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AN FMRI STUDY OF AMYGDALA ACTIVATION
DURING EMOTIONAL PROCESSING OF FACES AND PICTURES

by

Michelle L. Keightley

A thesis submitted in conformity with the requirements
For the degree of Masters of Arts
Graduate Department of Psychology
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AN FMRI STUDY OF AMYGDALA ACTIVATION
DURING EMOTIONAL PROCESSING OF FACES AND PICTURES

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Masters of Arts, 1999
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Abstract

The role of the amygdala during the emotional processing of faces and pictures was investigated in 10 young participants (5 male and 5 female). fMRI BOLD signal contrasts were obtained while participants performed an implicit or explicit emotional processing task, and during passive viewing of neutral stimuli. Data were processed using SPM and linear contrasts were specified to compare patterns of brain activation. The amygdala showed significant bilateral BOLD signal increases during processing of emotional faces compared to emotional pictures, and a non-significant bilateral increase during the emotional faces compared to the neutral faces condition. The amygdala was not activated during emotional or neutral processing of pictures. This supports the hypothesis that the amygdala evaluates biologically significant stimuli—particularly faces, for emotional content and possible threat.
Table of Contents

Acknowledgements..............................................................................................................iv
List of Tables.......................................................................................................................v
List of Figures.......................................................................................................................vi
List of Appendices...............................................................................................................vii
Introduction.........................................................................................................................1
  Anatomical Connections of the Amygdala.................................................................2
  Animal Behaviour Studies.........................................................................................4
  Clinical Neuropsychological Studies.....................................................................8
  Amygdala Neuroimaging Research Results.........................................................12
  Present Study...............................................................................................................19
  Predictions...................................................................................................................21
Methods............................................................................................................................22
  Participants...................................................................................................................22
  Assessment Instruments..........................................................................................22
  Emotional Stimuli.........................................................................................................22
  Experimental Paradigm...............................................................................................23
  Stimulus Presentation...................................................................................................23
  Image Acquisition.........................................................................................................25
  Image Analysis...............................................................................................................25
  Linear Contrasts.............................................................................................................26
  Amygdala Search............................................................................................................27
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Tables

Table 1.
Maxima of Regions Showing Significant BOLD Signal Changes
in Stimulus Comparisons.................................................................50

Table 2.
Maxima of Regions Showing Significant BOLD Signal Changes
in Face Comparisons........................................................................51

Table 3.
Maxima of Regions Showing Significant BOLD Signal Changes
in Picture Comparisons......................................................................52

Table 4.
Maxima of Amygdala Region Showing BOLD Signal Changes
Across All Comparisons...................................................................53
List of Figures

Figure 1.
A Statistical Parametric Map of Emotional Faces versus Emotional Pictures..............55

Figure 2.
A Statistical Parametric Map of Emotional Pictures versus Emotional Faces.............57

Figure 3.
A Statistical Parametric Map of Emotional Faces versus Neutral Faces..................59

Figure 4.
A Statistical Parametric Map of Emotional Pictures versus Neutral Pictures............61
List of Appendices

Appendix A.
Screening Form.................................................................63

Appendix B.
Information Sheet and Consent Form..................................65
An fMRI Study of Amygdala Activation During Emotional Processing of Faces and Pictures

Emotion contains physiological components (central and autonomic system activity), distinctive behaviours associated with emotional states (e.g. facial expression, tone of voice, posture etc.) and cognitive processes (e.g. subjective feelings, memories etc.) (Kolb & Wishaw, 1996). Emotion serves many functions in humans including: the elicitation of autonomic and endocrine responses that prepare the body for action, motivation (e.g. to avoid punishment and gain reward), communication (e.g. facial expressions) and social bonding. Thus, there are a wide range of functions and experiences that are considered to fall under the classification of "emotion".

Rolls (1999) defines emotions as "states elicited by rewards and punishers, including changes in rewards and punishments" (Rolls, 1999, p. 60-61), where a reward is anything an individual will work to achieve, and a punisher, anything an individual will work to avoid. For example, happiness is an emotion that results from a hug or a pleasant touch, while fear can be produced by an angry expression on a person’s face. He indicates that this theory provides an operational definition of what causes an emotion, which is important for scientific investigation. LeDoux (1995) suggests the need to abandon the search for a "global" theory of emotion. He believes that combining research findings on various emotional states such as fear, anger, aggression etc., does not facilitate an explanation of how emotion is represented in the brain. He suggests that it may be more useful to focus on "specific, well-defined and experimentally addressable aspects of emotion, through the use of model systems of emotion, rather than on the global concept of emotion" (LeDoux, 1995, p. 1049).
In line with such reasoning, the present study examines the role of the amygdala in the emotional processing of visual stimuli. Animal research has implicated the amygdala in fear-conditioned responses, learning stimulus-reward associations, as well as responding to novel and reinforcing stimuli including the processing of faces. In humans, the processing of emotional stimuli does not always require activation of the amygdala, and activity may depend on the biological significance of the stimuli (e.g. new faces) and the context in which it is presented. Thus, the study will compare the visual processing of emotional faces and pictures to clarify the nature of amygdala activation.

Anatomical Connections of the Amygdala

The amygdala is a subcortical structure located in the anterior part of the temporal lobe. The structural connections of the amygdala reveal its functional importance in a network designed to assign emotional significance to external stimuli. The amygdala receives anatomical inputs from the higher stages of sensory processing in the visual and auditory cortex including the inferior temporal visual cortex, the superior temporal auditory cortex, the cortex of the temporal pole, and the cortex in the superior temporal sulcus. Subcortical inputs to the amygdala come from the midline thalamic nuclei, the subiculum and CA1 portions of the hippocampal formation. It also receives inputs from the hypothalamus and substantia innominata, the nucleus of the solitary tract (which receives gustatory and visceral inputs), and from olfactory structures (Rolls, 1999). The connections are defined for the visual system given its relevance to the current study.

Visual information from the retina is transmitted over the optic nerve to the dorsal lateral geniculate body (LGd) of the thalamus, the superior colliculus and other targets. This quick description provided by LeDoux (1993) traces the flow of information from
the LGd, although he acknowledges the significance of other projections. The LGd receives lemniscal (retinotopic) inputs, which are relayed to laminae III and IV of the primary visual cortex (also known as striate cortex). Striate cortex projects to prestriate cortex, which in turn projects to inferotemporal cortex (IT). At each subsequent stage of projection, retinal input undergoes more intricate transformations. For example, neurons in the striate cortex extract simple features such as edges and angles, while IT processes more complex, higher-level characteristics such as global object properties.

Information processed in IT is transmitted to the amygdala and higher-order association areas of frontal, temporal and parietal lobes, which participate in multi-modal system integration of input. The amygdala is able to assign emotional significance to sensory stimuli, because its anatomical connectivity supplies it with information from later processing stages from polymodal association cortex (LeDoux, 1993).

It has been documented that information flow can proceed from the sensory thalamus directly to the amygdala without involving the visual cortex. This thalamo-amygdala projection is involved in the conditioning of emotional responses to simple stimuli (e.g. flashing light paired with foot shock) (LeDoux, Romanski, & Xagoraris, 1989). LeDoux (1993) postulates that such a pathway represents an evolutionary primitive system (developed in early vertebrates) which continues to function as an early warning system, allowing the amygdala to be activated by simple stimulus features that can become emotional triggers, particularly in situations which require quick responding.

Rolls (1999) summarizes the outputs from the amygdala that project to areas responsible for appropriate behavioural response to emotional stimuli. The lateral amygdala projects via the amygdalofugal pathway to the lateral hypothalamus, which is
involved in autonomic system functioning. The medial amygdala projects via the stria terminalis to the medial hypothalamus. The ventral amygdalofugal pathway includes some long descending fibres that project to the autonomic centres in the medulla oblongata, providing a route for cortically processed signals to reach the brainstem. The amygdala also projects to the ventral striatum including the nucleus accumbens, which gives information processed in the amygdala access to the basal ganglia to influence motor output. A further projection of the amygdala involves the medial part of the mediodorsal nucleus of the thalamus, which projects to the orbitofrontal cortex. The amygdala also projects directly to the orbital frontal cortex, anterior cingulate and temporal pole and there are many feedback loops to the temporal, orbitofrontal and insular cortices from which the amygdala receives inputs. The amygdala thus represents an important site of interaction between the emotional processing of external events and appropriate emotional response (LeDoux, 1993).

