean, detrending, and digital filtering to eliminate low and high frequencies outside the range of the primary blood flow response. The mean and linear trends were removed

using a least squares line-fit from each continuous data set. A pixel-by-pixel fast Fourier transform (FFT) was then performed, and all frequency components below (0.018) and above (0.071) Hz were removed. These cut-off frequencies were selected to reduce signal contributions slower than 1 cycle in 40 seconds (greater than the block length) and faster than one cycle in 15 s (about one ¼ of the block length), based on the On-Off cycle period of 56 s. A new filtered fMRI image dataset will be obtained by an inverse FFT.

The 14 reconstructed anatomical and functional images were visually inspected and matched to standard axial brain slices from the Talairach and Tournoux atlas (1988). The edges of the anatomical slices for each subject were traced and midline structures identified and marked using our own image-processing system program (Multi-Image Processing-System [MIPS]). The traced edges and identified landmarks were used for co-registration of each subject's functional and anatomical data and to morph the images into a standardized stereotactic space derived from 70 normal adults (Hazlett et al., 1998). This method produces symmetrical brain images about the midline so that hemispheric contrasts can be examined. The fMRI data of consecutive images (224 for scan 1 and 260 for Scan 2) were arranged as a pixel time series with each pixel in the image having entries representing the 2-s time points.

Statistical Analyses

Behavioral Data

With respect to the behavioral memory data, it was hypothesized (see above) that subjects would recall more emotional as compared to neutral words, immediately following the first scan. To assess this hypothesis, the percent of target words recalled (hits) on the recognition memory scan was calculated for each subject, and a two-tailed

paired t-test was conducted to compare memory performance for the unpleasant versus neutral word conditions.

Second, with respect to the state anxiety data, it was predicted (see above) that subject's self-reported state anxiety as measured by the STAI (Speilberger et al., 1970) would significantly increase when comparing scores immediately before entering the scanner to scores reflecting their anxiety level during the scanning session (measured immediately after the scan). To assess this hypothesis, a two-tailed paired t-test, comparing subject's scores for the two time points of the state anxiety measure (during scanning as assessed retrospectively and before scanning), was conducted.

Whole Brain Data

Although the current study focused on a number of ROIs (see above), whole brain images were acquired and analyzed on an exploratory basis for both the emotional decision and immediate recognition memory scans and summarized in tabular form (see Tables 2-5). Whole brain data are described to help establish the specificity of findings with respect to the ROIs and to facilitate comparisons with other studies.

The relative pixel intensity of the fMRI BOLD signal, which served as the dependent variable for all imaging analyses, was averaged across the four unpleasant and four neutral blocks of trials for the emotional decision scan (see Figure 1a and 1b) and across the six blocks of unpleasant and six blocks of neutral trials for the immediate recognition memory scan (see Figure 2a and 2b). For the emotional decision scan (scan 1), this yielded an averaged block of unpleasant and neutral trials consisting of a 28-image or 56-s time course. For the recognition memory scan (scan 2), this yielded an averaged block of unpleasant and neutral trials consisting of a 20-image or 40-s time

course. The 28-image time course for Scan 1 (see abscissa in Figure 3) included 6 images from the preceding resting period (12 s), 16 images from the actual block of trials including the cue (32 s), and 6 images from the subsequent resting period (12 s). The 20-image time course for Scan 2 included 5 images from the preceding resting period (10 s), 10 images from the actual block of trials (20 s), and 5 images from the subsequent resting period (10 s). The relative intensity of the BOLD signal was subjected to pixel-by-pixel two-way repeated-measures analysis of variance (ANOVA) involving Word Condition (unpleasant vs. neutral) and Time Course (28 images for Scan 1 and 20 images for Scan 2).

For whole brain analyses, the significance threshold was set at $P < 0.001$. In addition, only clusters with at least four contiguous pixels were included in analyses (see Tables 2-5). A significance threshold of $P < 0.001$ was chosen since this statistical threshold is most commonly used in functional neuroimaging studies (Maddock, 1999) and, thus, facilitates comparisons with studies from other research teams. The additional constraint of a four-pixel cluster-size has been used by other research groups (Lang et al., 1997) and is thought to be an adequate and appropriate correction for multiple comparisons in exploratory analysis of whole brain imaging data (Forman et al., 1995). All main effects and interactions that occurred in the ROIs and that met the above state statistical criteria were visually inspected. Only those main effects or interactions that demonstrated a time-locked BOLD response to stimulus onset and offset were considered as significant.

Region of Interest Data

Analyses of Variance. Coordinates from the Talairach atlas were used to identify activation in brain areas that served as ROIs. Given that the boundaries of the amygdala are relatively clearly demarcated in the Talairach atlas, the anatomical center and extent of the amygdala region were obtained *a priori* via the Talairach and Tournoux (1988) atlas coordinates (center: 23, -6, -12; with approximately a 10-mm diameter corresponding to 3 pixels; 3.6 mm^2/pixel). It should be noted that without very high-resolution MRI templates for each subject, differentiation of the amygdala from the end of the hippocampus is difficult. However, using coordinates from the Talairach atlas to identify activation in this study will allow for the replication of our findings by other imaging centers.

This 3-pixel diameter region, centered on the left and right amygdala, was subjected to a two-way repeated-measures analysis of variance (ANOVA) involving Word Condition (unpleasant vs. neutral) and Time Course (28 images for Scan 1 and 20 images for Scan 2). A 3-way Word Condition (unpleasant vs. neutral) x Time Course (28 images for Scan 1 and 20 images for Scan 2) x Hemisphere (right vs. left) ANOVA was conducted to assess hemispheric asymmetries. Again, only those main effects and interactions that demonstrated a time-locked BOLD response to stimulus onset and offset, upon visual inspection, were considered as statistically significant.

In contrast to the amygdala, the boundaries of the remaining ROIs are not clearly specified in Talairach space. Moreover, activation sites that have been reported in previous studies with respect to these regions vary considerably from study to study. Thus, whole brain data, as described in Tables 2-5, were used to identify activation sites

within these ROIs. Any cluster of pixels identified during the whole brain analyses that demonstrated a significant 2-way Word Condition (2) by Time Course (28) interaction and that falls within the Talairach space of the ROIs was further analyzed with repeated-measures ANOVA to assess hemispheric asymmetries and habituation effects (see above). Since the exact Talairach coordinates of these ROIs could not be specified *a priori*, the statistical criteria used for the whole brain analyses (see above) were also applied to these analyses to protect against Type I error.

Correlational Analyses. Correlational analyses (Pearson r) were also conducted to test several of the above stated a priori and exploratory hypotheses. These analyses were only conducted for pixel clusters within ROIs that demonstrated a significant 2-way Word Condition by Time Course interaction (i.e., where the BOLD response to the unpleasant words was greater than the response to the neutral words, thus demonstrating a selective response to the emotional manipulation). For these clusters, the peak BOLD response of the pixel of maximal activation within the cluster was used. The peak BOLD response for the unpleasant and neutral word conditions was derived by subtracting the maximal pixel intensity value during the stimulus-on period (averaged across the 4 blocks of each trial type) from the average value of the baseline preceding the stimulus-on period.

For correlational analyses involving a priori hypotheses, significance thresholds were set at $P < 0.05$. For exploratory analyses, findings will be corrected using a Bonferroni procedure to protect against inflated Type 1 error rates due to multiple comparisons.

Results

Behavioral data

During the emotional decision task scan, all subjects made an appropriate response (chose one word from each word set) on 100 % of the trials. This demonstrates that subjects attended to the stimuli and responded as instructed throughout the entire duration of the scan[1]. During the recognition memory scan, subjects recalled more emotionally negative as compared to neutral words. Overall, 91 $\pm$ 4.1% of the unpleasant and 82 $\pm$ 6.8% of the neutral targets were correctly identified (paired $t[8] = 3.59$, $P = 0.007$), demonstrating a significant memory enhancement for the unpleasant words.

State anxiety ratings went from a mean score of 33.3 $\pm$ 9.1 before scanning to 44.2 $\pm$ 8.8 after scanning (paired $t[8] = 2.69$, $P = 0.027$), demonstrating an overall significant increase in anxiety presumably due to the scanning procedure. Difference scores for each subject were also calculated (i.e., score during scan – prescan score). These scores ranged from -8 (relative decrease in anxiety during scan) to 24 (relative increase in anxiety during scan), with a mean of 8.9 $\pm$ 9.9 and a median of 10.

Whole Brain Exploratory Analyses of Variance

For scans 1 and 2, the main effects of Time Course (see Tables 2 and 3) and the two-way Word Condition (2) by Time Course (28) interactions (see Tables 4 and 5) are summarized in tabular form for clusters of pixels that met the above stated significance criteria (i.e., $P < 0.001$ for clusters with at least four contiguous pixels). For the main

[1] As a manipulation check, we questioned subjects immediately following the experiment about their experience in the scanner. Debriefing revealed that all subjects found the unpleasant word sets to be highly unpleasant, particularly when compared to the neutral word sets. This agreed with findings from our pilot work in which a number of individuals were asked to perform and assess the validity of the task. In the current study, subjects were not asked to rate each word separately in terms of emotional valence. Future studies using a similar lexical paradigm may find such rating data useful as an additional manipulation check in order to assess the degree to which subjects agree with the normative data used to select the lexical stimuli.

effect of Time Course, activations are described for sites in which the BOLD response to the unpleasant words did not significantly differ from the BOLD response to the neutral words. Both significant increases (see Table 2a) and decreases (see Table 2b) are included. For the 2-way Word Condition by Time Course interaction, activations are described for sites in which the BOLD response to the unpleasant condition demonstrated a greater increase in activation than the response to the neutral condition (see Table 4a & 5a) and for sites in which the BOLD response to the neutral condition demonstrated a greater increase in activation than the response to the unpleasant condition (see Table 4b & 5b). Tables include the location (i.e., verbal label of activation site, Brodmann area if applicable, and Talairach coordinates) of the maximum pixel within statistically significant clusters, the number of pixels within each cluster (Area of activation), and the corresponding F-value for each cluster of pixels.

Regions of Interest Analyses of Variance

Amygdala Activation

Emotional Decision Scan. A two-way ANOVA (Word Condition x Time Course) for the 3-pixel diameter ROI chosen *a priori* from the Talairach atlas (ROI: left and right amygdala) revealed a significant Word Condition x Time Course interaction for the right amygdala ($F[27,216]=5.95$, $P < 0.0001$), demonstrating greater time-locked activation for unpleasant than neutral words. Pixel-by-pixel ANOVAs surrounding the center of the right amygdala also revealed a significant Word Condition x Time Course interaction ($F[27,216]=5.81$, $P < 0.001$) for a total of 9 contiguous pixels (see Table 4a). The pixel with the maximal response was located approximately at the center of the amygdala (Talairach coordinates: 26, -6, -12) and was highly significant for the Word Condition x

Time Course interaction (see Fig. 3). A significant (F[27,216]=2.29, P = 0.0006) main effect of Time Course was also observed at this pixel (see Fig. 3).

A three-way ANOVA (Word Condition x Time Course x Hemisphere), involving the right amygdala, revealed a significant Time Course x Hemisphere interaction (F[27,216] = 2.84, P < 0.0001), demonstrating greater right- than left sided activation for both the unpleasant and neutral words. However, the Word Condition x Hemisphere and the Word Condition x Time Course x Hemisphere interactions were not significant.

The ROI analysis (i.e., for the 3-pixel diameter ROI chosen *a priori* from the Talairach atlas) centered on the left amygdala did not reveal a significant Word Condition x Time Course analysis (F[27,216]= 1.31, P < 0.10) or a Main Effect of Time Course (F[27,216]= 2.96, P < 0.10).

Immediate Recognition Memory Scan. Analyses, similar to those described above for the emotional decision task, were conducted for the recognition memory scan (scan 2) to examine the amygdalar response while subjects identified words presented during the first scan. The ROI analysis (i.e., for the 3-pixel diameter ROI chosen *a priori* from the Talairach atlas) and pixel-by-pixel ANOVAs around the center of the right and left amygdala revealed no significant Word Condition x Time Course interaction or significant increases to word recognition in general. These findings suggest that, unlike the emotional decision task scan (see above), amygdala activation was not elicited during the recognition of unpleasant or neutral words.

Orbitofrontal and Medial Frontal (BA 9) Cortex

Emotional Decision Scan. A cluster of 7 pixels extending bilaterally into both the left and right medial frontal gyrus (BA 9; Talairach coordinates: -2, 47, 24) revealed a

significant Word Condition x Time Course interaction (F[27,216]=6.54, $P < 0.0001$), demonstrating a time-locked response that was greater to the unpleasant than neutral words (see Table 4a). The pixel with the maximal response was located on the left side and was significant for the Word Condition x Time Course interaction (see Fig. 4). A main effect of time was not observed at this site. A three-way ANOVA (Word Condition x Time Course x Hemisphere), involving the activation site in medial frontal gyrus, revealed a significant Time Course x Hemisphere interaction (F[27,216] = 6.61, $P <$ 0.0001), demonstrating greater left than right-sided activation for both the unpleasant and neutral words. However, the Word Condition x Hemisphere and the Word Condition x Time Course x Hemisphere interactions were not significant. Hence, although the overall response to words was greater on the left than right side, the selective response of this ROI to the unpleasant words, as confirmed by the Word Condition by Time Course interaction (see above), occurred in both hemispheres. As expected, Orbitofrontal activation was not observed, presumably, due to susceptibility artifacts.

Immediate Recognition Memory Scan. Pixel-by-pixel ANOVAs in the orbitofrontal and medial frontal (BA 9) cortex did not revealed a significant Word Condition x Time Course interaction for the immediate recognition memory scan. However, significant main effects of Time Course were observed in the medial frontal gyrus (BA 9) (see Tables 3a & b). Similar to the amygdala, these findings suggest that, while the medial frontal gyrus (BA 9) is involved in making emotional decisions (see above), it is not selectively elicited during the recognition of previously seen unpleasant words.

Anterior Cingulate

Emotional Decision Scan. Pixel-by-pixel two-way ANOVAs in the anterior cingulate (BA 24, 25, 32, or 33) did not reveal significant Word Condition x Time Course interactions. However, it should be noted that a larger portion of the affective cingulate is found in the "subgenual" region (BA 25). This region of the anterior cingulate is highly vulnerable to susceptibility artifacts (see discussion above) and, therefore, could not be reliably visualized in the current study. Main effects of Time Course in the anterior cingulate were observed (see Table 2b).

Immediate Recognition Memory Scan. Pixel-by-pixel ANOVAs in the anterior cingulate did not reveal significant Word Condition x Time Course interactions for the immediate recognition memory scan. A number of different sites throughout the anterior cingulate did reveal significant main effects of Time Course, demonstrating both time-locked increases and decreases in activation to words in general (see Table 3a & b).

Retrosplenial Cortex

Pixel-by-pixel ANOVAs in the posterior cingulate did not reveal significant Word Condition x Time Course interactions for the emotional decision or immediate recognition memory scans. During the immediate recognition memory scan, a number of sites in the posterior cingulate did, however, reveal main effects of Time Course (see Table 3a & b). One of these sites demonstrating a time-locked decrease during the immediate memory scan (Talairach coordinates: -13, -56,12; $F[27,216]=4.1$, $P < 0.0001$) was located in the retrosplenial cortex (BAs 29 and 30). This finding suggests that the retrosplenial cortex becomes less active rather than more active during the immediate recognition of words.

Insular Cortex

Pixel-by-pixel ANOVAs in the left insular cortex revealed two sites in which a significant Word Condition x Time Course interaction for the emotional decision scan was observed (Talairach coordinates: -33, 0, -4; F[27,216]=3.73, $P < 0.0001$; Talairach coordinates: -27, 20, 4; F[27,216]=3.41, $P < 0.0001$). However, both of these sites demonstrated a greater time-locked increase in activation to neutral than unpleasant words (see Table 4b). No main effects of Time Course were observed during this scan. Insular activation (i.e., main effects of Time Course or Word Condition x Time Course interactions) was not observed during the immediate recognition memory scan.

Posterior Right Hemisphere Cortex

Emotional Decision Scan. Pixel-by-pixel ANOVAs in the posterior right hemisphere (i.e., parietal and temporal lobes) revealed two sites in the right temporal lobe (i.e., a 5-pixel cluster in the middle temporal gyrus [BA 21], Talairach coordinates: 63, -0.5, -12; F[27,216]=4.43, $P < 0.0001$; and a 6-pixel cluster in the superior temporal gyrus [BA 39], Talairach coordinates: 54, -56, 20; F[27,216]=2.98, $P < 0.0001$) that demonstrated a greater time-locked increase in activation to unpleasant than neutral words. The pixels of maximal activation within these clusters were also highly significant for the Word Condition x Time Course interaction (see Figs. 5 and 6). Pixel-by-pixel three-way ANOVAs (Word Condition x Time Course x Hemisphere) in the temporal lobe revealed a significant Word Condition x Time Course x Hemisphere interaction for the activation site in the right middle temporal gyrus (F[27,216]=4.61, $P < 0.0001$), demonstrating a significantly greater selective response to the unpleasant than neutral words in the right versus left hemisphere. This finding is consistent with the

putative role of the right posterior cortex in the perception of negatively valenced emotional information.

It should be noted that no Word Condition x Time Course interactions demonstrating a selective increase to the unpleasant words were observed in any part of the parietal lobe, including the somatosensory cortex. Numerous sites, however, in the temporal and parietal lobes demonstrated main effects of time course (see Table 2a,b).

A main effect of Time Course (i.e., general increase in activation to both unpleasant and neutral words) was observed in a cluster of 4 pixels located in the posterior part of the left superior temporal lobe, AKA Wernicke's area (BA 22; Talairach coordinates: -63, -53, 12 $F[27,216]=3.00$, $P < 0.0001$) (see Fig. 7 for the response from the pixel of maximal activation). A two-way Time Course x Hemisphere interaction ($F[27,216]=4.53$, $P < 0.0001$) was also observed for a cluster of 10 pixels at this site (Talairach coordinates: -61, -35, 20), demonstrating greater left-sided than right-sided activation. This finding confirms the asymmetrical involvement of the posterior superior temporal gyrus in the processing of verbal information.

Finally, with respect to the specificity of the right posterior cortex in processing emotional stimuli, it should be noted that a significant Word Condition x Time Course interaction, demonstrating a selective increase in activation to the unpleasant words, was also observed in the left temporal lobe (Talairach coordinates: -44, -31, -4; $F[27,216]=5.46$, $P < 0.0001$). However, a greater left hemispheric response to the unpleasant words was not observed at this left-sided site (i.e., a significant Word Condition x Time Course x Hemisphere interaction).

Immediate Recognition Memory Scan. Pixel-by-pixel ANOVAs in the posterior right hemisphere (i.e., parietal and temporal lobes) did not reveal any sites that demonstrated a time-locked selective response to the emotional condition in the right temporal lobe. Main effects of Time Course for this scan were observed in the right and left temporal and parietal lobes (see Table 2a & b).

Regions of Interest Correlational Analyses

Amygdala and Memory Performance Data

A correlational analysis (two-tailed Pearson r) was conducted to assess the possibility that the enhanced behavioral performance on the recognition memory task for the unpleasant words was related to the right amygdala activation observed during Scan 1 (see Amygdala Hypothesis #1). The peak BOLD response of the pixel of maximal activation (Talairach coordinates: 26, -6, -12) in the right amygdala during the presentation of unpleasant word sets was not significantly correlated with the number of correct responses (Hits) on the memory test (unpleasant words: $r = -0.11$, df = 7, $P = 0.782$; neutral words: $r = 0.08$, df = 7, $P = 0.84$). Similarly, the peak BOLD response of the pixel of maximal activation (Talairach coordinates: 26, -6, -12) in the right amygdala during the presentation of neutral word sets was not significantly correlated with the number of correct responses (Hits) on the memory test (unpleasant words: $r = -0.05$, df = 7, $P = 0.899$; neutral words: $r = 0.48$, df = 7, $P = 0.196$). These findings suggest that the differential enhancement in recognition memory for the unpleasant words as described above (see behavioral results) is not related to the increase in amygdala activation observed during scan 1. Hence, the observed selective amygdala activity for the unpleasant words during during scan 1 (i.e., memory encoding) did not appear to account

for the enhanced short-term recall of unpleasant versus neutral words. Similar correlations were not conducted for the immediate recognition memory scan since amygdala activation was not observed during this particular task.

Amygdala and Occipital Cortex Activation

Morris et al. (1998) have proposed that the amygdala response to emotional stimuli modulate early processing of visually presented information in the occipital cortex in a category-specific way. Hence, a correlational analysis (one-tailed Pearson r) was conducted to assess the hypothesis (see Amygdala Hypotheses #2 above) that the increased activation observed in the right amygdala to the evaluation of unpleasant but not neutral words during scan 1 is positively correlated with the response observed in the occipital cortex to the visual presentation of words [2] (see Fig. 8).

The correlation analysis revealed that the peak BOLD response in the right amygdala to the unpleasant words was highly correlated ($r = 0.87$, df = 7, $P = 0.001$) with the overall peak BOLD response (i.e., averaged across Word Condition) in the occipital cortex (Talairach coordinates: -25, 85, 12). On the other hand, the peak BOLD response in the right amygdala to the neutral words did not correlate with the occipital response to words ($r = -0.04$, df = 7, $P = 0.456$) (see Fig. 9). Correlation analyses between the left amygdala and the occipital cortex were not performed since significant amygdala activation was not observed on the left side. Also, correlational analyses between

[2] Pixel-by-pixel two-way ANOVAs (i.e., Word Condition x Time Course; see Table 2a) in the visual cortex (Talairach coordinates: -25, -85, 12; Brodmann areas 17, 18, and 19) revealed widespread bilateral activation confirmed for the Main Effect of Time Course (108 contiguous pixels; $F[27,216] = 16.23$, $P < 0.0001$), but not for the Word Condition x Time Course interaction during the emotional decision scan. Similar results in visual cortex were observed for the immediate recognition scan (See Table 3a). Here 31 contiguous pixels on the left side (Talairach coordinates: -29, -82, 12; $F[19,152] = 17.67$, $P < 0.0001$) and 28 pixels on the right side (Talairach coordinates: 21, -93, 12; $F[19,152] = 9.20$, $P < 0.0001$) revealed a significant main effect of Time Course. This time-locked activation in primary and secondary visual cortices (Brodmann areas 17, 18, and 19) to both unpleasant and neutral words is consistent with the putative role of the occipital cortex in processing visually presented information.

amygdala and occipital activation for the immediate recognition memory scan were not performed since amygdala activation was not observed during this task.

Retrosplenial Cortex and Memory Performance Data

In contrast to the amygdala, it was hypothesized (see above) that the response of the retrosplenial cortex to the unpleasant words would be positively correlated with immediate recognition memory performance for the unpleasant but not neutral words (see Retrosplenial Cortex Hypotheses above). However, since this region did not demonstrate selective activation to the emotional condition used in the current study, correlational analyses similar to those conducted for the amygdala were not conducted.

Exploratory Correlational Analyses

Correlational analyses (one-tailed Pearson r) were conducted on an exploratory basis to assess the degree to which the observed increases in activation to the unpleasant words in the various ROIs (i.e., for scan 1: right amygdala, medial frontal cortex [BA 9], right temporal lobe, and right precentral gyrus; for scan 2: right temporal lobe) were positively correlated to each other and, hence, possibly function as an integrated emotional processing system. One-tailed tests were used here because only positive correlations were expected. This expectation was based on the fact that significant ROI activation sites were by definition required to demonstrate a greater time-locked increase to the unpleasant than to the neutral words.

Of the five ROI activation sites that demonstrated a significantly greater increase to the unpleasant than neutral words during scan 1 (i.e., in the right amygdala, medial frontal gyrus [BA 9], right middle temporal gyrus, right superior temporal gyrus, and right precentral gyrus), only the peak BOLD responses observed in the right amygdala

and right middle temporal gyrus (Talairach coordinates: 63, 0, -12) were significantly correlated ($r = 0.82$, $P = 0.004$; Bonferoni corrected alpha level = .005) (see Table 6a for correlation matrix). This finding suggests that these two ROIs may function as part of a neural network that mediates the processing of unpleasant, threat-related information.

Similar correlational analyses were not conducted for scan 2, since the ROI activation sites for this scan did not demonstrate a selective time-locked increase in activation to the unpleasant words (see above).

As described above, two-tailed correlations revealed that the selective activation in the right amygdala to the unpleasant words during the emotional decision scan (e.g., memory encoding) was not related with the memory performance for the unpleasant words (see above), as measured by an immediate recognition memory test. Similarly, no significant correlations were observed between the memory performance for the unpleasant or neutral words and the corresponding peak BOLD response (i.e., response to the unpleasant and neutral words respectively) from any of the other ROI activation sites (see Table 6b for correlation matrix). This finding suggests that the ROI activations observed in the current study during scan 1 (i.e., memory encoding) do not appear to account for the enhanced short-term recall of the unpleasant vs. neutral words

To assess the effect of anxiety due to the scanning procedure on the BOLD response, two-tailed correlational analyses were conducted between the difference scores for the two time points of the state anxiety measure (during scanning as assessed retrospectively and before scanning) and the peak BOLD response to the unpleasant and neutral words from the pixel of maximal activation in each of the ROI activation sites (i.e., right amygdala, medial frontal gyrus [BA 9], right middle temporal gyrus, right

superior temporal gyrus, and right precentral gyrus). State anxiety difference scores (scan report minus pre-scan report) were not significantly correlated at the corrected Bonferoni alpha level ($P < .01$) with any of the ROI responses to the unpleasant or neutral words (see Table 6c for correlation matrix). Hence, while self-reported state anxiety levels did increase as a result of the scanning procedure (see above), this increase was not related to the observed BOLD response to the word-type condition used in the current study. While it could be argued that increases in self-reported state anxiety levels due to the scanning procedure (see above) may influence and thus confound brain activations in response to experimental manipulations (e.g., presentation of unpleasant versus neutral words), the lack of a significant correlation between the state anxiety difference scores and ROI activation sites here argue that this was not the case in the current study.

Discussion

To date, a plethora of lesion and imaging studies have implicated a number of brain regions in the processing of emotional information. These areas, which also served as ROIs in the current study, include the amygdala, the ventromedial sectors of the prefrontal cortex, the affective division of the anterior cingulate, the retrosplenial cingulate, the insular cortex, and the right posterior cortex. An important aspect of emotional processing involves the appraisal (i.e., perception and evaluation) of stimuli in terms of the degree to which they threaten the survival and/or well being of an organism. Another important aspect of emotional processing involves the formation of emotional memories that are related to such salient stimuli and that facilitate responses that increase the likelihood of survival and/or the well being of the organism during future encounters. An extensive review of the emotion literature (see above) has provided evidence that the

ROIs selected for the current study are part of an extended neural network of brain structures which mediate the appraisal of emotionally significant stimuli and, to varying degrees, the formation of emotional memories. Recent human lesion and imaging research have placed special emphasis on the amygdala, providing evidence that the amygdala plays a central role in mediating the appraisal of emotionally arousing, and particularly threatening, stimuli. In addition, the amygdala has been implicated in the modulation of memory storage and consolidation processes and in the early processing of salient visual information in the visual cortex. Much of the evidence implicating these ROIs in emotional processing has come from studies that have used emotional facial expressions, vocal expressions, and highly provocative scenes as stimuli. To date, only a few imaging studies have used lexical stimuli to probe the neural substrates of emotional processing.

The primary goal of the current fMRI study was to assess the extent to which the above-mentioned ROIs are recruited in response to the appraisal and recall (i.e., immediate recognition memory) of highly unpleasant words. A special focus is placed on the amygdala, since this brain region is thought to sit at the hub of the neural network mediating emotional processing.

Overall, our results revealed a time-locked selective emotional response during the emotional decision scan in the following ROIs: the right amygdala, the medial frontal gyrus (BA 9), and the right middle temporal gyrus. A selective response, however, was not observed in the orbitofrontal cortex, affective division of the anterior cingulate, retrosplenial cingulate, or insular cortex. Furthermore, for the immediate recognition scan, selective time-locked responses were not observed in any of the ROIs.