**Animal Behaviour Studies**

Evidence of the amygdala's involvement in emotion was first observed through animal research. Klüver and Bucy (1937, 1939) discovered that temporal lobe lesions in monkeys resulted in the taming of pre-operatively wild and aggressive animals. Lesioned monkeys were found to no longer fear previously threatening stimuli, display inappropriate sexual advances (e.g. attempt copulation with members of other species) and to eat a variety of things that "normal" primates found undesirable (e.g. feces, rocks and meat). They isolated the amygdala as the critical site for producing this behaviour.

Downer (1961) expanded on this research and found that unilateral lesions in the amygdala resulted in hypoemotional response to visual stimuli in monkeys. He
An fMRI Study of Amygdala Activation

suggested that the affective significance of visual stimuli will not be recorded unless the visual information processed by cortical areas is also processed in the amygdala. The results of this study have led to the view that sensory stimuli are endowed with emotional and motivational significance by processing that takes place in the amygdala (LeDoux, 1992). Amygdala lesions in primates also appear to interfere with the formation of cross-modal associations (LeDoux, 1992). Kluver-Bucy syndrome may therefore result from an inability to integrate sensory input from different modalities as well as defective processing of affective significance (LeDoux, 1992).

Neural activity has been recorded in the amygdala during exposure to emotional stimuli (Fried, MacDonald & Wilson, 1997). Amygdala neurons are receptive to sensory stimuli from various modalities, but are most sensitive to stimuli containing biological significance for the organism (LeDoux, 1992). For example, amygdala units demonstrate responsiveness to faces and complex visual stimuli with clear emotional significance (Fried et al., 1997). A group of neurons that respond primarily to faces has been found in the basal accessory nucleus. These neurons probably receive inputs from a group of neurons in the superior temporal sulcus which respond to faces on the basis of features such as eyes, hair or mouth (Rolls, 1999). The tameness of Kluver-Bucy syndrome and the inability of amygdalectomized monkeys to interact normally in social settings could be the result of damage to this system (Rolls, 1999).

Some amygdala neurons appear to be selectively sensitive to rewarding and aversive stimulus properties. Neurons that respond to reward also respond to novel visual stimuli. This effect was demonstrated in a serial recognition memory task where neurons in the primate amygdala responded the first and second time a visual stimulus was
shown. The repeated presentation of a stimulus resulted in rapid habituation of the neuronal response and behavioural approach, if the stimulus was not associated with a primary reinforcer (Rolls, 1999). Amygdala neurons thus act as filters, and are increasingly active if a biologically significant stimulus is unfamiliar and less active if the stimulus is familiar.

Studies of fear conditioning use a classical conditioning paradigm to examine the role of the amygdala in emotion response (LeDoux, Iwata, Cicchetti & Reis, 1988). Classical conditioning experiments induce emotional reactions to emotionally neutral stimuli when they are temporally paired with an aversive event. For example, LeDoux and colleagues (LeDoux et al., 1988) have extensively investigated fear conditioning in rats and demonstrated that when a pure tone is paired with foot shock, it evokes a conditioned fear reaction consisting of freezing behaviour accompanied by autonomic adjustments (including increases in arterial pressure and heart rate). This response was no longer observed following amygdala lesions. The amygdala is involved in both the acquisition and expression of fear conditioning, as it has been demonstrated that posttraining lesions of the amygdala inhibit fear conditioning, even with extensive overtraining prior to the surgery (Kim & Davis, 1993).

Emotional associations formed through subcortical inputs to the amygdala are immune to extinction and forgetting processes (LeDoux, 1992). Visual cortex lesions were not found to interfere with the acquisition of fear responses conditioned to visual stimuli. In addition, when animals were subsequently given an unreinforced presence of the conditioned stimulus, they failed to extinguish the fear response over the duration of a month (LeDoux et al., 1989). These results suggest inflexibility in the emotional valence
assigned to a stimulus by the amygdala. Rolls (1999) supports this theory by
demonstrating that when the association between a visual stimulus and reinforcement was
altered by reversal (e.g. visual stimulus associated with juice reward becomes associated
with aversive saline and vice versa), ten out of eleven neurons in the primate amygdala
did not reverse the response. Such a change probably requires the use of other
structures, such as the orbitofrontal cortex (LeDoux, 1992; Rolls, 1999).

There appears to be evidence from animal research implicating different areas of
the amygdala involved in fear versus anxiety (Davis, 1998). Lesions of the central
nucleus in rats block expression of fear-potentiated startle to either a visual or auditory
conditioned stimulus. A similar effect is produced by the blockade of glutamate receptors
in the central nucleus of the amygdala (via local infusion of a non-NMDA glutamate
receptor agonist). The fear-potentiated startle effect is dependent on Pavlovian
conditioning as it occurs when a light is paired (three to four seconds prior) with a shock
a few times, but does not occur when the lights and shocks are presented randomly. The
startle effect is elicited by a loud sound five to twenty minutes after a bright light has
been turned on and does not depend on prior conditioning. According to Davis (1998),
this reflects a more unconditioned anxiogenic effect. Rats with bilateral cannulas
inserted into the bed nucleus of the stria terminalis, basolateral complex of the amygdala
or the central nucleus of the amygdala were tested following glutamate antagonist NBQX
infusion. Local inactivation of the basolateral nucleus of the amygdala or bed nucleus of
the stria terminalis significantly decreased light-enhanced startle, an effect that was not
found during local inactivation of the central nucleus. Davis (1998) concludes that the
central nucleus of the amygdala may be more involved in fear, while the basolateral areas of the amygdala are more active during anxiety.

The amygdala is clearly involved in the learning and retention of fear conditioned responses. Research has also established the importance of amygdala-ventral striatal interactions in reward-related processes (Everitt & Robbins, 1992). The basolateral parts of the amygdala project to the ventral striatum, which may be a site where affective processes occurring in the limbic forebrain connect with subcortical elements of the motor system and influence action. Amygdala lesions were found to attenuate rats' ability to maintain conditioned responses when a previously neutral stimulus was paired with sexual reinforcement, as well as abolish expression of place preference conditioned to the presence of food. It was suggested that subsequent stimulus-reward associations were prevented by damage to the basolateral parts of the amygdala (Everitt & Robbins, 1992).

The results of animal behaviour studies have provided significant contributions to the understanding of basic emotion responding, which can be conceptually transferred to human emotion. Research in this area has traditionally focused on the functional effects of amygdala lesions in humans.

Clinical Neuropsychological Studies

Stereotaxic amygdalotomies have been performed on patients exhibiting aggressive and antisocial behaviour in order to reduce emotional excitability. A review of surgeries has concluded that small amygdala lesions can produce a calming effect, but not the global hypoemotionality observed in primates. The more extensive the lesion, the wider range of emotion affected (Narabayashi & Shima, 1973; as cited in Aggleton, 1992).
Sixty aggressive/hyperactive patients received small unilateral or bilateral stereotaxic lesions to approximately one-third of the amygdala. Post-operative assessment determined that fifty-one (eighty-five percent) of the patients exhibited decreased emotional excitability and "normalization" of social behaviour, but were not classified as emotionless or apathetic (Narabayashi, Nagao, Saito, Yoshida & Naghata, 1963). Hitchcock and Cairns (1973) examined the effects of unilateral/bilateral medial amygdala lesions in fifteen epileptic patients exhibiting abnormal aggressive behaviour. They found that approximately half demonstrated a clear decrease in destructive and antisocial behaviour. An investigation of a woman who received subcaudate tractomy followed by a two-stage bilateral amygdalotomy for treatment of self-mutilation, revealed a blunting of emotions as a consequence of surgery. This effect included a marked placidity demonstrated by an absence of anger that extended across all social situations. Subjective self-report indicated that her emotions felt different and unfamiliar, but not dull (Jacobson, 1986). It thus appears that amygdala lesions can result in some loss or change of affect that extends beyond aggression, but that the extent and likelihood of change depends on the size and possibly the location of the lesion (Aggleton, 1992).

Case studies of patients suffering from Urbach-Wiethe disease have also provided researchers with indication of amygdala function in emotion in humans. One such patient, S.M., had nearly complete bilateral destruction of the amygdala, but spared hippocampus and surrounding neocortical structures. Adolphs and colleagues (Adolphs, Tronel, Damasio & Damasio, 1994) used facial expressions of emotion to examine if bilateral destruction of the amygdala in S.M. would impair recognition of basic emotional facial expressions and recognition of several emotions shown in a single expression.
They found that S.M. rated expressions of fear, anger and surprise as less intense than did brain-damaged controls, and exhibited severe recognition impairments specific to fear. Ratings of fearful faces correlated less with normal subjects' ratings than did those of any brain-damaged controls. The researchers concluded that the amygdala is involved in processing the expression of single, basic emotions, specifically in the recognition of fear.

A patient with bilateral damage to the amygdala did not acquire conditioned autonomic response to visual/auditory stimuli, but did acquire declarative facts about which visual/auditory stimuli were paired with the unconditioned stimulus (Bechara et al., 1995). In contrast, a patient with bilateral damage to the hippocampus failed to acquire the declarative knowledge, but did acquire conditioning. A patient with bilateral damage to both the amygdala and hippocampus acquired neither the conditioning nor the facts about the conditioning paradigm. This suggests a double dissociation of conditioning and declarative knowledge in humans and emphasizes the role of the amygdala in conditioned responding.

Skin conductance responses (SCR's) have been demonstrated as being a reliable index of conditioning in humans (Fredrikson, Annas, Georgiades, Hursti & Tersman, 1993). LaBar and colleagues (LaBar, LeDoux, Spencer & Phelps, 1995) examined fear conditioning in human subjects with unilateral anteromedial temporal lobe resection to control medically intractable epilepsy. Simple and conditional discrimination tasks were conducted to examine the role of the medial temporal lobe in simple and complex aspects of associative responding. In the simple discrimination task, two tones served as conditioned stimuli (CS), and the unconditioned stimulus (US) was a white noise burst.
During the conditional discrimination task, subjects received a 2000 Hz tone as the CS and a white noise burst as the US, which they had to learn to associate with a green light. Patients demonstrated impaired conditioning primarily attributable to deficits in responding during paired CS-US acquisition trials. The authors conclude that amygdala damage in patients was primarily responsible for learning impairments because the patients exhibited similar response patterns across both simple and complex tasks, suggesting a common neurobiological substrate (LaBar et al., 1995). Furthermore, animal studies have also shown that selective amygdala lesions disrupt both simple and complex aspects of fear conditioning (LeDoux et al., 1988).

Research investigating the effects of amygdala lesions in humans has been complicated by many factors, such as the lack of a disease that affects just the amygdala. One exception may be Urbach-Wiethe disease, which may occasionally result in selective amygdala damage. Many patients have received either unilateral or bilateral amygdala lesions in an attempt to control epilepsy. This complicates subsequent investigations given that the pre-operative brain was already abnormal, and may have contained unsuspected neuropathology at the time of the surgery (Aggleton, 1992). A related problem refers to the type of person undergoing neurosurgery. A significant number of patients have been assessed as possessing a lower level of intelligence, and/or behavioural disorders. Also, there is inconsistency in the literature, and cases where patients with bilateral amygdala damage do not show a deficit in facial affect processing (Aggleton, 1992) indicating that while the amygdala is involved in the interpretation of facial expressions, it is not clear how critical it is.
Studies examining neural networks of emotion have utilized recently developed neuroimaging methods to enhance experimental control. Improvement in imaging techniques such as regional cerebral blood flow (rCBF) associated with positron emission tomography, (PET) have allowed researchers to determine if activation patterns observed during emotional induction differ from baseline or emotionally "neutral" measures, and if the pattern is characteristic of a specific type of emotion. Functional magnetic resonance imaging (fMRI) has evolved even more recently, and provides the additional advantage of representing a non-invasive method for scanning, which could control for potential confounds when examining emotional reactivity, possibly caused by the anxiety associated with invasive techniques.

**Amygdala Neuroimaging Research Results**

**Fear Conditioning In Humans.** Activation in the amygdala and periamygdaloid cortex has been observed in humans during conditioned fear acquisition. LaBar, Gatenby, Gore, LeDoux and Phelps (1998) investigated the effects of pairing one visual conditioned stimulus (CS; a blue square) with electric shock (unconditioned stimulus; US), while a second CS (yellow square) was presented alone. During habituation and extinction both CS were presented alone. Group-averaged results for conditioned fear acquisition found activation in the right hemisphere with a focus in the medial periamygdaloid cortex. Individual data revealed activation of the left amygdala in several subjects, with the extent of activation during acquisition correlating significantly with skin conductance responses during conditioning. The response profile of the right amygdaloid region showed habituation from early to late stages of acquisition and extinction, but intensity reduction was only statistically reliable during extinction. The
authors conclude that the amygdala may be preferentially active during the novel or initial stages of learning when the emotional meaning of stimuli is actively encoded (LaBar et al., 1998).

A PET study performed by Furmark, Fischer, Wik, Larsson and Fredrikson (1997) examined rCBF in the amygdala in eight women before and after aversive conditioning to videos of snakes. Change in amygdala activation was correlated with differences in conditioned autonomic nervous system activity as measured by non-specific electrodermal fluctuations (EDA). The fear conditioning procedure involved a habituation phase where a snake video was presented without any shocks while rCBF was being measured. In the acquisition phase, the video was paired with six shocks (CS) but no indices of rCBF were recorded. In the final extinction phase, the snake video was displayed without shocks while rCBF was again assessed. The authors found a significant positive correlation between rCBF and increased EDA in the right but not the left amygdala.

Amygdala activity was recorded during the processing of "unseen" fear in ten male subjects. Morris, Ohman and Dolan (1999) used a conditioning paradigm with four different conditions. In the unseen CS+, a noise-paired angry face was presented as the target, while the neutral face was the mask. The seen CS+ condition contained a neutral face as the target and a noise-paired angry face as the mask. An angry face (not noise-paired) was the target in the unseen CS- condition, while the neutral face was the mask. Finally, in the seen CS- condition the CS- angry face was the mask, while the neutral face was the target. Morris et al. (1999) found significant bilateral amygdala response to the noise-paired angry faces. However the right amygdala responded only to the unseen
noise-paired angry faces whereas the left amygdala demonstrated a differential response only to the seen noise-paired angry faces. This suggests that conscious attention to emotional stimuli is not required for amygdala activity.

There is some evidence that the amygdala is activated during fear in humans beyond classical conditioning paradigms. Birbaumer et al. (1998) conducted a fMRI session comparing seven female patients with social phobia (intense, irrational fear of social situations and evaluation by others) to five normal females. Subjects were presented with two slides of neutral faces, an aversive foul odour and a neutral air puff, each repeated ten times. Both groups demonstrated more bilateral activation of the amygdala during aversive odours. The neutral face stimuli were associated with significantly increased bilateral activation of the amygdala in the social phobics, but not in the healthy controls, while subjective ratings of the faces did not differ for the two groups. The latter finding suggests abnormal amygdala activation to non-emotional stimuli in social phobics.

**Face Processing.** Neuroimaging studies have extensively investigated amygdala activation during the processing of faces, based on results from animal research, clinical neuropsychological data and conditioned fear responses. Breiter et al. (1996) used fMRI to measure amygdala activity in right-handed males during rapid visual presentations of fearful, happy and neutral faces. They observed anterior amygdala activation during visual processing of fearful versus neutral faces, with the left hemisphere demonstrating greater activation than the right. They also found left anterior amygdala activation for the comparison of happy versus neutral faces, suggesting amygdala activation across emotional expressions. Posterior amygdala activation showed positive signal changes to
neutral faces relative to a low-level baseline of simple visual stimuli. These results suggest that along with the control region of the fusiform gyrus, the posterior amygdala might respond to faces in general. The relative magnitude of amygdala activation decreased significantly from the first to the second epoch of neutral, fearful and happy faces, suggesting a within-run habituation effect (Breiter et al., 1996).

A study by Whalen et al. (1998) led to the observation that masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. They used fMRI to examine the role of the amygdala in response to emotional stimuli in the absence of explicit knowledge that such stimuli were presented. Pictures of human faces (fearful or happy expressions) were presented to ten normal subjects using a backward masking procedure. Although subjects only reported seeing neutral faces, blood oxygen-level dependent (BOLD) fMRI signal in the amygdala increased significantly in both hemispheres, in response to masked fearful faces and decreased significantly in both hemispheres, to masked happy faces. Unlike the previous experiment this study suggested that the level of amygdala activation is affected differentially by the emotional valence of external stimuli (Whalen et al., 1998).