The current study also assessed the laterality of each ROI activation site via an analysis specifically testing for hemispheric asymmetries (i.e., Word Condition x Time Course x Hemisphere ANOVA). First, while amygdala activation to the unpleasant words was statistically confirmed only in the right hemisphere, a significant Word Condition x Hemisphere or Word Condition x Time Course x Hemisphere interaction for the three-pixel diameter ROI centered on the amygdala was not observed. Similarly, higher-order interactions involving Word Condition and Hemisphere were also not observed for the ROI activation site in the medial frontal gyrus (BA 9). On the other hand, the ROI activation site in the right middle temporal gyrus revealed a lateralized response to the unpleasant words as confirmed by a significant Word Condition x Time Course x Hemisphere interaction.

To assess a number of secondary hypotheses, correlational analyses were also conducted. In summary, these analyses revealed a significant correlation between activation in the right amygdala and right temporal lobe. Moreover, while subjects showed significantly enhanced short-term memory for the emotional as compared to neutral words on a test of immediate recognition memory, their memory performance was not correlated with any of the observed ROI activation sites during scan 1 (encoding) or scan 2 (recognition). Correlational analyses revealed that the increase in state anxiety experienced by subjects while in the scanner did not correlate with the observed ROI responses to the unpleasant or neutral words. Finally, as predicted, the response observed in the occipital cortex to words in general (i.e., unpleasant and neutral) was strongly correlated with right amygdala activation in a category specific way (i.e., to the unpleasant but not neutral words).

With respect to the findings for the amygdala, consistent with the findings of Kiehl et al. (1998), the present study did find a robust BOLD signal in the right amygdala that was greater for unpleasant than neutral word sets. A number of previous imaging studies (i.e., Beauregard et al., 1997; Maddock & Buonocore1997; Whalen, Bush et al., 1998) presenting words have not reported selective amygdala activation in response to the presentation of unpleasant words. The discrepancy between the findings from the current study and those from previous studies that did not observe amygdala activation in response to the presentation of unpleasant words may be due to methodological differences. While these three studies employed more implicit processing tasks, such as passive viewing of emotional words or counting the number of negative versus neutral words on a screen, in the present study, subjects were required to explicitly evaluate the relative emotional significance of either highly unpleasant or neutral word sets in terms of their own personal experiences. For example, subjects were presented with a series of highly unpleasant word sets, such as "cancer, bomb, morgue," and asked to choose, based on their own experiences with the concepts and connotations conveyed by the words, the most unpleasant or most threatening word in each word set. During the nonemotional task, subjects were presented with sets of neutral words (e.g., "printer, cafeteria, growth") and asked to choose the most nonemotional or non-threatening word. In this way, the current study attempted to increase the emotional salience of the lexical stimuli used and thereby engage brain areas involved in evaluating aversive, threat-related information.

Although activation to unpleasant words was statistically confirmed only in the right amygdala, a more direct test of laterality (Word Condition x Time Course x Hemisphere ANOVA) did not reveal an asymmetric response for the three-pixel diameter

ROI centered on the amygdala. Hence, while our findings are suggestive of right greater than left amygdala activation, they underscore the need to perform appropriate laterality tests before claiming hemispheric asymmetries as suggested elsewhere (Davidson & Irwin, 1999a,b). Higher resolution BOLD images, larger samples, and anatomical coregistration for each subject may be necessary to confirm lateralization effects. This is particularly true since the right and left amygdalae may not be centered on the same 5-mm thick slice across subjects.

With respect to the orbitofrontal cortex, the current fMRI study was unable to image activation in this region due to BOLD signal dropout (AKA susceptibility artifacts; see above discussion). However, selective activation to the emotional condition was observed bilaterally in the medial frontal gyrus (BA 9), a region that extends dorsally beyond the ventromedial sectors and is hence not vulnerable to susceptibility artifacts. Previous work (Lane, Reiman, & Ahern et al. 1997; Lane, Reiman, & Bradley, 1997; Reiman et al., 1997) has implicated the medial frontal gyrus (BA 9) in the conscious monitoring of one's emotional state while making personally relevant decisions (Reiman et al., 2000). Selective activation in this ROI during the emotional decision scan is consistent with this view since the task required subjects to evaluate groups of highly emotional words in terms of personal experience. Interestingly, while the PET-O15 study by Beauregard et al (1997) reported orbital frontal activation in response to the passive viewing of highly negative words, it did not report medial frontal activation. Together with the current findings, the lack of activation in the Beauregard et al. study further supports the notion that the medial frontal gyrus plays a role in emotional decision-making rather than in the passive processing of emotional information.

Similar to the orbital frontal cortex, susceptibility artifacts in the ventromedial sectors of the prefrontal cortex precluded viewing a large portion of the affective division of the anterior cingulate (i.e, the subgenual region; BA 25) for analysis. Previous studies (George et al., 1994; Whalen, Bush et al., 1998), using lexical stimuli as part of an emotional Stroop paradigm, have reported activation in a more dorsal region of the "affective" anterior cingulate (i.e., BAs 24 and 32; AKA the pregenual region) that is not vulnerable to susceptibility artifacts. The current study, however, did not observe any selective activation to unpleasant words in this portion of the anterior cingulate. Task differences between the current study and previous studies most likely account for this discrepancy. In emotional Stroop studies, subjects are required to make nonemotional judgments (e.g., the color of the ink in which the words were printed or the number of times a word was written) about emotional and neutral words. The affective content of the words (e.g., sadness or anxiety) in the emotional condition of the Stroop task is thought to interfere with the Stroop task at hand, particularly when it is congruent with subjects' current or recent emotional experience or mood. Selective anterior cingulate activation is thus believed to reflect the monitoring of conflicting streams of information and the active suppression of the interfering emotional lexical content. The lack of selective anterior cingulate activation in the current study thus possibly reflects the fact that while subjects were required to simultaneously evaluate and compare the emotional connotations of a set of words that were all similar in emotional valence and intensity, the current emotional decision task did not require subjects to actively suppress information. Together, these findings lend support to a role for the affective anterior cingulate in the suppression rather than evaluation of emotional information.

With respect to the retrosplenial cortex, a recent fMRI study by Maddock & Buonocore (1997) reported selective activation in this ROI while subjects listened to single threat-related versus neutral words. The current study did not replicate this finding. Moreover, in the Maddock & Buonocore (1997) study, the only site in the entire brain that demonstrated a selective response to the emotional condition occurred in the retrosplenial cortex; in the current study, numerous brain regions demonstrated selective responses to the unpleasant word condition. These discrepancies may be accounted for by a number of methodological differences. For example, the Maddock study required 5 male and 5 female subjects to listen to 8 alternating blocks of 10 threat-related (i.e., terror, victim, injury, cancer, panic, dangerous, threatening, emergency, violence, and destroyed) and 10 neutral words (i.e., detect, locate, track, border, margin, measurement, impression, pertinent, arrangement, and translation). Words were presented at a rate of 1.3 sec/word, and each word was repeated approximately 10 times. Although subjects were instructed to silently categorize each word as either unpleasant, neutral, or pleasant, they were not required to make an overt response. In contrast, the current study used only male subjects. For the emotional task, on each trial, subjects were required to explicitly evaluate the personal emotional significance of a set of three highly unpleasant words. Subjects were then required to choose, based on their personal experiences, the word from each word set that was the most threatening or unpleasant. Similarly, for the nonemotional task, subjects were asked to choose the most nonemotional word from each word set of neutral words. In the current study, subjects had up to 6 seconds to make their choice and were required to make an overt response (i.e., press one of three buttons on a response pad). In light of these methodological differences, future imaging studies

that experimentally manipulate factors such as gender of subjects (i.e., using gender as a between subjects factor), the number of words presented to subjects per trial (e.g., word sets vs. single-word presentations), the behavioral task used (e.g., making personal emotional decisions about words vs. more abstract evaluations about the emotionality of words), the rate at which stimuli are presented (e.g., 1 sec vs. 6 sec), the degree to which stimuli are repeated over the course of the scan (i.e., unique vs. repeated trials), and the type of response made by subjects (e.g., covert vs. overt), will be needed to further elucidate the role of the retrosplenial cortex in lexical emotional processing.

The current study did not reveal selective insular activation to unpleasant words. A possible reason for the lack of a response to the unpleasant words used in the current study is that both lesion and imaging studies have implicated the insular cortex in the processing of aversive stimuli that evoke a sense of disgust (see literature review above). Particularly pertinent to the current study are findings from a recent imaging study that reported insular activation in response to the evaluation of facial expressions of digust but not fear (Phillips et al., 1998). In the current study, while some of the selected words (e.g., pollution and sewer) may have evoked a sense of disgust, subjects were required to evaluate a variety of highly unpleasant words that were not selected to represent discrete emotional categories. Future studies comparing insular activation in response to the perception/evaluation of words from discrete emotional categories such as disgust and fear are needed to determine if the findings by Phillips et al. (1998) generalize to the lexical channel of emotional perception.

The posterior region of the right hemisphere (i.e., parietal and temporal lobes) also served as an important ROI for the current study. This brain region has been

implicated by lesion studies in the perception/evaluation of negatively valenced stimuli. Results from the current study revealed a selective response to the unpleasant words at two sites within the right temporal lobe. A direct test of laterality (Word Condition x Time Course x Hemisphere ANOVA) revealed that the selective emotional response in the middle temporal gyrus was significantly greater on the right than left side. With respect to the specificity of these temporal lobe findings, it should be noted that a selective response to the unpleasant words was also noted in the left temporal lobe. However, this left-sided response did not reveal a significant laterality effect. Together, these results do provide some support for the notion that the posterior right hemisphere (i.e., temporal lobe) is involved to a greater degree than the posterior left hemisphere, but not exclusively, in the perception/evaluation of lexical emotional information. These findings are also consistent with the unilateral lesion literature and other recent imaging studies (see literature review above) that support greater right- than left-hemisphere involvement with respect to evaluation of lexical stimuli. Finally, in an attempt to establish the specificity of the temporal lobe findings, it is interesting to note that a strongly lateralized time-locked response to visually presented words irrespective of emotional task manipulation was observed in Wernicke's area (i.e., posterior superior temporal lobe [BA 22]). This finding is consistent with the demonstrated function of this brain area in language comprehension.

Exploratory correlational analyses were also conducted to assess the degree to which the selective responses to the unpleasant words in the ROI activation sites were interrelated. The peak BOLD responses in the right amygdala and right middle temporal gyrus were the only ROI activation sites that demonstrated a significant positive

correlation. Interestingly, the activation site in the middle temporal gyrus was also the only site that demonstrated a statistically verified right-lateralized response. This finding suggests that the specific role of the right posterior cortex in the perception of emotional information may be mediated by direct anatomical links between subcortical limbic structures (e.g., the amygdala) and the right posterior cortex.

Exploratory correlation analyses also revealed that the memory performance data, as assessed by the immediate recognition memory test, did not correlate with any of the observed ROI activation sites. This finding suggests that the enhanced short-term recall for the emotional versus neutral words did not depend on the involvement of the various ROIs examined in this study. Based on the extant literature (Maddock, 1999), it was hypothesized that activation in the retrosplenial cortex (BA 29 and 30) would be related to immediate recognition memory for emotional stimuli. Activation in this region was not observed in the current study and, hence, the current study did not support this hypothesis. Future imaging studies will be needed to elucidate the role of the retrosplenial cortex in emotional memory.

The amygdala has also been implicated in the formation of emotional memories. However, while a selective amygdala response to the unpleasant words was observed during scan 1 (encoding), this activation did not correlate with memory performance on the immediate recognition memory test. The implications of this finding, and need for future studies investigating the role of the amygdala in short versus long-term memory processes using lexical stimuli, are discussed below in a more extended discussion of the role of the amygdala in emotional processing.

Finally, exploratory correlational analyses were also conducted to assess the effects of anxiety during the scanning procedure on the ROI activation sites. While state anxiety scores increased significantly due to the scanning procedure (i.e., difference between anxiety level as measured before versus immediately following the scan), this increase in state anxiety was not significantly correlated (i.e., at the corrected Bonferoni alpha level) with any of the ROI activation sites. Hence, although the fMRI scanning procedure did induce elevated levels of anxiety in subjects (Gur et al., 1987), the observed ROI responses were not significantly related to this increase in state anxiety levels. While it could be argued that increases in self-reported state anxiety levels due to the scanning procedure may influence and thus confound brain activation in response to experimental manipulations (e.g., presentation of lexical stimuli), the lack of a significant correlation between the state anxiety difference scores and ROI activation sites here argue that this was not the case in the current study.

In summary, overall findings from the current study suggest that the amygdala, right posterior cortex, and medial frontal gyrus play a role in the perception/evaluation of unpleasant words. Each of these areas demonstrated a selective response to the emotional condition of the current study. Although activation was not observed in the orbitofrontal cortex and the subgenual region of the affective anterior cingulate, involvement of these regions cannot be ruled out as susceptibility artifacts made it impossible to image activation in these areas. Correlational analyses revealed a direct relationship between activation in the amygdala and the temporal lobe. This finding is suggestive of a cortical-subcortical link between these two regions. Moreover, the finding that the selective response in the middle temporal gyrus was lateralized to the right hemisphere is

consistent with the unilateral brain-damaged literature implicating the right posterior cortex in the appraisal of emotional information (Adolphs et al., 1996, 2000; Borod, 1996; Heilman et al., 2000; also see literature review above). A specialized link between the amygdala and right temporal lobe is also consistent with the speculation (Borod, 1992) of a right-sided cortical/subcortical connectivity that preferentially mediates the processing of emotional information.

Future studies, using more sophisticated statistical methods than the bivariate correlations used here (e.g., for one statistical approach to establish functional connectivity between ROIs, see Morris, Ohman, & Dolan, 1999), should be conducted to further elucidate the relationship between ROIs such as the amygdala and right posterior cortex. Elucidating the functional interrelationships between ROIs would provide us with a better understanding of the neural circuitry underlying specific aspects of emotional processing (e.g., appraisal) in healthy individuals. An emphasis on establishing condition-specific functional connectivity between ROIs represents an important contribution of functional brain imaging techniques in that it allows us to go beyond the more traditional lesion/deficit approach.