Morris et al. (1996, 1998) also found a differential neural response in the human amygdala to fearful and happy facial expressions. Morris and colleagues examined rCBF in four men and one woman while subjects viewed pictures of facial affect (happy or fearful) which ranged across six levels of intensity. They found that the left amygdala and left periamygdaloid cortex were the most significant areas of activation when fearful faces were contrasted with happy faces (there was no right amygdala activation). The contrast of happy with fearful expressions was associated with activation in the right
medial temporal gyrus, right putamen, left superior parietal lobe and left calcarine sulcus. Changes in the intensity of facial expressions resulted in a monotonic increase in left amygdala activation from the most happy to the most fearful condition. This suggests that the amygdala may play a crucial role in mediating neural response to fearful facial expressions, and supports the theory that the amygdala is involved in assigning affective significance to external stimuli.

Blair and colleagues (1999) examined neural response in thirteen men during a gender discrimination task performed on sad and angry facial expressions. They found left amygdala and right inferior and middle temporal gyri activation during the processing of sad but not angry expressions. The right orbitofrontal cortex was significantly activated during the angry but not sad expressions and anterior cingulate cortex and right temporal pole activation were common to both expressions. The authors interpret the lateralization of the amygdala as resulting from the modulation of left hemisphere systems such as language, but they did not clarify the reason for this suggestion.

In contrast with other research findings, Schneider et al. (1997) did not find evidence of dissociation for amygdala activity according to emotional valence. They had seven men and five women induce a happy and sad mood according to the facial expressions presented to them. The two moods did not have a differential effect on neural activation patterns measured with fMRI. In particular, the left amygdala demonstrated an increase in signal intensity in response to both sad and happy moods.

Nakamura et al. (1999) failed to find amygdala activation when they examined the effects of a facial emotion task versus an assessment of facial attractiveness, or colour discrimination. In their study, they had men assess female faces that were presented on
either a red, yellow or blue background. This would be expected if the amygdala is active in both explicit and implicit emotional processing as indicated by Morris et al. (1996, 1998) and Whalen et al. (1998). In a separate study, there was also no evidence for amygdala activation when eight female subjects were instructed to hold a happy or neutral face in memory during a 45 second delay, and then match it to one of two faces (Dolan et al., 1996). Taken together, these variable findings suggest that the role of the amygdala may be very specific and its activity during emotional processing of faces may depend on factors such as emotional valence and type of task.

Picture Processing. Amygdala activation during assessment of affective stimuli has been investigated beyond the processing of facial expressions. A PET study performed by Lane et al. (1997) examined neural activity in twelve women while viewing pleasant, unpleasant and neutral pictures taken from the International Affective Picture System (IAPS), a standardized set of images designed to elicit a range of emotional responses. The results revealed significant increase in activation of the thalamus, hypothalamus, midbrain and medial prefrontal cortex associated with the pleasant and unpleasant pictures, compared to neutral pictures. Pleasant versus neutral pictures activated the above structures plus the head of the caudate nucleus, while unpleasant versus pleasant and neutral pictures were also found to activate the left amygdala, hippocampus, parahippocampal gyrus, bilateral occipito-temporal cortex and the cerebellum.

Lane, Chua & Dolan (1999) examined the effects of emotional valence, arousal and attention on neural activation in six men during the visual processing of pictures taken from the IAPS. This study differed from the previous one by having subjects
perform a subjective rating following each picture sequence to provide an indication of arousal. The results of the rCBF data measured with PET found activation in the putamen, medial prefrontal cortex, right anterior temporal cortex and left extrastriate visual cortex for the pleasant versus neutral pictures. Unpleasant versus neutral pictures revealed significant activation in the right extrastriate visual cortex. Bilateral extrastriate visual cortex and the right anterior temporal region demonstrated significant activation when pleasant and unpleasant pictures were contrasted with neutral pictures. Amygdala activation was found only when high arousal pleasant and unpleasant pictures were contrasted with low arousal pleasant and unpleasant pictures and it occurred in the left hemisphere. These results seem to suggest that amygdala activation during picture processing is not based on the emotion of the stimulus, but interacts with the biological significance of the stimuli as indicated by indices of arousal. Taylor et al. (1998) also found left amygdala activation in eight women during the processing of fear and disgust pictures taken from the IAPS. However, this activation was only associated with the initial presentation of negative stimuli and demonstrated rapid habituation.

A study by Lane, Fink, Chau and Dolan (1997) investigated subjective emotional responses in men while they were viewing emotional pictures taken from the IAPS. This is different from the previous studies that focused on the assessment of external emotional valence of stimuli. During the internal focus condition, subjects were instructed to evaluate whether the picture evoked a pleasant, unpleasant or neutral feeling. During the external focus condition, subjects determined whether the picture took place indoors or outdoors. Contrasting the internal versus external conditions resulted in a significant increase in activity in the anterior cingulate cortex, medial
prefrontal cortex and right temporal pole. Contrasting the external versus internal conditions produced a significant increase in activation of the left parieto-occipital cortex, while there was no evidence of amygdala activation in either contrast. This is consistent with imaging research examining mood induction which does not show amygdala activation but does show cingulate activation (Mayberg, 1997).

Neuroimaging studies have implicated the amygdala as a potentially important area involved in the processing of emotional faces, particularly those can be interpreted as threatening, such as fear or anger. It appears that the amygdala serves to assign affective significance through its extensive multimodal sensory inputs from the association areas of the cortex. However, its role in emotional processing beyond the specific context of emotional faces is unclear. In particular, neuroimaging studies provide some evidence for amygdala activation during picture processing but this has been less consistent than that seen for faces. No one has yet compared these two types of stimuli directly.

Present Study

The current study is designed to investigate the role of the amygdala during visual processing of emotional faces and pictures using functional magnetic resonance imaging (fMRI). Of particular interest is whether the amygdala is generally activated during the emotional processing of visual stimuli (e.g. faces and pictures) or if it is stimulus-dependent (e.g. just faces). Also, is the amygdala activated during explicit (conscious) emotional processing, implicit (subconscious) emotional processing or both? Is the amygdala activated by faces per se, or only in response to expressions of emotion?
Finally, when the amygdala is activated, does the signal increase occur in the left amygdala, right amygdala or bilaterally?

It is expected that the amygdala will emerge as a critical component in the emotional processing of faces, based on previous neuroimaging research (Whalen et al., 1998; Breiter et al., 1996; and Morris et al. 1996). The studies reviewed, however, contain methodological shortcomings that limit their generalizability to account for other forms of emotional processing. Many studies are limited by not including baseline comparisons which are important in order to partial out the regions that are activated while attending to faces versus the regions that are unique to processing the emotion depicted by the face. For example, Morris et al. (1996) had subjects viewing happy or fearful faces, but did not include neutral expressions for comparison.

A further limitation is the absence of a comparison task. The cognitive effort involved in making discriminations based on the visual stimuli is likely to activate regions independent of the emotion depicted. The present study attempts to control for this effect by including a gender discrimination task as well as a judgement of emotional valence to determine if brain regions are uniquely activated during the explicit versus implicit processing of the emotion associated with the face. It also remains unclear as to whether the amygdala's role in emotional processing is dependent upon the nature of the stimulus. The present study controls for stimulus type by having participants perform similar discrimination tasks in response to pictures as well as faces.

There has been variability in the literature concerning lateralization effects. For example Breiter et al. (1996) indicate bilateral amygdala activation when comparing fearful versus neutral expressions as well as happy versus neutral expressions with
greater activation occurring in the left amygdala. However Morris et al. (1996) reports a monotonic increase in left amygdala activation from most happy to most fearful facial expressions. Morris et al. (1996, 1998) found only left amygdala activation when comparing fearful versus happy facial expressions. Conditioning experiments seem to find right or bilateral amygdala activation (Furmark et al., 1997; Morris et al., 1999) while perceptual experiments find left or bilateral amygdala activation (Morris et al., 1996, 1998). The present study will investigate the possibility of lateralization effects for facial expressions of emotion in an exploratory manner, given the inconsistency of previous reports.