An important focus of the current study was on further examining the role of the amygdala in emotional processing, especially as it pertains to the lexical channel of emotional communication. Given the emphasis on the amygdala in the extant emotional processing literature, the implications of the current findings with respect to this ROI will now be discussed in greater depth.

As indicated in the above literature review, the selective amygdala response to unpleasant words observed in the current study is consistent with a large body of animal

and human literature suggesting that the amygdala plays some role during the evaluation of emotionally significant or biologically relevant cues, particularly those that predict possible threat to the organism. However, it should be emphasized here that the exact nature of this role remains controversial (Adolphs, Tranel et al., 1999). While a number of studies have demonstrated selective emotional processing deficits following bilateral amygdala lesions in humans (Adolphs et al., 1994; Adolphs et al., 1995; Adolphs et al., 1998; Broks et al., 1998; Canli et al., 1998; Young et al., 1995, 1996), others have not (Adolphs & Tranel, 1999; Adolphs, Tranel et al., 1999; Anderson & Phelps, 1998; Hamann et al., 1996, 1999; Lang et al., 1997). Moreover, bilateral lesion studies in humans generally do not block normal autonomic (Bechara et al., 1995; Tranel & Damasio, 1993) and self-reported emotional reactions (Adolphs et al., 1997; Cahill et al., 1995; Hamann et al., 1997) to emotionally significant stimuli. Similarly, while studies have implicated the amygdala in conditioned emotional responses and as the place where conditioned memories are indelibly stored (LeDoux, 1995; Maren & Franselow, 1996), other studies (see Cahill et al. [1999] for review of this literature) have demonstrated that the amygdala is not necessary for fear-based autonomic responses (Tranel & Damasio, 1993) or for fear-conditioned learning (Vazdarjanova & McGaugh, 1998).

The response of the amygdala to the evaluation of unpleasant words in this study may, on the one hand, reflect retrieval of past emotional experiences for the purpose of appraising the emotional significance of current stimuli in the context of the emotional decision task (i.e., choosing the most unpleasant word from a set of three highly unpleasant words based on subjective experience). Such emotional memories may be stored in the amygdala per se or in widespread associative neural networks of the cortex

that are reciprocally connected to the amygdala through the hippocampal system (Damasio, 1995). This interpretation is consistent with some imaging studies that have found right amygdala activation during retrieval of highly personal emotional memories (Rauch et al., 1996) and during the retrieval of affect-laden autobiographical memories with personal emotional significance (Fink et al., 1996).

On the other hand, a recent PET study by Reiman et al. (1997) found that, although viewing emotionally arousing films activated the amydala, recall of previously experienced emotional events did not. Further, a number of imaging studies (Cahill et al., 1996; Hamann et al., 1999) have reported that amygdala activity while viewing emotional stimuli (i.e., highly aversive emotional scenes) is strongly related to long-term memory performance for emotionally significant, as opposed to, neutral material. These findings are consistent with the memory modulatory framework (Cahill, 1999; Cahill et al., 1998; McGaugh, 2000) discussed above which suggests that amygdala activation in response to emotionally significant stimuli regulates the long-term storage of this information in other brain areas in a time-dependent manner. Hence, according to this view, the increase in amygdala activity observed in the current study reflects the amygdala's response to the explicit evaluation of the unpleasant words. This activity, in turn, influences the degree to which the unpleasant versus neutral words are stored and consolidated in long-term memory (Cahill, 1999).

During the memory scan of the current study, which occurred immediately after the first (encoding) scan, subjects were simply instructed to rapidly identify any word that occurred in the previous scan. Consistent with a large body of behavioral literature, subjects were able to more accurately recognize the emotional than nonemotional words.

However, in the current study, the enhanced memory performance for the emotional words was not related to an increase in amygdala activation. The lack of an amygdala response during the immediate recognition memory task used in this study (Scan 2) is consistent with the memory modulatory view of amygdala function (Bianchin et al., 1999; Cahill, 1999; Cahill et al., 1998; Hamann et al., 1999) which posits that the amygdala is not involved in memory retrieval processes but is involved in memory consolidation. Moreover, similar to the Hamann et al. study (1999), amygdala activation during encoding (Scan 1) was not correlated with the short-term memory performance. This finding is also consistent with the memory modulatory view that predicts amygdala activity during encoding to be correlated with long-term but not short-term memory (Bianchin et al., 1999). Of note, although the current study did not administer a test of long-term memory for the lexical stimuli, both Cahill et al. (1996) and Hamann et al. (1999), using highly aversive emotional scenes as stimuli (e.g., car accidents, mutilations), did find a significant correlation between amygdala activation at encoding and long-term memory performance (i.e., after one month). Future imaging studies evaluating memory for emotional lexical stimuli are needed to determine if the findings by Cahill et al. (1996) and Hamann et al. (1999) also generalize to the lexical channel of emotion (see below discussion).

In the current study, similar to the findings by Morris et al. (1998), there was a strong correlation between the overall occipital response to words and the selective amygdala response to the unpleasant word condition (see Fig. 9). This finding is consistent with a number of studies (Lane et al., 1999; Lang et al., 1998; Morris et al., 1998; Reiman et al., 1997; Wik, Fredrickson, Eriksson, Stone-Elander, & Greitz, 1993)

that provide support for the notion that the amygdala modulates early visual processing in the occipital cortex. Such a modulatory effect on the occipital cortex is thought to occur via reciprocal connections between the amygdala and occipital cortex (Amaral et al., 1992). In this vein, Whalen (1998) has recently proposed that the amygdala is part of a larger vigilance system that selectively responds to aversive stimuli that are ambiguous or pose an uncertain threat to the organism. When activated by the amygdala, according to Whalen (1998) this vigilance system potentiates neuronal responsiveness or cortical information processing to gather additional information about the predictive biological significance of the stimuli.

In summary, the amygdala findings just discussed and those from previous studies support the view that the amygdala is involved in processing of emotional information independent of presentation modality. While the exact nature of the amygdala's role in emotional processing remains controversial, overall findings from the current study fit with the memory modulatory view of amygdala functioning. Amygdala activity during encoding (scan 1) was not correlated with short-term memory performance. This finding is consistent with a major premise of McGaugh's memory modulatory framework of amygdala function, which suggests that the amygdala facilitates the acquisition of long-term but not short-term declarative knowledge about emotionally significant material. Unfortunately, the current study did not include a long-term memory condition and therefore was unable to directly assess the degree to which amygdala activity during encoding selectively modulates memory for highly unpleasant words at longer delays.

To more fully assess the memory modulatory view with respect to lexical stimuli, future studies should assess long-term as well as short-term memory (e.g., immediately

after encoding, and 1 hour, 24 hours, 1 week, and 3 weeks after the original encoding scan). Such multiple memory assessments at increasing time intervals would allow one to determine whether the correlation between the amygdala activation observed during encoding (i.e., Scan 1) and memory performance for the unpleasant versus neutral words becomes stronger as more time passes. According to the memory modulatory view, this should be the case since memory consolidation is a gradual process that occurs over extended time periods.

Of note, in contrast to the memory modulatory view, a number of other hypotheses have been proposed to explained memory enhancement for emotional versus neutral stimuli (see Wasserman, 1997, for an extensive review of theories regarding how emotionality affects memory). For example, according to the associative network model of Bower (1981, 1992), emotionality enhances memory by increasing the "meaningfulness" of words (e.g., the neural network involved in the processing of an emotional word includes a larger number of "nodes" than the neural network involved in the processing of a neutral stimulus), which in turn results in greater cognitive processing (e.g., processing on a deeper level) and more focused attention to, and rehearsal of, the emotional words, thereby enhancing subsequent recall. In a similar vein, Phelps, LaBar, and Spencer (1997) have argued that the emotional component in lexical stimuli is largely semantic and, hence, the benefit to memory is one of organizational strategies, such that the emotional content benefits encoding or serves as a retrieval cue much in the same way that any overarching category might. Such semantic and more general cognitive factors, and not amygdala activity per se, most likely account for the enhanced

immediate recognition memory of emotional versus neutral words observed in the current study.

Future studies should also obtain physiological (e.g., galvanic skin response) and self-report measures of emotional arousal from subjects while they engage in the lexical emotional decision task. Such manipulations would make it possible to assess the degree to which decisions about highly unpleasant words elicit autonomic arousal. Measures of autonomic arousal could then be correlated with amygdala and other ROI activity obtained via fMRI, and with short- and long-term measures of memory performance. Such a design would allow one to determine the degree to which emotional arousal is related to amygdala and other ROI activity, and the degree to which each of these components are involved in the encoding, short-term memory performance, and regulation of memory consolidation processes (LaBar & Phelps, 1998).

In the current study, the words used as stimuli were selected from the Toglia and Battig (1978) normative database. As part of this database, words were rated by a large group of subjects to be either highly unpleasant or neutral. While debriefing revealed that all subjects found the unpleasant word sets to be highly unpleasant, particularly when compared to the neutral word sets, the current subjects were not asked to rate each word separately in terms of emotional valence (i.e., unpleasant, neutral, and pleasant). Future studies using a similar lexical paradigm may find such rating data useful as an additional manipulation check in order to assess the degree to which subjects agree with the normative data used to select the lexical stimuli.

Future studies should also include highly positive words as a third word condition, since this would allow one to directly assess brain lateralization hypotheses as

a function of emotional valence (Borod & Madigan, 2000; Canli et al., 1998; Davidson & Irwin, 1999a,b). In a similar vein, lexical imaging paradigms should be designed that allow ROI activations to be analyzed in terms of discrete emotional categories (e.g., disgust, fear, and happiness). Such designs would allow one to determine the degree to which findings from ROIs, such as the insular cortex and amygdala, which have been implicated in the processing of discrete facial expressions of disgust and fear respectively (i.e., see above review of the literature) can be generalized to the lexical channel of emotional communication.

Finally, as mentioned above, future lexical emotional imaging studies would benefit from experimentally manipulating a number of methodological factors that differ in the extant literature and, thus, make the interpretation of discrepant findings very difficult. For example, imaging studies using language-related stimuli should include gender as a between-subjects variable. This is particularly important since a large body of literature has demonstrated gender differences in brain organization with respect to language (for a review of this literature, see Kimura, 1999). Other factors that should be systematically investigated are: 1) the number of words presented to subjects per trial (e.g., single words, groups of words, or sentences); 2) the behavioral task used (e.g., passive viewing of words, making a nonemotional judgment about the words [e.g., stating the color of the ink with which the words are printed], making abstract evaluations about the emotional characteristics of words [e.g., emotional intensity, valence, or category], or making decisions about words based on personal experiences); 3) the rate at which stimuli are presented (e.g., 1 trial/sec vs. 1 trial/6 sec); 4) the degree to which stimuli are repeated over the course of the scan leading to possible habituation effects; 5) and the

type of response made by subjects to the stimuli (covert vs. overt). Systematically manipulating these and other factors will help to further elucidate the neural substrates of lexical emotional processing.

Tables

Table 1a. Word stimuli used as stimuli in the emotional decision scan and as targets in the immediate recognition scan of the current study, selected from Toglia and Battig (1978).

Neutral		Unpleasant	
following	differences	cancer	failing
step	sequel	murder	pollution
referee	doorman	slavery	dead
rows	suit	morgue	bomb
academy	age	greedy	prejudice
cable	cents	kill	ugly
size	garment	gun	death
meant	boot	polio	agony
therefore	angle	measles	coffin
loop	mile	misery	tragedy
chart	rapid	war	sewer
pots	wind	cruel	trouble
glasses	tradition	hate	hell
empire	root	crime	rape
tray	chestnut	poor	vulgar

Table 1b. Word stimuli used as foils in the immediate recognition scan of the current study, selected from Toglia and Battig (1978).

Neutral		Unpleasant	
proof	exposure	jail	suffocate
astute	stone	morbid	hostage
botany	drama	grave	rancid
alcohol	frog	dandruff	deface
theme	hut	fraud	dungeon
blew	tail	trash	bad
tube	stand	nag	guilt
enough	conference	lice	fail
frank	next	slay	sick
prevalent	knoll	destroyer	ashamed
wash	dense	nervous	disappoint
enamel	cape	die	disease
manor	little	ache	rejected
question	raincoats	drab	pimple
sheepskin	plan	decay	perjury

Table 2a. Whole brain activation sites in Talairach space for the Main Effect of Time Course during the emotional decision task where the BOLD response increased during stimulus presentation of both unpleasant and neutral word sets. Significance thresholds were set at $P < 0$ .001 and a minimum of at least 4 contiguous pixels.

Main Effect of Time Course	Location	Talairach Coordinates			Area	F Value
		x	y	z		
Increase	Middle Temporal Gyrus	-60	-6	-12	6	3.58
	Parahippocampal Gyrus	21	-33	-12	120	21.34
	Parahippocampal Gyrus	-35	-21	-12	29	7.29
	Superior Temporal Gyrus (BA 38)	-55	8	-12	6	3.78
	Cerebellum	-7	-60	-4	100	17.07
	Midbrain	-13	-22	-4	5	3.32
	Temporal Lobe	-44	-29	-4	8	6.03
	Cuneus (BA 17)	12	-90	4	19	11.29
	Lingual Gyrus	-23	-86	4	6	5.21
	Lingual Gyrus	9	-72	4	12	8.41
	Middle Occipital Gyrus	-27	-72	4	5	4.62
	Sub-lobar Extra-Nuclear White Matter	-37	-28	4	6	3.34
	Sub-lobar Extra-Nuclear White Matter	-5	-24	4	4	3.57
	Sub-lobar Extra-Nuclear White Matter	-48	6	4	5	3.68
	Cuneus (Resampled)	-25	-85	12	**108**	**16.23**
	Sub-lobar Extra-Nuclear Gray Matter (BA 13)	-40	13	12	24	6.96
	Sub-lobar Extra-Nuclear White Matter	21	13	12	7	3.4
	Superior Temporal Gyrus (BA 22)	-63	-53	12	4	3
	Thalmus	-6	-12	12	28	7.96
	Frontal Lobe	-32	9	20	6	3.78
	Middle Occipital Gyrus	-24	-83	20	29	28.71
	Middle Occipital Gyrus	28	-80	20	17	21.34
	Superior Temporal Gyrus (BA 22)	-65	-39	20	6	4.21
	Frontal Lobe	-42	3	24	4	4.17
	Inferior Parietal Lobule (BA 40)	-60	-30	24	4	2.88
	Posterior Cingulum	2	-41	24	6	6.13
	Sub-lobar Extra-Nuclear White Matter	-20	-37	24	4	3.83
	Temporal Lobe	-27	-74	24	26	13.51
	Temporal Lobe	31	-74	24	33	13.2
	Cuneus	-10	-85	32	9	10.14
	Cuneus (BA 19)	6	-89	32	30	7.18
	Middle Frontal Gyrus	48	15	32	5	4.16
	Middle Frontal Gyrus (BA 9)	-55	15	32	4	5.32
	Parietal Lobe	-29	-67	32	8	9.11
	Precentral Gyrus (BA 6)	-59	4	32	12	10.87
	Superior Frontal Gyrus (BA 9)	-40	41	32	10	5.1
	Frontal Lobe	16	19	40	4	5.5
	Inferior Parietal Lobule	54	-49	40	10	11.4
	Inferior Parietal Lobule (BA 40)	-61	-42	40	15	8.14
	Medial Frontal Gyrus (BA 8)	-3	30	40	20	6
	Precentral Gyrus (BA 4)	-54	-11	40	44	14.84
	Precuneus	-16	-64	40	4	3.82
	Inferior Parietal Lobule (BA 40)	-44	-56	45	13	7.79
	Inferior Parietal Lobule (BA 40)	-45	-35	45	4	4.84
	Medial Frontal Gyrus (BA 8)	3	23	45	12	8.59
	Postcentral Gyrus (BA 1)	-54	-14	45	7	4.28
	Postcentral Gyrus (BA 2)	-58	-23	45	5	3.94
	Superior Frontal Gyrus (BA 8)	-3	31	45	19	11.12
	Superior Frontal Gyrus (BA 8)	-20	47	45	4	3.17
	Superior Frontal Gyrus (BA 8)	-17	45	45	4	3.01
	Inferior Parietal Lobule (BA 40)	-38	-39	55	12	9.69
	Medial Frontal Gyrus (BA 6)	-2	2	55	24	11.6
	Precentral Gyrus (BA 4)	-38	-21	55	4	4.01

Table 2b. Whole brain activation sites in Talairach space for the Main Effect of Time Course during the emotional decision task where the BOLD response decreased during stimulus presentation of both unpleasant and neutral word sets. Significance thresholds were set at $P < 0$ .001 and a minimum of at least 4 contiguous pixels.

Main Effect of Time Course	Location	Talairach Coordinates x	y	z	Area	F Value
Decrease	Parahippocampal Gyrus	-16	-3	-12	10	13.33
	Frontal Lobe	-16	35	-12	7	4.45
	Frontal Lobe	16	41	-12	4	2.89
	Inferior Frontal Gyrus (BA 47)	-45	23	-12	8	4.24
	Inferior Frontal Gyrus (BA 47)	45	23	-12	11	5.82
	Parahippocampal Gyrus	-21	-34	-4	14	5.1
	Parahippocampal Gyrus	24	-31	-4	15	3.27
	Putamen	-30	-8	-4	11	3.56
	Putamen	21	16	-4	19	3.51
	Sub-lobar Extra-Nuclear Gray Matter (BA 13)	41	-8	-4	7	3.79
	Sub-lobar Extra-Nuclear White Matter	16	-12	-4	4	3.15
	Middle Temporal Gyrus	48	-50	4	4	3.75
	Sub-lobar Extra-Nuclear White Matter	-37	-28	4	14	7.61
	Superior Temporal Gyrus	41	-28	4	37	7.73
	Superior Temporal Gyrus	-55	-24	4	4	2.66
	Anterior Cingulum (BA 32)	6	42	12	13	4.1
	Frontal Lobe	25	46	12	7	6.19
	Inferior Frontal Gyrus (BA 46)	44	31	12	8	7.13
	Middle Temporal Gyrus (39)	48	-56	12	4	3.92
	Transverse Temporal Gyrus (BA 41)	40	-23	12	10	8.43
	Transverse Temporal Gyrus (BA 41)	52	-23	12	8	5.18
	Transverse Temporal Gyrus (BA 42)	-63	-9	12	4	3.45
	Medial Frontal Gyrus (BA 10)	6	57	20	9	4.97
	Sub-lobar Extra-Nuclear Gray Matter (BA 13)	39	-24	20	23	11.17
	Sub-lobar Extra-Nuclear White Matter	-9	-43	20	5	3
	Superior Frontal Gyrus	-13	57	20	4	3.54
	Superior Temporal Gyrus (BA 39)	50	-61	20	8	8.23
	Frontal Lobe	-31	36	24	16	4.15
	Middle Frontal Gyrus	-42	22	24	4	3.17
	Precuneus	13	-55	24	10	6.19
	Supramarginal Gyrus	53	-52	24	8	5.29
	Cuneus (BA 7)	13	-67	32	6	4.67
	Frontal Lobe	-25	-33	32	9	6.41
	Frontal Lobe	-25	-22	32	5	4.68
	Parietal Lobe	25	-37	32	25	9.05
	Postcentral Gyrus (BA 40)	-40	-29	32	6	6.93
	Precuneus (BA 7)	-6	-59	32	26	14.02
	Cingulate Gyrus (BA 31)	10	-26	40	29	14.88
	Frontal Lobe	-22	-34	40	4	9.3
	Frontal Lobe	-29	-23	40	4	4.36
	Inferior Parietal Lobule	55	-34	40	5	5.39
	Middle Frontal Gyrus	-31	30	40	4	4.64
	Middle Frontal Gyrus	42	25	40	4	6.46
	Middle Frontal Gyrus (BA 8)	-22	35	40	4	3.76
	Postcentral Gyrus (BA 4)	54	-15	40	4	4.24
	Precuneus	16	-45	40	5	4.38
	Cingulate Gyrus	17	2	45	12	7.05
	Frontal Lobe	-24	-19	45	5	3.78
	Inferior Parietal Lobule (BA 40)	53	-39	45	4	4.65
	Middle Frontal Gyrus (BA 8)	-38	31	45	21	6.53
	Parietal Lobe	31	-35	45	8	4.95
	Postcentral Gyrus	55	-23	45	4	3.38
	Postcentral Gyrus (BA 3)	52	-14	45	6	5.14
	Precuneus	-17	-43	45	9	6.15
	Frontal Lobe	-18	9	55	4	3.69
	Paracentral Lobule	6	-36	55	23	5.59
	Precuneus	-10	-47	55	14	4.71
	Superior Frontal Gyrus	10	16	55	4	3.62

Table 3a. Whole brain activation sites in Talairach space for the Main Effect of Time Course during the recognition memory task where the BOLD response increased during stimulus presentation of both unpleasant and neutral word sets. Significance thresholds were set at $P < 0$ .001 and a minimum of at least 4 contiguous pixels.

Main Effect of Time Course	Location	Talairach Coordinates x	y	z	Area	F Value
Increase	Cerebellum	12	-39	-12	9	8.1
	Fusiform Gyrus	-45	-36	-12	57	11.17
	Lingual Gyrus	-27	-83	-4	84	18.28
	Lingual Gyrus	19	-90	-4	85	29.53
	Middle Temporal Gyrus	49	-21	-12	73	27.89
	Middle Temporal Gyrus	-54	-15	-12	27	19.57
	Cuneus	20	-90	4	33	15.46
	Middle Occipital Gyrus (BA 18)	-30	-83	4	35	14.93
	Putamen	20	2	4	5	4.04
	Putamen	-23	9	4	5	5.03
	Anterior Cingulum (BA 24)	-2	31	12	4	5.02
	Caudate	10	6	12	5	4.15
	Cuneus	21	-93	12	28	9.2
	Cuneus (BA 17)	6	-82	12	9	6.06
	Middle Ocipital Gyrus (BA 18, 19)	-29	-82	12	31	17.67
	Sub-lobar Extra-Nuclear Gray Matter (BA 13)	-33	24	12	16	11.88
	Sub-lobar Extra-Nuclear White Matter	-25	13	12	4	5.72
	Thalmus	-10	-5	12	11	7.21
	Caudate	-13	-10	20	10	9.56
	Cuneus	-24	-80	20	16	14.67
	Frontal Lobe	-32	16	20	26	10.64
	Frontal Lobe	46	9	20	11	6.61
	Middle Occipital Gyrus	28	-80	20	21	11.39
	Sub-lobar Extra-Nuclear White Matter	17	-6	20	4	3.86
	Frontal Lobe	-38	3	24	16	6.14
	Frontal Lobe	35	25	24	22	5.54
	Inferior Parietal Lobule	53	-37	24	4	3.88
	Middle Frontal Gyrus (BA 10)	31	44	24	9	9.47
	Posterior Cingulum	2	-41	24	12	13.8
	Temporal Lobe	-24	-70	24	23	15.98
	Temporal Lobe	27	-70	24	26	16.24
	Cingulate Gyrus	6	19	32	7	6.85
	Cingulate Gyrus (BA 24)	2	4	32	7	6.79
	Cuneus (BA 19)	-6	-85	32	5	5.88
	Frontal Lobe	-25	-18	32	7	4.63
	Frontal Lobe	-29	-11	32	4	4.89
	Medial Frontal Gyrus (BA 9)	-6	30	32	4	7.57
	Middle Frontal Gyrus	-48	15	32	27	13.43
	Middle Frontal Gyrus	36	19	32	36	12.35
	Parietal Lobe	-29	-55	32	13	20.64
	Parietal Lobe	32	-63	32	32	6.58
	Supramarginal Gyrus (BA 40)	-55	-48	32	4	3.63
	Cingulate Gyrus	-10	15	40	4	6.32
	Inferior Parietal Lobule (BA 40)	54	-53	40	28	12.92
	Medial Frontal Gyrus	-10	42	40	32	16.46
	Middle Frontal Gyrus	-43	8	40	17	8.72
	Middle Frontal Gyrus	41	15	40	5	5.98
	Middle Frontal Gyrus	46	23	40	7	5.87
	Precentral Gyrus (BA 6)	42	-4	40	5	5.85
	Cingulate Gyrus (BA 24)	-3	-2	45	4	5.08
	Inferior Parietal Lobule (BA 40)	-58	-39	45	4	5.15
	Medial Frontal Gyrus (BA 32)	-10	10	45	4	5.39
	Middle Frontal Gyrus	45	10	45	5	8.27
	Precentral Gyrus	-58	-6	45	4	6.18
	Superior Frontal Gyrus (BA 40)	-10	31	45	27	21.41
	Inferior Parietal Lobule	-38	-36	55	10	8.77
	Medial Frontal Gyrus	-2	2	55	41	21.18
	Medial Frontal Gyrus (BA 6)	-6	-21	55	4	4.97
	Middle Frontal Gyrus	38	5	55	5	4.59
	Middle Frontal Gyrus	-42	-2	55	4	6.04

Table 3b. Whole brain activation sites in Talairach space for the Main Effect of Time Course during the recognition memory task where the BOLD response decreased during stimulus presentation of both unpleasant and neutral word sets. Significance thresholds were set at $P < 0.001$ and a minimum of at least 4 contiguous pixels.

Main Effect of Time Course	Location	Talairach Coordinates x	y	z	Area	F Value
Decrease	Inferior Frontal Gyrus (BA 47)	35	17	-12	6	5.82
	Subcallosal Gyrus	12	2	-12	7	7.86
	Temporal Lobe	-30	0	-12	42	23.42
	Anterior Cingulum	-2	33	-4	8	5.58
	Anterior Cingulum (BA 25)	2	2	-4	4	5.2
	Medial Frontal Gyrus (BA 10)	-16	64	-4	4	3.68
	Parahippocampal Gyrus	-23	-44	-4	18	8.7
	Parahippocampal Gyrus	19	-36	-4	27	14.82
	Sub-lobar Extra-Nuclear Gray Matter (BA 13)	41	-2	-4	15	7.89
	Sub-lobar Extra-Nuclear White Matter	-37	6	-4	21	11.22
	Inter-Hemispheric	-2	-35	4	4	4.95
	Frontal Lobe	-23	42	4	14	7.47
	Medial Frontal Gyrus (BA 10)	5	50	4	50	11.09
	Parahippocampal Gyrus	27	-53	4	27	11.9
	Sub-lobar Extra-Nuclear Gray Matter (BA 13)	41	-20	4	11	13.86
	Sub-lobar Extra-Nuclear White Matter	-37	-20	4	53	19.63
	Sub-lobar Extra-Nuclear White Matter	2	24	4	12	9.83
	Temporal Lobe	-34	-50	4	5	9.32
	Medial Frontal Gyrus (BA 10)	6	46	12	30	8.57
	Middle Frontal Gyrus	33	53	12	7	5.82
	Middle Temporal Gyrus	52	-60	12	8	8.09
	Posterior Cingulum	-13	-56	12	12	15.86
	Sub-lobar Extra-Nuclear White Matter	-29	-34	12	12	9.51
	Superior Temporal Gyrus (BA 41)	-52	-27	12	7	6.98
	Transverse Temporal Gyrus	36	-27	12	28	24.03
	Transverse Temporal Gyrus (BA 42)	-56	-12	12	9	6.56
	Anterior Cingulum (BA 24)	-2	31	20	6	6.28
	Medial Frontal Gyrus (BA 9)	-2	49	20	15	8.81
	Middle Temporal Gyrus	-39	-72	20	5	6.17
	Middle Temporal Gyrus	43	-76	20	15	9.83
	Precuneus (PCu)	-6	-58	20	21	11.66
	Sub-lobar Extra-Nuclear Gray Matter (BA 13)	46	-32	20	34	11.77
	Sub-lobar Extra-Nuclear White Matter	-46	-17	20	4	4.81
	Superior Frontal Gyrus	9	60	20	6	6.84
	Superior Frontal Gyrus (BA 10)	-20	57	20	10	8.63
	Superior Temporal Gyrus (BA 39)	-50	-58	20	7	7.33
	Medial Frontal Gyrus (BA 9)	13	40	24	5	5.34
	Middle Temporal Gyrus	-49	-72	24	8	4.77
	Middle Temporal Gyrus (BA 39)	53	-59	24	15	6.42
	Posterior Cingulum	-5	-59	24	27	17.68
	Sub-lobar Extra-Nuclear White Matter	27	-37	24	4	5.44
	Sub-lobar Extra-Nuclear White Matter	35	-26	24	11	7.26
	Superior Frontal Gyrus	-20	44	24	6	7.34
	Parietal Lobe	-32	-33	32	9	4.41
	Postcentral Gyrus	40	-18	32	31	14.09
	Precuneus (PCu)	6	-55	32	54	33.29
	Superior Frontal Gyrus (BA 9)	-2	49	32	34	15.04
	Supramarginal Gyrus (BA 40)	-55	-48	32	4	3.63
	Cingulate Gyrus (BA 24)	10	-15	40	8	8.94
	Frontal Lobe	22	-26	40	11	6.7
	Frontal Lobe	22	0	40	7	8.4
	Inferior Parietal Lobule	-48	-42	40	57	6.45
	Precental Gyrus (BA 4)	50	-11	40	4	7.76
	Inferior Parietal Lobule	49	-35	45	18	5.14
	Paracentral Lobule (BA 31)	-3	-27	45	30	13.08
	Postcentral Gyrus (BA 2)	51	-23	45	7	5.25
	Postcentral Gyrus (BA 40)	-38	-27	45	4	4.52
	Precuneus	17	-56	45	10	5.26
	Frontal Lobe (BA 6)	-22	5	55	4	4.95
	Precuneus (BA 7)	18	-50	55	66	13.84