Predictions

Given its role in assigning affective significance to external events, the amygdala is hypothesized to demonstrate significant activation during the emotional processing of faces, in both the explicit and implicit conditions (Whalen et al., 1998; Breiter et al., 1996; Morris et al., 1996, 1998). Based on previous neuroimaging results which found significant activation of the amygdala in fearful and happy faces versus neutral faces (Breiter et al., 1996), it is not expected to be significantly active during the processing of non-emotional faces. Lane et al. (1999) did not find significant amygdala activation when pleasant or unpleasant pictures were contrasted with neutral pictures, only when high arousal emotional pictures were contrasted with low arousal emotional pictures. In addition, Lane et al. (1997) found no evidence for amygdala activation in an earlier PET study performed with pictures taken from the IAPS. Therefore the amygdala is expected to not be active during the emotional processing of pictures.
Methods

Participants

Scanning was performed on 10 young right-handed individuals (mean age = 23.00 years, standard deviation = 2.10 years), with equal numbers of males and females. Participants were screened to ensure that there was no history of psychiatric, neurological, or other medical illness, or a history of substance abuse. Participants' level of emotional awareness, personality, mood and mental status were also assessed.

Assessment Instruments

Participants were screened using a standard 'Screening and Information Form' (Rotman Research Institute, see Appendix A). They also completed the Twenty-Item Toronto Alexithymia Scale (Bagby, Parker & Taylor, 1993) to assess their level of emotional awareness and the NEO Five-Factor Inventory (Costa and McCrae, 1992) to measure personality traits. The Positive and Negative Affect Schedule (PANAS-Short; Watson, Clark & Tellegen, 1988) was administered to participants to assess mood and the Mini-Mental Status Exam (Folstein, Folstein, & McHugh, 1975) for an indication of basic cognitive functioning.

Emotional Stimuli

Pictures of faces with positive, negative and neutral expressions of emotion and static pictures depicting positive, negative or neutral events (all pictures contained 1 or more people) were obtained from various magazines. Reliability for the emotional valence of the stimuli was established using inter-rater reliability procedures. The stimuli used in the experiment were unanimously rated by all six raters as emotionally positive,
negative or neutral. The raters also indicated the familiarity of each face, and only faces that were unfamiliar to all six raters were used in the experiment.

**Experimental Paradigm**

Prior to the experiment, participants were informed that the study would be examining brain activation patterns obtained by functional magnetic resonance imaging (fMRI), while they are being presented with visual stimuli consisting of faces and pictures (see Appendix B). They were also told that they would be required to make perceptual judgements in response to the stimuli. During each task run, participants were presented with six blocks of stimuli, each lasting 30 sec and alternating with 30 sec of a fixation cross for a total of 6 minutes. Two scanning sequences presented positive and negative emotional facial expressions. Two scanning sequences depicted emotionally positive and negative static pictures and one scanning sequence consisted of participants passively viewing alternating blocks of neutral faces and neutral pictures. Each face and picture was unique and only shown once to the subject. Stimuli were separated by a brief fixation cross. The order of scans was counterbalanced across participants.

**Stimulus Presentation**

**Facial Expressions.** Participants were presented with alternating 30 second epochs of experimental and control conditions. The experimental conditions required the participant to perform an implicit or explicit emotional processing task. The implicit task was a gender discrimination task, where participants received random presentations of emotionally positive and negative facial expressions and told to press the left finger button if the face was male, and the right finger button if the face was female. The explicit processing task required participants to identify the facial expression as positive
or negative, and press the left finger button if the facial expression was positive, and the right finger button if the facial expression was negative. Each experimental condition was followed by a 30 second epoch of the presentation of a single cross that served as a low-level fixation control condition (+). There were 2 lists of stimuli for each condition. In each list half the faces were male and half female. Also within each list half the faces were positive and half were negative. Conditions and stimulus lists were counterbalanced across and within subjects.

Static Pictures. Participants were presented with alternating 30 second epochs of experimental and control conditions. The experimental conditions required the participant to perform an implicit or explicit emotional processing task. The implicit task required participants to count the number of people in the picture, and press the left finger button if there were 1 or 2 people, and the right finger button if there were 3 or more people. During the explicit task, participants indicated if the context of the picture was emotionally positive by pressing the left finger button, or emotionally negative by responding through the right finger button. There were two stimulus lists for each condition. In each list half the pictures had 1 or 2 people, and half had 3 or more people. Also within each list half the pictures were positive and half were negative. Conditions and stimulus lists were counterbalanced across and within subjects.

Neutral Faces and Pictures. During the presentation of neutral stimuli, participants received alternating blocks of neutral faces and pictures, and were instructed to simply view the facial expressions and pictures as they were presented. Each block of stimuli was followed by a 30 second epoch of the presentation of a single cross that served as a low-level fixation control condition (+).
Image Acquisition

A General Electric Signa 1.5 Tesla magnet was used to obtain a T1 weighted anatomical volume SPGR (0.8 x 0.8 x 1.2 mm voxels) and T2* echoplanar images (EPI, TE = 30 msec) with blood oxygenation level-dependent (BOLD) contrast. Each EPI sequence consisted of approximately 17 7mm axial slices taken every 3 sec, positioned to image the whole brain. A total of 126 volume images were obtained with a repetition time (TR) of 3 seconds per volume. The first 26 volumes (the first block in each scan plus 18 sec dead time) in each session were removed in order to compensate for magnetization equilibrium effects.

Image Analysis

Images were analyzed using statistical parametric mapping (SPM99b, Wellcome Department of Cognitive Neurology, London, UK). Volumes were realigned to volume 27 (head movement was less than 3 mm in all participants, except subject 6 whose data was not included in subsequent analyses) and resliced using a sinc interpolation which adjusted for residual movement-related signal changes. A mean image created from the realigned volumes was coregistered with the structural T1 volume and the structural volumes were spatially normalized to a standard template of 3 x 3 x 3 mm voxels in the space of Talairach and Tournoux (1988). The derived spatial transformation was applied to the realigned T2* volumes which were then spatially smoothed with a 10mm full width at half maximum isotropic Gaussian kernel which allows for comparisons across participants and application of random field theory for corrected statistical inference (taken from Henson, Shallice & Dolan, 1999).
Condition effects at each voxel were estimated using the general linear model and regionally specific effects were investigated using linear contrasts in nine subjects. Each contrast produced a statistical parametric map of the $t$ statistic for each voxel, which was then transformed to the unit normal $Z$ distribution. Significant areas of activation consisted of voxels that survived a corrected $p$-value of 0.05. The maxima of these areas were localized on a T1-weighted template brain (averaged MRI for 152 subjects) and labelled using the nomenclature of Talairach and Tournoux (1988).

**Linear Contrasts**

Contrasts were performed on the full brain in an exploratory fashion and calculated by comparing the interaction between conditions and their baseline comparisons (fixations). This was done in SPM by specifying 32 sessions and selecting a single scanning sequence to be associated with a single session. For example, data for subject 1 comprised the first four sessions, with the explicit face condition representing session one, the implicit face condition session two, the explicit picture condition session three and the implicit picture condition session four. This was performed in 8 subjects, as data from one subject was lost due to technical difficulties.

The fMRI time series model was estimated after it was specified and configured in SPM. In order to control for signal intensity changes associated with different scans, contrasts were specified to compare the interaction between the processing of the different conditions and their fixations. For example, in the first contrast this was accomplished by comparing the difference between face processing and its fixation condition to that of picture processing and its fixation condition (using contrasts of 1, -1,
-1, 1). Contrast specifications (1 and -1) were reversed in order to determine significant activation associated with emotional pictures versus faces.

The first contrast specified was faces greater than pictures (both implicit and explicit emotional processing) and pictures greater than faces (both conditions). The second contrast was between explicit processing of emotional faces and implicit emotional processing of faces (as well as the reversal, implicit versus explicit) to determine if amygdala activity requires conscious processing of external stimuli.

The third contrast compared emotional face conditions (explicit and implicit) to the neutral face condition to examine whether the amygdala responds to faces in general, or only when the face expresses an emotion. A comparison of the neutral face condition with its fixation was the fourth contrast. The fourth as well as the fifth contrast comparing neutral faces to neutral pictures explored this question further. Finally, a contrast examining the emotional picture conditions (explicit and implicit) and the neutral picture condition was performed to conclude whether the amygdala plays a role in the processing of emotional stimuli in general, or whether it is specific to faces.