Table 4. Whole brain activation sites in Talairach space for the Word Condition by Time interaction during the emotional decision task. (a) Sites where the BOLD response during stimulus presentation was greater to the unpleasant than neutral word condition. (b) Sites where the BOLD response during stimulus presentation was greater to the neutral than unpleasant word condition. Significance thresholds were set at $P < 0.001$ and a minimum of at least 4 contiguous pixels. The Area specifies the number of contiguous pixels in the patch.

Condition by Time Interaction	Location	Talairach Coordinates			Area	F Value
		x	y	z		
a) Unpleasant > Neutral	Amygdala	26	-6	-12	9	5.81
	Subcallosal Gyrus	-7	3	-12	4	6.58
	Middle Temporal Gyrus (BA 21)	63	-0.5	-12	5	4.43
	Midbrain	-4	-24	-4	4	3.32
	Temporal Lobe	-44	-31	-4	11	5.46
	Parahippocampal Gyrus	-24	-48	-4	5	3.9
	Sub-lobar Extra-Nuclear White Matter	29	-31	12	4	3.76
	Precentral Gyrus (BA 6)	58	1	20	8	4.57
	Superior Temporal Gyrus (BA 39)	54	-56	20	6	4.84
	Medial Frontal Gyrus (BA 9)	-2	47	24	7	6.54
	Superior Frontal Gyrus (BA 10)	13	55	24	4	2.98
	Cuneus (BA7)	2	-67	32	5	4.8
	Precentral Gyrus (BA 6)	-50	-4	40	7	4.57
b) Neutral > Unpleasant	Fusiform Gyrus (BA 37)	-40	-56	-12	4	3.02
	Inferior Frontal Gyrus (BA 47)	-49	23	-12	4	4.63
	Parahippocampal Gyrus (BA 36)	35	-33	-12	5	5.49
	Superior Temporal Gyrus (BA 38)	60	11	-12	5	3.86
	Claustrum	-33	0	-4	5	3.73
	Internal Capsule	-24	-22	-4	4	6.61
	Parahippocampal Gyrus	21	-45	-4	7	4.29
	Claustrum	-27	20	4	4	3.41
	Lingual Gyrus	23	-79	4	10	4.47
	Inferior Frontal Gyrus (BA 44)	-44	13	12	4	2.55
	Temporal Lobe	-48	-63	12	8	4.63
	Thalamus	10	-5	12	13	5.83
	Inferior Frontal Gyrus (BA 45)	58	12	20	7	3.68
	Frontal Lobe	-31	22	24	5	3.8
	Middle Frontal Gyrus (BA 46)	-46	25	24	5	3.56
	Middle Frontal Gyrus (BA 8)	35	38	40	4	4.97

Table 5. Whole brain activation sites for the Word Condition by Time interaction during the recognition memory task. (a) Sites where the BOLD response during stimulus presentation was greater to the unpleasant than neutral word condition. (b) Sites where the BOLD response during stimulus presentation was greater to the neutral than unpleasant word condition. Significance thresholds were set at $P < 0.001$ and a minimum of at least 4 contiguous pixels. The area specifies the number of contiguous pixels in the patch.

Condition by Time Interaction	Location	Talairach Coordinates			Area	F Value
		x	y	z		
a) Unpleasant > Neutral	Midbrain	2	-29	-4	6	5.52
	Sub-lobar Gray Matter (BA 13)	-35	-28	20	7	3.46
	Precental Gyrus (BA 6)	-53	0	40	9	5.83
	Middle Frontal Gyrus (BA 8)	-24	23	45	4	3.57
	Superior Frontal Gyrus	-10	16	55	7	4.89
b) Neutral > Unpleasant	Caudate	13	5	20	4	2.78
	Sub-lobar White Matter	-16	-44	24	9	4.66
	Frontal Lobe	-27	22	24	4	1.87
	Frontal Lobe	31	36	24	5	3.91
	Precuneus	16	-60	40	4	6.44
	Medial Frontal Gyrus (BA 8)	4	51	40	5	5.63

Table 6.
Correlation Matrices for Exploratory Analyses

a) Correlations between Observed ROI activation Sites

ROIs	Right Precentral Gyrus	Right Superior Temporal Gyrus	Right Middle Temporal Gyrus	Medial Frontal Gyrus (BA 9)
Right Amygdala	*r*=.342 *P*=.183	*r*=.548 *P*=.063	*r*=.817* *P*=.004	*r*=.232 *P*=.274
Medial Frontal Gyrus (BA 9)	*r*=.067 *P*=.432	*r*=.347 *P*=.180	*r*=.209 *P*=.295	
Right Middle Temporal Gyrus	*r*=.591 *P*=.047	*r*=.147 *P*=.353		
Right Superior Temporal Gyrus	*r*=.270 *P*=.241			

*Significant at the corrected Bonferoni alpha level P<.005

b) Correlations between Performance on an Immediate Recognition Memory task for Unpleasant and Neutral Words and the corresponding ROI Activations (i.e., to Unpleasant and Neurtal words).

ROI Activation Sites	Right Amygdala	Medial Frontal Gyrus (BA 9)	Right Middle Temporal Gyrus	Right Superior Temporal Gyrus	Right Precentral Gyrus
Memory Performance for Unpleasant Words	*r* = -.11 *P* = .782	*r*=-.043 *P*=.912	*r*=200 *P*=.607	*r*=.343 *P*=.367	*r*=-.242 *P*=.530
Memory Performance for Neutral Words	*r* = .48 *P* = .196	*r*=-.357 *P*=.345	*r*=.284 *P*=.460	*r*=.365 *P*=.334	*r*=-.008 *P*=.984

c) Correlations between Self-reported State Anxiety Difference Scores (i.e., during scan – prescan scores) and ROI Activations to Unpleasant and Neutral Words.

ROI Activation Sites	Right Amygdala	Medial Frontal Gyrus (BA 9)	Right Middle Temporal Gyrus	Right Superior Temporal Gyrus	Right Precentral Gyrus
State Anxiety Difference Score (Unpleasant)		*r*=.581 *P*=.101	*r*=.532 *P*=.140	*r*=.279 *P*=.467	*r*=.231 *P*=.551
State Anxiety Difference Score (Neutral)		*r*=.741 *P*=.022	*r*=.018 *P*=.963	*r*=.122 *P*=.755	*r*=-.232 *P*=.548

Figures

Emotional Decision Scan

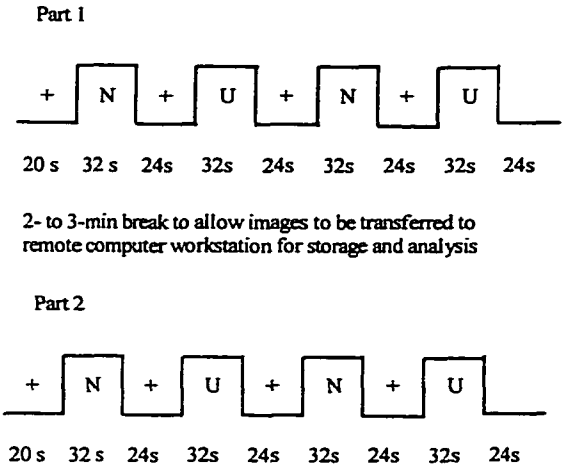


Fig. 1a. Overview of blocked stimulus presentation paradigm for the Emotional Decision Scan. Eight alternating blocks of Neutral (N) and Unpleasant (U) trials separated by Rest Periods (+). Total scan time is 488 s (8 min and 8 s) yielding 244 images of 14 axial slices (3,416 slices). Each slice contains 64 x 64 pixels, where each pixel is 3.59^2 mm (FOV = 23 cm^2).

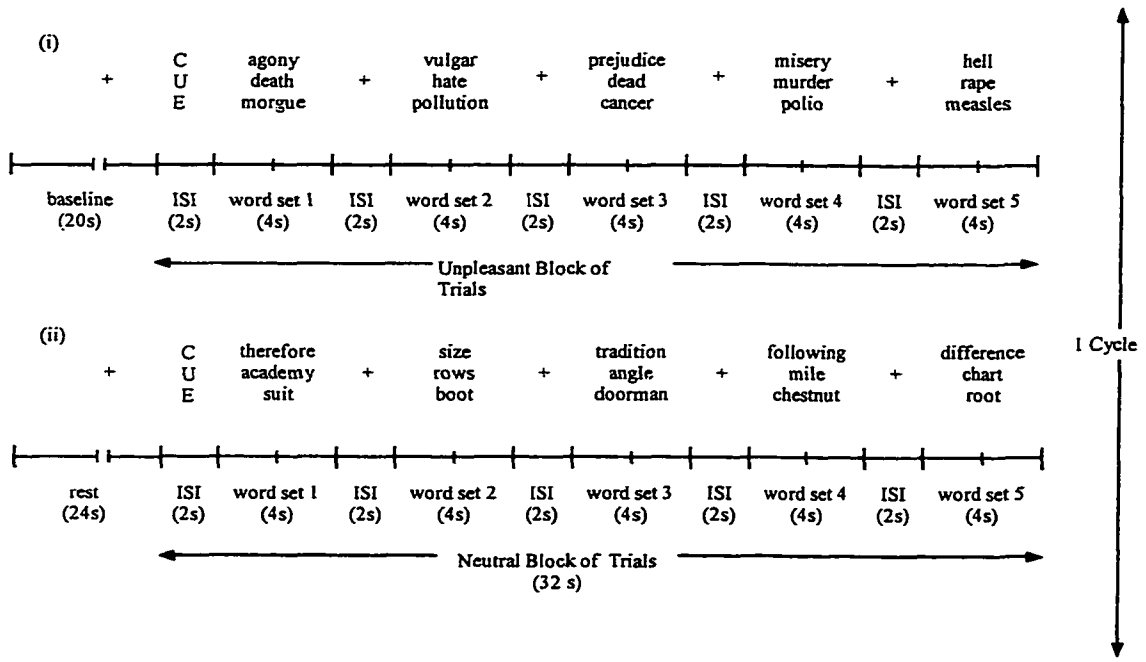


Fig. 1b. Summary of the stimulus presentation parameters within a block of unpleasant and neutral trials for the Emotional Decision Task (one complete cycle of unpleasant and neutral trials). (i) Block of unpleasant trials and preceding baseline. (ii) Block of neutral trials precede a rest period. Each block begins with a cue indicating "Unpleasant" or "Neural." Subjects select the word judged to be the most unpleasant or neutral for each word set by pressing one of three buttons.

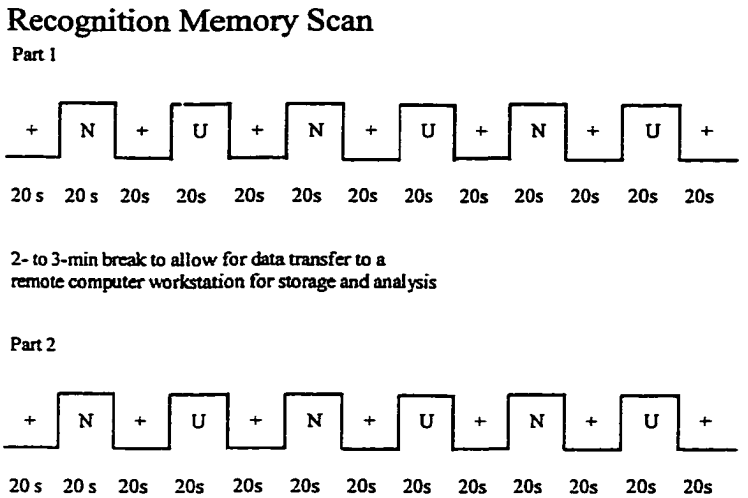


Fig. 2a. Overview of blocked stimulus presentation paradigm for the Recognition Memory Scan. Ten alternating blocks of Neutral (N) and Unpleasant (U) trials separated by Rest Periods (+). Total scan time is 520 s (8 min 36 s) yielding 260 images of 14 axial slices (3,640 slices). Each slice contains 64 x 64 pixels where each pixel is 3.59 mm^2 (FOV = 23 cm^2).