**Amygdala Search**

In line with the study's rationale, and based on a priori reasoning, a search for left and right amygdala activation was performed after each contrast was specified and calculated. This was accomplished in SPM by entering the x, y and z coordinates for the centre of the left amygdala (-21, -3, and -15 respectively) which were selected from the Co-Planar Stereotaxic Atlas of the Human Brain (Talairach & Tournoux, 1988). A small volume correction was applied for a 10 mm sphere surrounding those coordinates. This
process was repeated to conduct a search for activity in the right amygdala using the
coordinates $x = 21, y = -3, \text{ and } z = -15$.

Results

**Behavioural Data**

A preliminary analysis was performed on the accuracy of manual responses
recorded during the processing of emotional stimuli. The proportion of left and right
finger responses for each subject was compared to the correct number of left and right
finger responses for each condition. The mean percentage of correct finger responding
was greater than 90% in all four conditions for all participants. The mean percentage of
correct finger responding was 95.67%, 91.11%, 97.00% and 91.83% in the implicit
picture, explicit picture, implicit face and explicit face conditions respectively. Due to
difficulty with the recording of one subject's responses, the mean percentage was
calculated for only nine participants in the explicit picture condition.

The results of the SPM contrasts that survived a corrected p-value of 0.05
obtained from whole brain neuroimaging data are presented in Tables 1-3. All regions of
activation contained at least 50 voxels. The results of the small volume search for
amygdala activation are presented in Table 4.

Insert Table 1

About Here
Linear Contrasts

Comparison of Stimulus Type

Emotional Faces > Emotional Pictures (Explicit and Implicit). Significantly increased signal during processing of emotional faces, compared to pictures, was seen in the parietal lobe including left superior parietal lobule and right inferior parietal lobule ($p < 0.001$). There was also significant activity in the bilateral angular gyrus ($p < 0.001$) and right post-central gyrus ($p < 0.05$). Areas significantly activated in the frontal lobes included the left precentral gyrus ($p < 0.01$), and bilateral superior frontal gyrus ($p < 0.05$). The right superior temporal gyrus ($p < 0.05$) and bilateral middle temporal gyrus ($p < 0.001$) were significantly activated in the temporal lobes. The results of the small volume search revealed significant bilateral activation of the amygdala region ($p < 0.001$). Areas of activation are illustrated in Figure 1.

Emotional Pictures > Emotional Faces (Explicit and Implicit). This comparison revealed significant activation during picture processing in the inferior temporal gyrus ($p < 0.001$), lingual gyrus ($p < 0.001$), cuneus ($p < 0.001$) and superior frontal gyrus ($p < 0.05$) all in the right hemisphere. The small volume search did not find any voxels activated in the amygdala region. Whole brain regions of activation are depicted in Figure 2.

Neutral Faces > Neutral Pictures. Contrasting the neutral faces against the neutral pictures did not reveal any activations that survived a corrected $p$-value of 0.05. The small volume search did not reveal any activity in the amygdala region.
Comparison of Face Conditions

Explicit Emotional Processing v. Implicit Emotional Processing. The result of this comparison did not find any significant voxel activation ($p > 0.05$). In addition, the small volume search did not reveal any amygdala activity.

Emotional Faces > Neutral Faces. The results of this comparison revealed significant activation of the right precentral gyrus ($p < 0.001$), right medial frontal gyrus ($p < 0.001$), left postcentral gyrus ($p < 0.05$) and right superior temporal gyrus ($p < 0.05$). There was also significant bilateral activation of the cerebellum ($p < 0.001$). The small volume search revealed bilateral amygdala activation which did not reach statistical significance ($p > 0.05$ corrected). The whole brain pattern of neuronal activity is illustrated in Figure 3.

Neutral Faces > Fixation Cross. A comparison of the neutral face condition versus its fixation cross found significant bilateral activity in the occipital cortex ($p < 0.001$) and cerebellum ($p < 0.001$). In the frontal lobes, significant activity occurred in the right middle frontal gyrus ($p < 0.001$) and left superior frontal gyrus ($p < 0.05$). The small volume search did not reveal any amygdala activation.
Comparison of Picture Conditions

Emotional Pictures > Neutral Pictures. This comparison depicted significant activation in the right cerebellum ($p < 0.001$) and right inferior temporal gyrus ($p < 0.001$). In the frontal lobes, significant activity occurred in the left precentral gyrus ($p < 0.001$), and right middle frontal gyrus ($p < 0.001$). Significant activation was also found in the left inferior parietal lobule ($p < 0.001$). A small volume search did not reveal any activity in the amygdala region. Areas of activation are illustrated in Figure 4.

Discussion

Since the goal of the present study was to clarify the role of the amygdala during the processing of emotional faces and pictures, the discussion of changes in neural activity will focus solely on the results of the small volume search for the amygdala. The data from this experiment indicate that the amygdala plays a very specific role in the emotional processing of external stimuli. In particular, it only demonstrated a significant increase in activity during the processing of faces with clear emotional content.
emotional processing of external stimuli. In particular, it only demonstrated a significant increase in activity during the processing of faces with clear emotional content.

The comparison of the emotional face processing conditions versus the emotional picture processing conditions produced the greatest increase in amygdala activity. Significant increases in BOLD fMRI signal were found in both the left and right hemisphere, although Z-values were larger in the left hemisphere, suggesting slightly more activation. This is the only known study to directly compare amygdala activity in emotional faces to that in emotional pictures, so there is an absence of comparable findings. This result is particularly interesting given that all of the pictures contained people in some context, and many posed people with clear facial expressions in the foreground. This difference between faces and pictures indicates specific activity in the amygdala for facial expressions per se and not the social significance or context of the stimulus.

The comparison of the emotional face processing conditions to the neutral face processing condition was the only other contrast to find amygdala activity as a result of the small volume search. The Z-values produced for this region did not reach statistical significance using the stringent criteria of corrected p-values. Activity was found in both the left and right amygdala, although the Z-value in the left amygdala was again slightly larger. The results of these two comparisons seem to suggest that the amygdala is primarily involved in processing the emotional valence of faces, and increased activity in this region is related to registering the increased emotion on the face.

This process does not seem to require conscious processing of the facial expressions, as there was no increase in amygdala activation when comparing the explicit
and implicit face processing conditions. Instead, the amygdala appears to perform an obligatory function in emotional face processing that is triggered regardless of conscious mediation. This observation may explain why Nakamura et al. (1999) failed to find evidence of an increase in rCBF to the amygdala when they examined the effects of a facial emotion task versus an assessment of facial attractiveness or colour discrimination. All tasks required the processing of unique faces. Therefore the amygdala would be significantly activated across all conditions.

Amygdala activation without conscious awareness of stimuli has been previously demonstrated in an earlier study by Morris, Ohman and Dolan (1999), in which amygdala activity was recorded during the processing of masked angry faces in males. Morris et al. (1999) found a differential response for the left and right amygdala according to conscious mediation of angry faces. The left amygdala responded only to “seen” angry faces while the right responded to the unseen angry faces. Whalen et al. (1998) also presented masked facial expressions, both happy and fearful, and found a significant signal increase in the amygdala in response to fearful expressions and a significant decrease to masked happy faces, even though subjects only reported seeing neutral faces. It would be interesting to include masked faces in the current paradigm to evaluate whether this effect is replicable.

The results of the present study do not support the idea that the amygdala is specialized to respond to faces per se, regardless of their emotional content or the context in which they are presented. Comparing the neutral face condition to the presentation of a fixation cross (which served as a low-level control condition) did not result in an increase in amygdala activation in either the left or right hemisphere. This could be
related to its role in evaluating the significance of biologically meaningful stimuli. The experimental paradigm did not require participants to make cognitive evaluations during the neutral face condition, rather they were instructed to passively view the stimuli as they were presented on the screen. The neutral, non-threatening faces may have interacted with a passive approach to the stimuli to produce a context that does not require amygdala activation for the processing of faces. Comparing the neutral face condition with the neutral picture condition provides further support for this idea. The small volume search did not replicate the increase in amygdala activity revealed when emotional faces and pictures were compared. However the emotional faces versus neutral faces showed much reduced activity in the amygdala although still "significant" with more liberal criteria. Trial unique neutral faces probably cause some low level amygdala activation that would not be seen with the Ekman and Friesen (1976) faces (based on habituation idea).

The amygdala does not appear to be involved in emotional processing per se, without consideration for the context and nature of the external stimuli. A comparison of the combined emotional picture processing conditions versus the neutral picture processing condition did not reveal an increase in amygdala activity in either hemisphere. Lane et al. (1999) report similar findings and only found a significant increase in amygdala activation when high arousal pleasant and unpleasant pictures were contrasted with low arousal pleasant and unpleasant pictures.

An earlier study performed by Lane et al. (1997) also failed to find any increase in amygdala activity while investigating subjective emotional responding to pictures taken from the International Affective Picture System (IAPS). The amygdala may not be
areas 18 and 19) that are activated in response to increased visual complexity and object assimilation. Facial expressions of emotion presented in isolation without any context to facilitate evaluation may trigger the activation of a more instinctual neural system that involves the amygdala.

These results support findings obtained from earlier studies, but there has been inconsistency in the literature concerning lateralization of amygdala activity. The present study found bilateral activation of the amygdala with slightly larger Z-values produced for the left amygdala. Bilateral or left amygdala activity appears to be predominant in perceptual studies which examine the processing of faces (Blair et al., 1999; Breiter et al., 1996; Morris et al., 1996, 1998). Studies that examine the effects of conditioning more frequently report bilateral or right amygdala activity (Birbaumer et al., 1998; Furmark et al., 1997; LaBar et al., 1998; Morris et al., 1999). Disparity between results from different studies could be related to methodological issues. However, even when bilateral activation is present, the left amygdala still appears to generate a stronger signal in response to emotional faces suggesting that the signal intensity may be biased towards the left amygdala and right activity may be sub-threshold. In addition, previous experiments used Ekman and Friesen (1976) faces rather than trial-unique faces. This may confound the results because the same people pose the different facial expressions. The set only utilizes 6 or 8 people to depict a range of emotions and it has been documented that the amygdala habituates to familiar faces (Breiter et al., 1996) which also could account for failure to find right activity if it's lower to begin with and then falls off.
Further evidence of the difference between novel faces and familiar ones was found by Dubois et al. (1999) who required eleven male subjects to perform a gender discrimination task on known and unknown faces. Subjects were exposed to the known faces during a long-term visual face familiarization utilizing videotapes depicting these people in action. The researchers found left amygdala activation only in the unknown face condition. They suggest that these results could be related to the relatively aversive status associated with unknown faces, because unknown faces could potentially represent a danger or threat when presented the first time. The present study attempts to control for habituation effects by presenting each face once, thereby ensuring that all stimuli are unique. This may lead to increased activation in the amygdala bilaterally that remains detectable even after multiple face presentations.

There also has been discussion in the research literature regarding the type of emotion that activates the amygdala. Most studies seem to suggest that the amygdala responds primarily to potentially threatening stimuli, such as expressions of anger or fear (Morris et al., 1996, 1998, 1999; Whalen et al., 1998). However, some studies have not found evidence for a dissociation for amygdala activity according to emotional valence of the expression (Breiter et al., 1996; Schneider et al., 1997). The current experiment utilized a block design so it is not possible to determine whether the amygdala was differentially activated during the processing of unpleasant versus pleasant facial expressions. Therefore it would be of interest to perform the study on more participants utilizing an event-related design in order to separate the signal effects associated with the valence of the facial expression. While it is unclear as to whether the amygdala would be activated across a range of emotional expressions, it would be expected to demonstrate a
greater increase in signal intensity during the processing of fearful or angry faces, as they represent a potentially threatening social cue.

One interpretation of the pattern of amygdala activity during emotion processing is that it serves to evaluate biologically significant stimuli for potential threat, especially during the absence of contextual cues. This may form the basis for the difference in amygdala activity between the face and picture conditions. For example, based on the early work of Darwin (1872, 1975; as cited in Camras, Holland & Patterson, 1993) and Ekman (1972; as cited in Camras et al., 1993) there is support for a set of universal facial expressions. This has been explained by assuming an underlying innate neural network for each of the “primary” emotions (Camras et al., 1993). Animal research results suggest that the amygdala is part of a neural subsystem for fear, and in humans it may be part of a neural pathway that instinctively evaluates sensory stimuli for possible “flight or fight” responses when there is a potential threat to the individual. If increased emotion can be related to this potential, then this would partially explain why the amygdala demonstrates a greater increase in activity in response to emotional versus neutral facial expressions, particularly when the faces are not familiar and are depicting anger or fear.

A limitation to the present study involves the use of a blocked design. This type of design only allows for comparison between blocks of trials. The improved temporal resolution of fMRI allows for event-related designs where the BOLD signal associated with a single stimulus presentation can be measured. If the current paradigm were manipulated to allow for event-related analyses, the amygdala may emerge as being activated in response to the pictures that clearly depict people and facial expressions in the foreground. Amygdala activation may be masked in the current paradigm by the
activated in response to the pictures that clearly depict people and facial expressions in the foreground. Amygdala activation may be masked in the current paradigm by the number of pictures containing people in the background, where their facial expressions are not clearly visible.

In the present study, the amygdala is differentially activated according to the type of visual stimuli. Its activation in response to faces but not pictures may reflect an automatic processing of the emotion of the face in order to evaluate potential threat to the organism. This mode of reactivity may extend beyond the visual modality, given that the amygdala receives inputs from polymodal sensory regions. D.R. is a female patient who had a series of stereotaxic lesions targeted at the amygdala to treat epilepsy (Scott et al., 1997). D.R. exhibits impaired perception of intonation patterns that are necessary for interpreting the emotional valence of speech. Audiometric testing demonstrated that the results were not due to a generalized hearing deficit. She displayed impaired ability in identifying whether sentences with neutral content were read in a happy, angry or sad manner, despite adequate ability to comprehend the emotional content of different sentences. D.R. was also given a task in which single words were spoken with intonations of happiness, sadness, anger, fear or disgust. She demonstrated significant impairments in recognizing anger and fear and borderline impairments in recognizing happiness and sadness. Further testing revealed highly significant impairments in recognizing basic emotions communicated through non-verbal sounds, such as laughing and crying (Scott et al., 1997). These results provide support for the idea that the amygdala evaluates the affective significance of social cues beyond the visual modality.
Future research should apply neuroimaging techniques such as fMRI to examine patterns of brain activity in healthy controls while performing sensory processing tasks beyond the visual modality (e.g. auditory). BOLD fMRI signal contrasts could be measured while participants are performing similar tests taken by D.R. It is likely that the amygdala would be activated by intonation patterns associated with vocal affect, especially those echoing fear and anger. It would be interesting to determine if such activation would include a range of emotional tones (e.g. happiness, sadness, anger etc.), and if it would occur irrespective of sentence content (e.g. neutral statements read in an emotional tone). It is hypothesized that vocal affect would activate the amygdala regardless of how the sentence was processed based on the finding in the present study that activity did not require explicit processing of the emotional content of faces. Thus, the amygdala is likely to respond instinctually to the threat potential associated with the tone of voice, even if someone were attending to sentence content and not the emotional tone of the statement. It may demonstrate differential responding in relation to various emotional tones, in particular it may be more strongly activated in response to anger and fear.

Deficits in emotional processing in clinical populations may be associated with abnormal activation of the amygdala. The central nucleus of the amygdala has been implicated during the experience of anxiety and fear associated with phobias. For example, the amygdala is activated in social phobics relative to normal controls when viewing neutral faces despite similarities in subjective ratings of the emotional content of the faces (Birbaumer et al., 1998). Visual stimuli received from the primary sensory cortex could lead to panic attacks through projections to the basolateral nucleus of the
Amygdala (Ballengher, 1999). The symptoms associated with panic disorder include arousal, fearful avoidance and autonomic symptoms such as increased heart rate and blood pressure as well as “freezing versus flight” behaviour. Cortical projections and feedback loops to and from the amygdala could help explain the cognitive aspects of panic attacks and the beneficial aspects of cognitive therapy (Ballengher, 1999). The influence of the amygdala in panic disorder is supported by the observation that benzodiazepine agonists applied to amygdala nuclei are anxiolytic. Diazepam or GABA administered directly into the amygdala leads to more rapid habituation of a contextual fear stimulus (Ballengher, 1999).