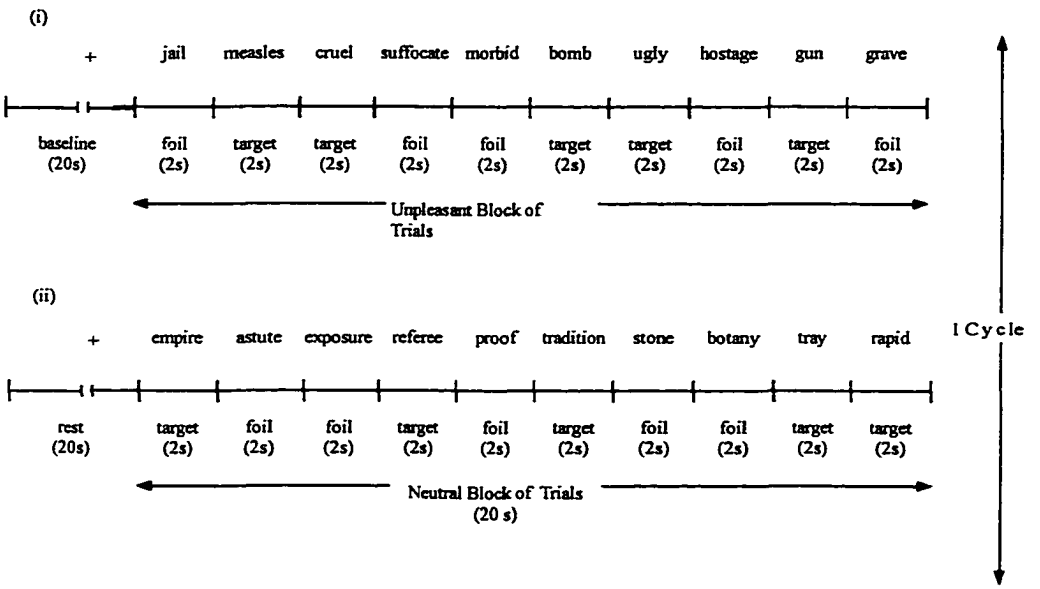


Fig. 2b. Summary of the stimulus presentation parameters within a block of unpleasant and neutral trials for the Recognition Memory Task (one complete cycle of unpleasant and neutral trials). (i) Block of unpleasant trials and preceding baseline. (ii) Block of neutral trials precede a rest period. The 30 unpleasant and 30 neutral words presented during scan 1 (targets) will be randomly mixed with 30 foils of each word type (0.5 probability of target appearing). Subjects select a word judged to be the most unpleasant or neutral for each word set by pressing one of three buttons.

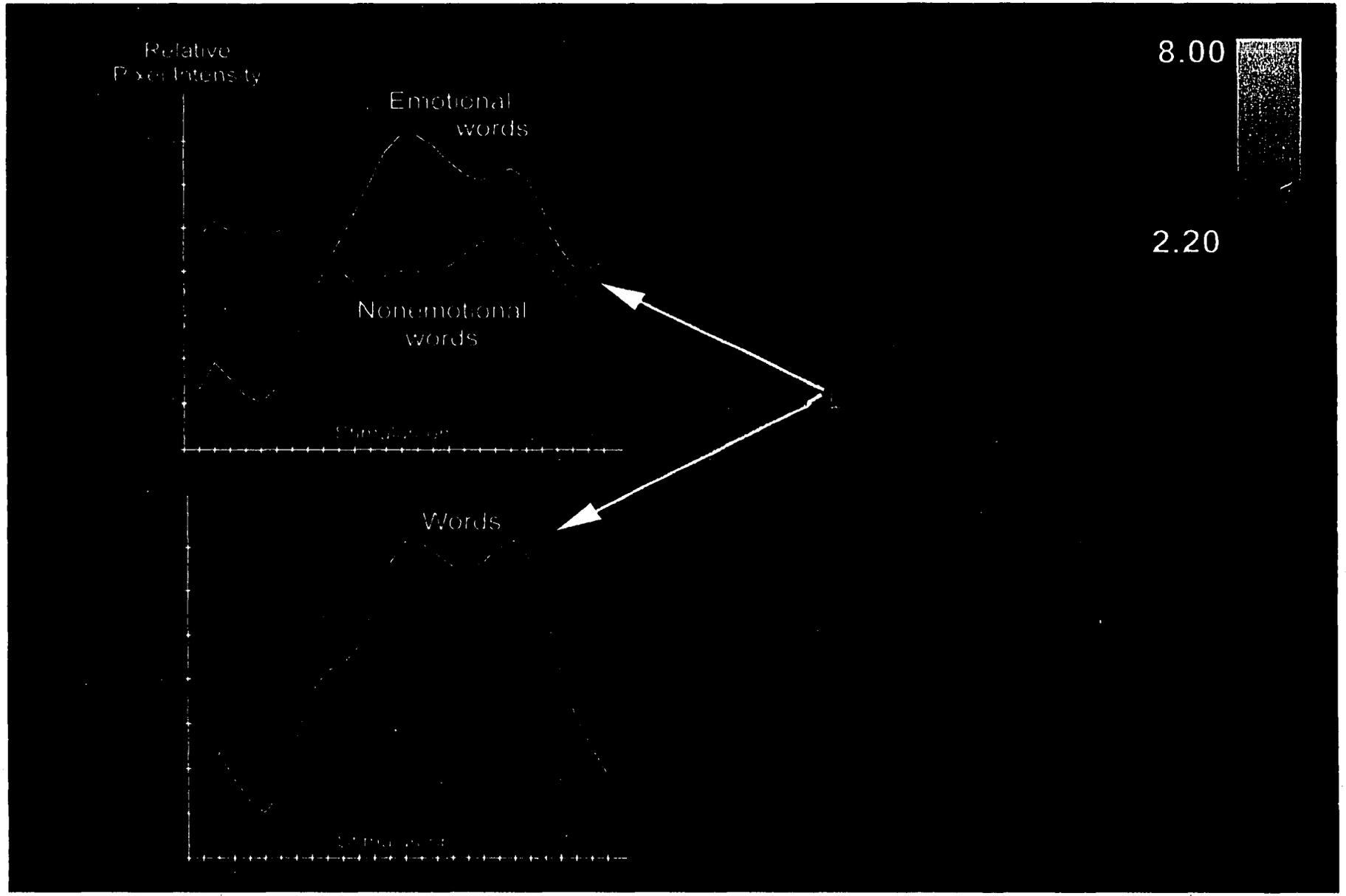


Fig. 3. Emotional Decision Task: (Top left) The Word Condition by Time Course interaction [$F(27,216)=5.25$; $P<0.0001$] in the pixel with maximum activation (26, -6, -12) within a patch of 9 contiguous pixels surrounding the center of the right amygdala. (Bottom left) The main effect of Time Course [$F(27,216)=2.29$, $P = 0.0006$] for the pixel with the maximal response (26,-6,-12) within the same patch of 9 contiguous pixels. (Right) This 9-pixel patch was the largest area/volume of activation (maximum patch) on this axial slice. Other areas that met the statistical threshold criteria for significance were omitted for clarity.

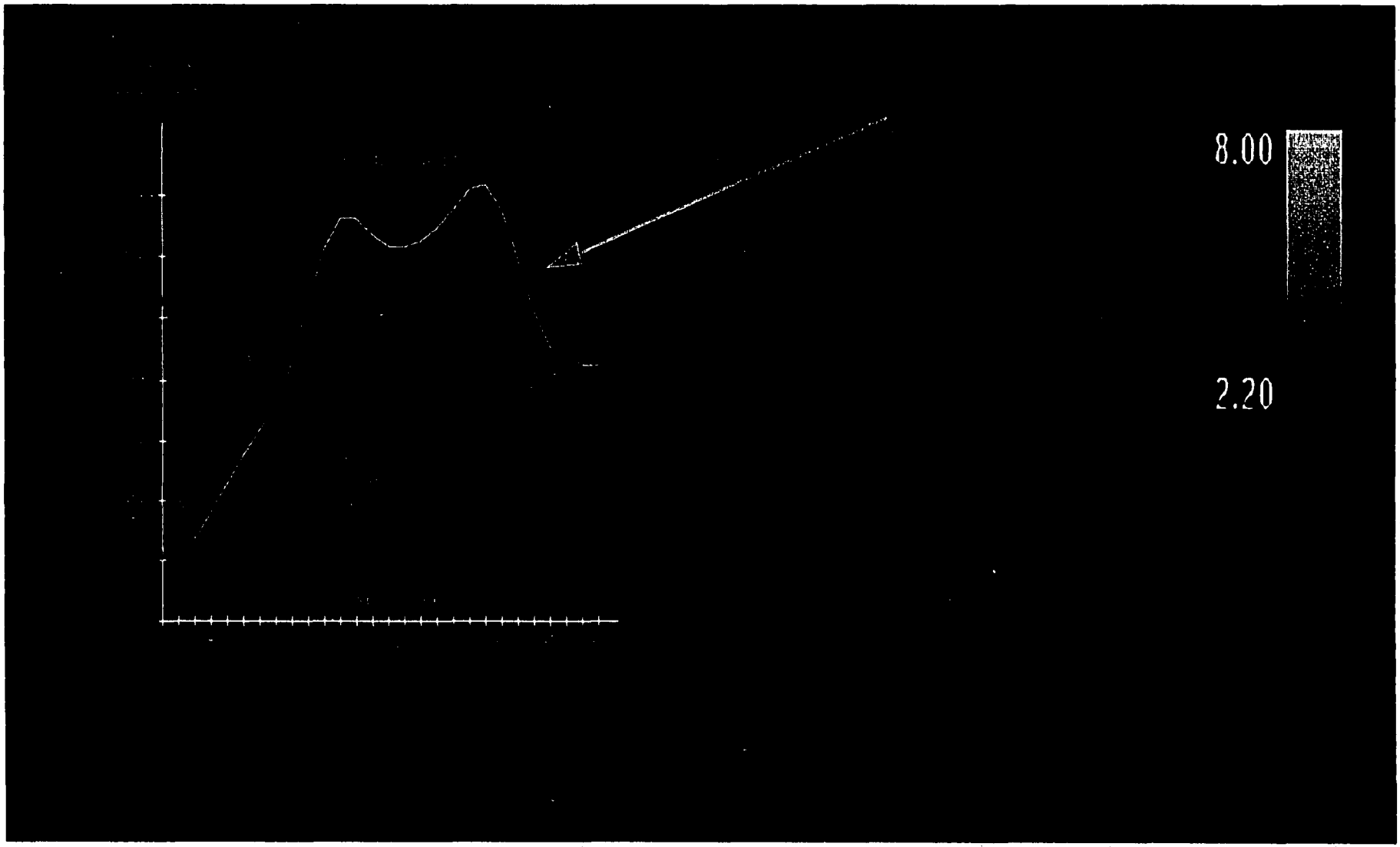


Fig. 4. Emotional Decision Task: (Top left) The Word Condition x Time Course interaction [$F(27,216)=3.89$; $P<0.0001$] in the pixel with maximum activation (-2, 47, 24) within a patch of 7 contiguous pixels (Right) located in the medial frontal gyrus (BA 9). Other areas on this slice that met the statistical threshold criteria for significance were omitted for clarity.

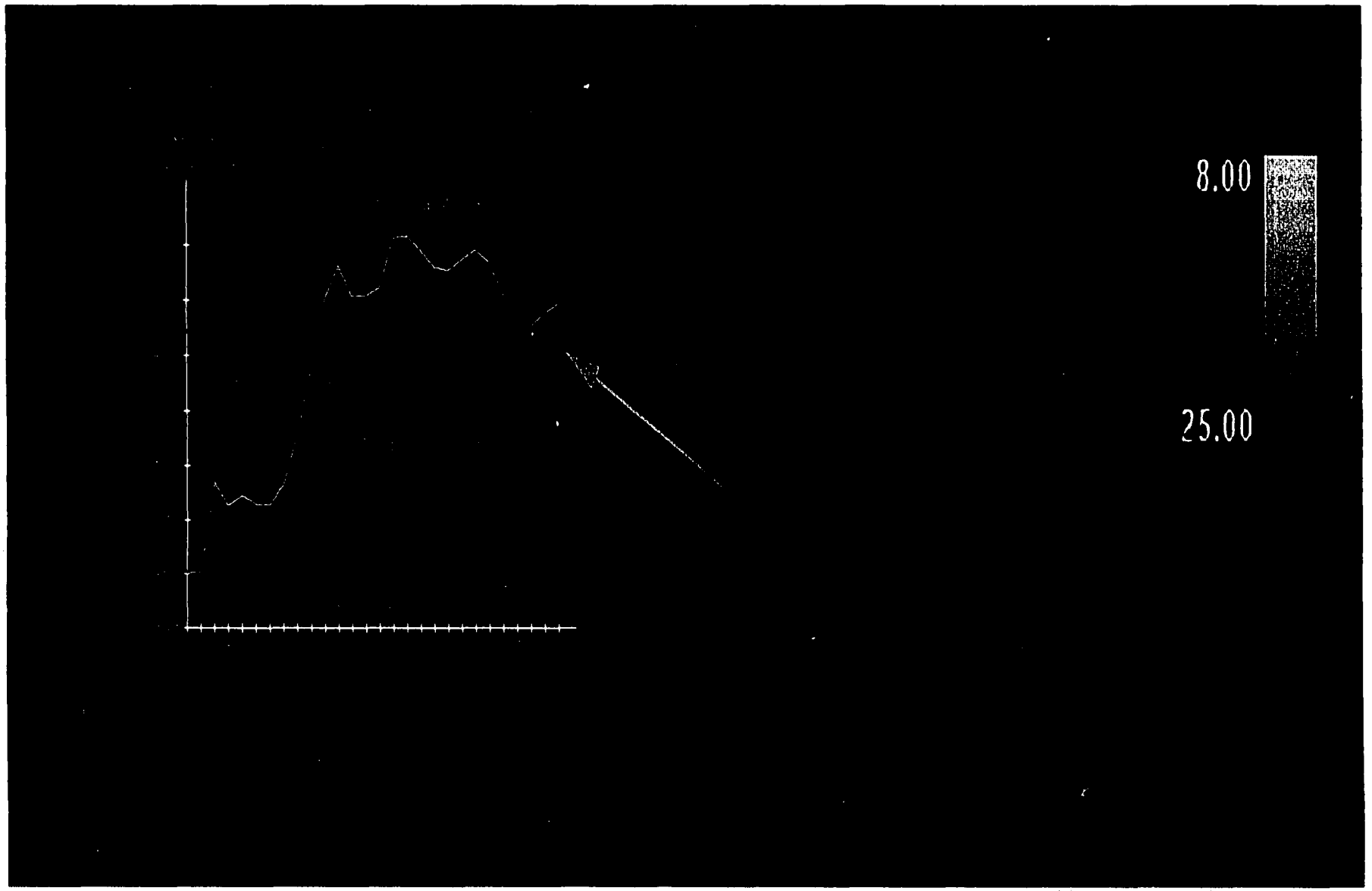


Fig. 5. Emotional Decision Task: (Top left) The Word Condition by Time Course interaction [$F(27,216)=3.52$; $P<0.0001$] in the pixel with maximum activation (63, -0.5, -12) within a patch of 5 contiguous pixels (Right) located in the right middle temporal gyrus (BA 21). Other areas on this slice that met the statistical threshold criteria for significance were omitted for clarity.

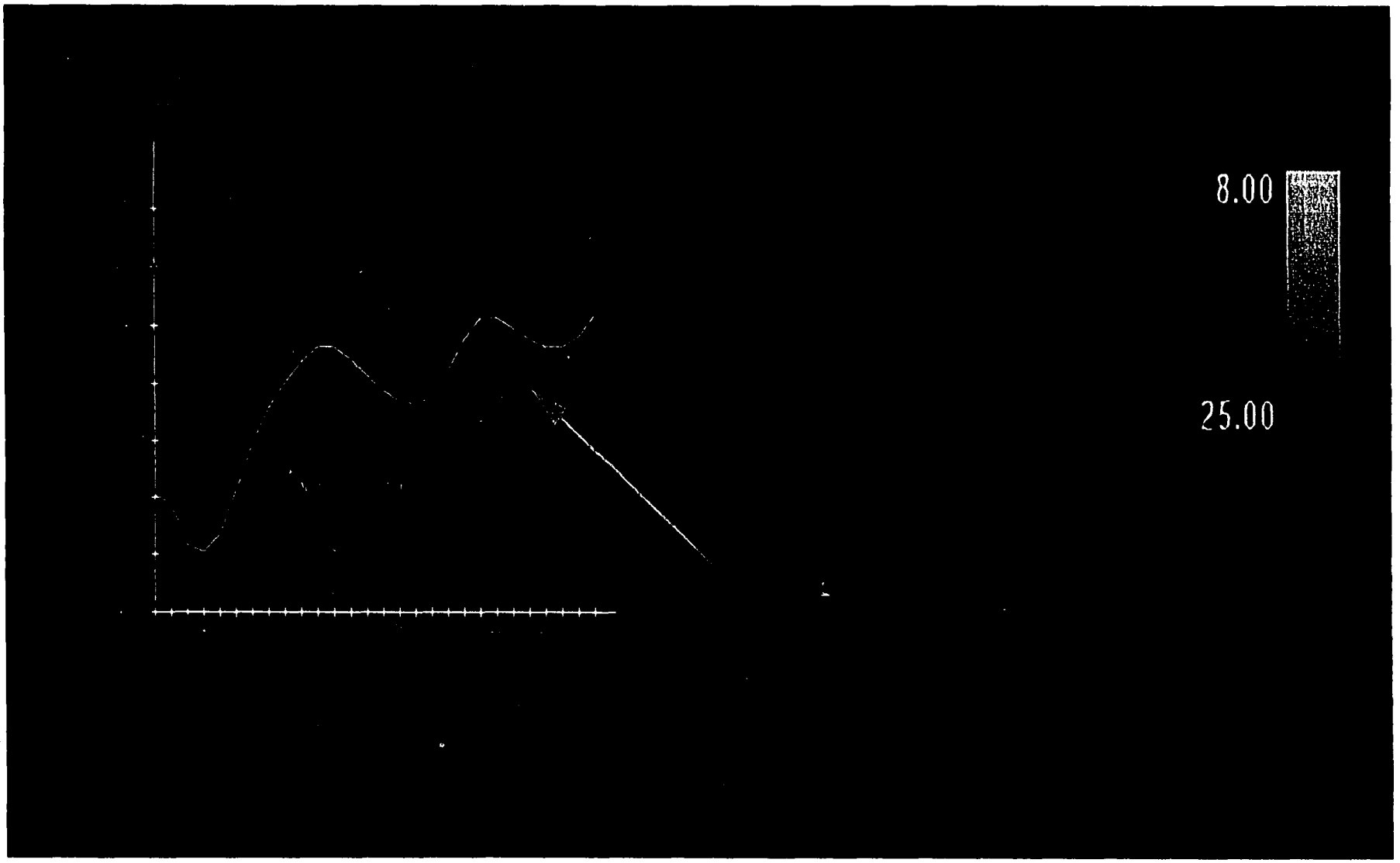


Fig. 6. Emotional Decision Task: (Top left) The Word Condition by Time Course interaction [$F(27,216)=3.40$; $P<0.0001$] in the pixel with maximum activation (54, -56, 20) within a patch of 6 contiguous pixels (Right) located in the right superior temporal gyrus (BA 39). Other areas on this slice that met the statistical threshold criteria for significance were omitted for clarity.

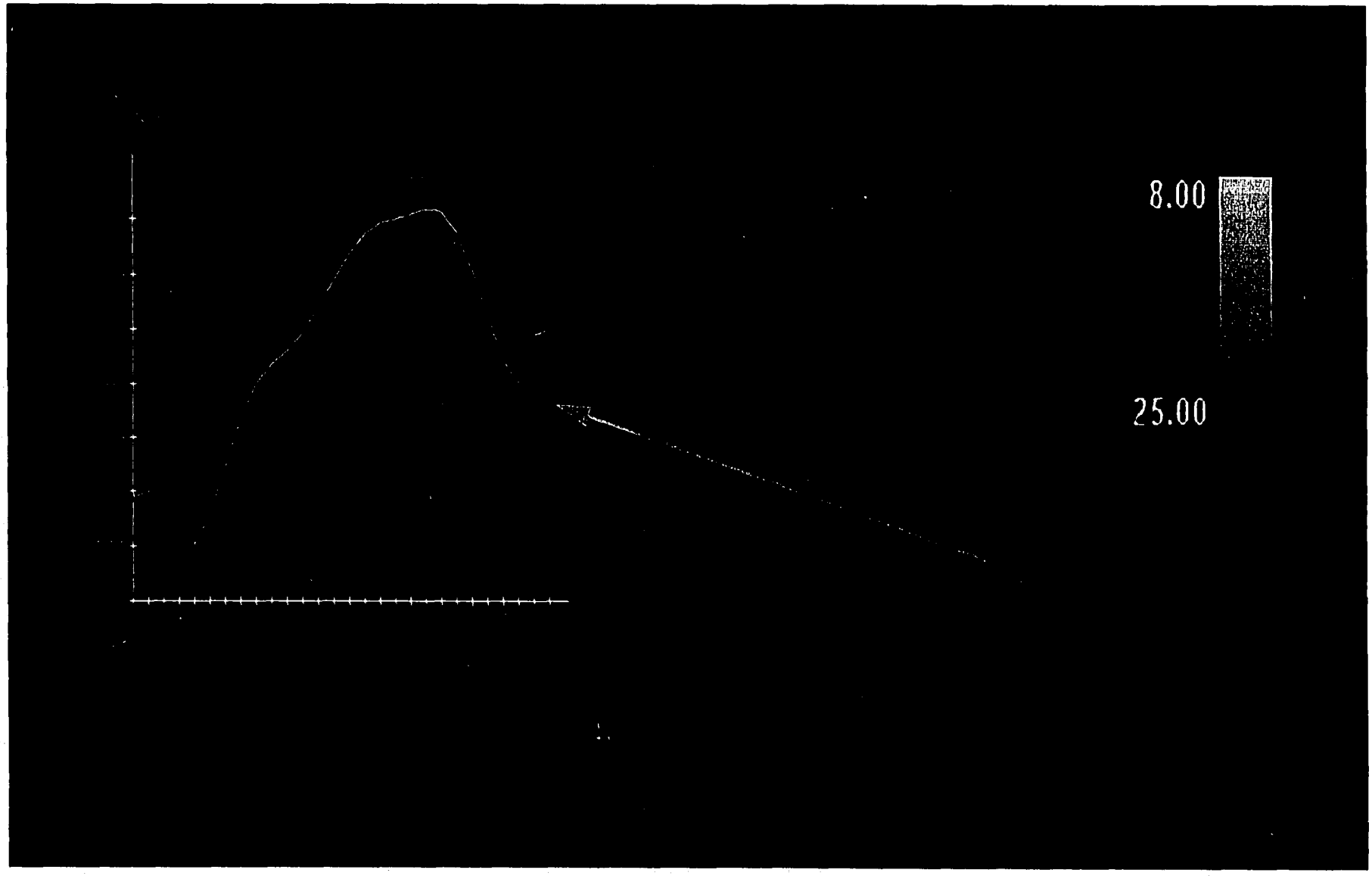
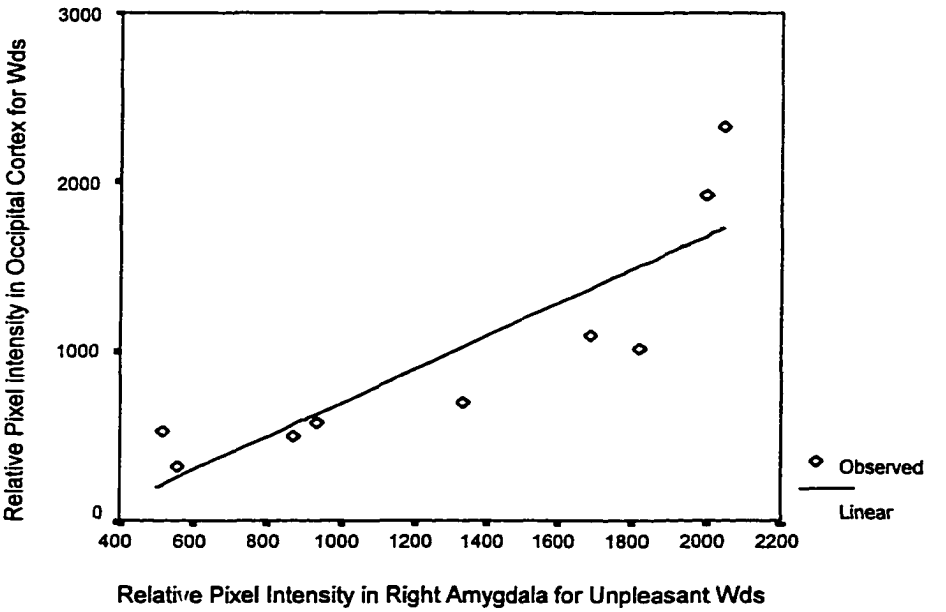


Fig. 7. Emotional Decision Task. (Top left) The main effect of Time Course [$F(27,216)=3.00$; $P<0.0001$] in the pixel with maximum activation (-63, -53, 12) within a patch of 4 contiguous pixels (Right) located in Wernicke's area (right posterior superior temporal gyrus, BA 22). Other areas on this slice that met the statistical threshold criteria for significance were omitted for clarity.

Fig. 8. Emotional Decision Task: (Left) The main effect of Time Course [$F(27,216)=13.57$; $P<0.000$] for the pixel of maximum activation (-25,-85,12) within a atch of 108 contiguous pixels (Right) located in visual cortex (Brodmann areas 17, 18, 19). This 108-pixel patch is the largest area/volume of activation (maximum patch) on this axial slice. Other areas that met statistical threshold criteria for significance are omitted for clarity.

(a)



(b)

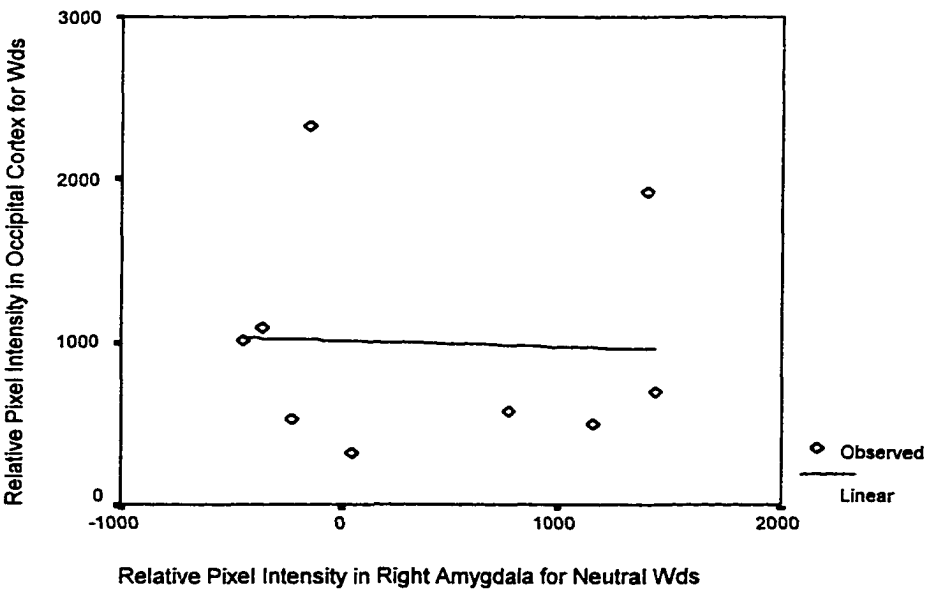


Fig. 9. Scatterplots illustrating the correlation between the peak BOLD response in the pixel of maximum activation in the right amygdala (26,-6,-12) and occipital cortex (-21,-85,12). (a) Amygdala response to unpleasant words (Wds) vs. the overall occipital response to words (i.e., unpleasant and neutral). (b) Amygdala response to neutral words vs. overall occipital response to words. Regression lines have been fitted to the data (slopes: +0.989 and -0.038, respectively; correlation coefficients (r): +0.866 and -0.043, respectively).

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