Functional MRI has been used to model abnormal neural activity associated with different psychiatric illnesses. Schneider et al. (1998) compared amygdala activity using fMRI in thirteen male schizophrenia patients with thirteen male controls. Sad and happy facial expressions were presented to the participants and they were instructed to try and feel the corresponding emotion. They also performed a facial discrimination task that involved indicating the emotion of each face according to a seven-point intensity scale. The facial discrimination task also required them to estimate the age of the face in decades from one to seven, with one representing the teens and seven, the seventies. Results of the fMRI analyses found significant increases in amygdala activation during the sad mood induction only for the controls despite matched indices of negative affect in both groups. The happy mood induction did not lead to amygdala activation in either the patient group or the control group. The patient group demonstrated significant impairment in the discrimination of happy and sad facial expressions relative to the age discrimination task consistent with abnormal amygdala activity.
Breiter and Rauch (1996) used fMRI to study obsessive compulsive disorder (OCD) using a symptom provocation paradigm. They compared measures of neural activity taken during a baseline condition followed by a provoked condition. In the baseline condition, OCD patients held a “neutral” stimulus (e.g. a clean towel) while during the provoked condition, they held a more “threatening” stimulus (e.g. a dirty towel). Patients exhibited isocortical (lateral frontal), paralimbic (medial orbital gyrus, anterior cingulate, temporal cortex, insular cortex), limbic (amygdala) and striatal (caudate and lenticulate) activations in relation to OCD symptoms. The cortico-striatal pathway involving activation of the orbitofrontal cortex and caudate nucleus is specific to OCD (Breiter & Rauch, 1996). The paralimbic activation is more characteristic of anxiety in general, as amygdala activation has been observed in association with other anxiety disorders such as posttraumatic stress disorder (Rauch et al., 1996). The increase in amygdala activation during symptom provocation has been associated with the increased magnitude of perceived threat, and emphasizes its role in rapid assessment of threat (Breiter & Rauch, 1996).

The present study sheds light on the nature of amygdala activity during the emotional processing of visual stimuli. As hypothesized, the amygdala was found to respond to the increased emotional intensity of faces, and reiterates its function in assessing the biological significance of external stimuli. Angry or fearful faces represent potentially threatening social cues, particularly when they are presented without context for interpretation. This mode of presentation stimulates an innate neural circuitry involving the amygdala that is designed to prepare the body for “fight or flight” responses. The study also indicates that there regions in the brain beyond the amygdala
involved in the emotional processing of external stimuli. The amygdala may not be critical for emotion per se, but specialized for one aspect of it, namely assessment of threat represented in facial expression. Future research should use mapping techniques and define functional connections between cortical and subcortical structures to provide a more complete working model of brain activity during emotional processing.
References


An fMRI Study of Amygdala Activation


*Psychiatry Research: Neuroimaging Section, 76*, 75-82.


Table 1

Maxima of Regions Showing Significant (p < 0.05 corrected) BOLD Signal Changes in Stimulus Comparisons

<table>
<thead>
<tr>
<th>Region of Activation</th>
<th>Brodmann</th>
<th>Talairach coordinates</th>
<th>T value</th>
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<tr>
<td></td>
<td>Left/Right</td>
<td>Area</td>
<td>x</td>
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<tr>
<td><strong>Emotion: Faces &gt; Pictures</strong></td>
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<tr>
<td>Superior parietal lobule</td>
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<tr>
<td>Angular gyrus</td>
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<td></td>
<td></td>
<td></td>
<td>-6</td>
</tr>
<tr>
<td><strong>Emotion: Pictures &gt; Faces</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior temporal gyrus</td>
<td>R</td>
<td>37</td>
<td>51</td>
</tr>
<tr>
<td>Lingual gyrus</td>
<td>R</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>R</td>
<td>8</td>
<td>33</td>
</tr>
<tr>
<td><strong>Neutral: Faces &gt; Pictures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*No significant voxels activated</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

L = left; R = right; B = bilateral.
Table 2
Maxima of Regions Showing Significant (p < 0.05 corrected) BOLD Signal Changes in Face Comparisons

<table>
<thead>
<tr>
<th>Region of Activation</th>
<th>Brodmann</th>
<th>Talairach coordinates</th>
<th>T value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>x</td>
<td>y</td>
</tr>
<tr>
<td>Faces: Emotional &gt; Neutral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precentral gyrus</td>
<td>L</td>
<td>4</td>
<td>-39</td>
</tr>
<tr>
<td>Postcentral gyrus</td>
<td>L</td>
<td>20/21</td>
<td>-57</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>B</td>
<td></td>
<td>-42</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>33</td>
</tr>
<tr>
<td>Superior temporal gyrus</td>
<td>R</td>
<td>38</td>
<td>51</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>B</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Faces: Neutral &gt; Fixation Cross</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cuneus</td>
<td>B</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-24</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>B</td>
<td>39</td>
<td>-63</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-42</td>
</tr>
<tr>
<td>Inferior occipital gyrus</td>
<td>R</td>
<td>19</td>
<td>45</td>
</tr>
<tr>
<td>Frontal medial gyrus</td>
<td>R</td>
<td>9</td>
<td>57</td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>L</td>
<td>8</td>
<td>-9</td>
</tr>
</tbody>
</table>

L = left; R = right; B = bilateral.
### Table 3

**Maxima of Regions Showing Significant (p < 0.05 corrected) BOLD Signal Changes in Picture Comparisons**

<table>
<thead>
<tr>
<th>Region of Activation</th>
<th>Brodmann</th>
<th>Talairach coordinates</th>
<th>T value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left/Right</td>
<td>Area</td>
<td>x</td>
</tr>
<tr>
<td><strong>Pictures: Emotional &gt; Neutral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>R</td>
<td>42</td>
<td>-69</td>
</tr>
<tr>
<td>Inferior temporal gyrus</td>
<td>R</td>
<td>37</td>
<td>51</td>
</tr>
<tr>
<td>Precentral gyrus</td>
<td>L</td>
<td>4</td>
<td>-36</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>R</td>
<td>9</td>
<td>54</td>
</tr>
<tr>
<td>Inferior parietal lobule</td>
<td>L</td>
<td>40</td>
<td>-48</td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>R</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td>Inferior frontal gyrus</td>
<td>R</td>
<td>46</td>
<td>54</td>
</tr>
</tbody>
</table>

L = left; R = right.
Table 4
Maxima of Amygdala Region Showing BOLD Signal Changes Across All Comparisons

<table>
<thead>
<tr>
<th>Region of Activation</th>
<th>Left/Right</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>T value</th>
<th>p-corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotion: Faces &gt; Pictures</td>
<td>L</td>
<td>-18</td>
<td>3</td>
<td>-9</td>
<td>4.69</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>-24</td>
<td>0</td>
<td>-6</td>
<td>4.69</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>-21</td>
<td>-3</td>
<td>-15</td>
<td>3.42</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>18</td>
<td>-3</td>
<td>-12</td>
<td>4.27</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>21</td>
<td>-3</td>
<td>-12</td>
<td>3.71</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Emotion: Pictures > Faces      | *no significant voxels activated |
Neutral: Faces > Pictures      | *no significant voxels activated |
Faces: Explicit > Implicit     | *no significant voxels activated |
Faces: Implicit > Explicit    | *no significant voxels activated |
Faces: Emotional > Neutral    |                                      |
| L                             | -24        | 0   | -9  | 2.41 | 0.090   |
| L                             | -21        | -3  | -15 | 1.98 | 0.188   |
| R                             | 15         | 0   | -15 | 1.99 | 0.188   |

Faces: Neutral > Fixation Cross | *no significant voxels activated |
Pictures: Neutral > Fixation   | *no significant voxels activated |

L = left; R = right.
Figure Caption

Figure 1. A statistical parametric map (SPM) demonstrating bilateral amygdala activation during the emotional processing of faces versus pictures. An uncorrected p-value of 0.001 was used as the threshold for the contrast. Views of the brain are shown for orthogonal slices, with the cross-hair placed at the left amygdala voxel (x = -21, y = -3, z = -15). The significant areas of activation are displayed on a mean structural MRI.
Emotional Faces > Emotional Pictures

x = -21, y = -3, z = -15

Z-Value
Figure Caption

**Figure 2.** A statistical parametric map (SPM) demonstrating a lack of amygdala activation during the emotional processing of pictures versus faces. An uncorrected p-value of 0.001 was used for the contrast. Views of the brain are shown for orthogonal slices with the cross-hair placed at the left amygdala voxel \((x = -21, y = -3, z = -15)\). The significant areas of activation are displayed on a mean structural MRI.
Emotional Pictures > Emotional Faces

x = -21, y = -3, z = -15
Figure Caption

Figure 3. A statistical parametric map (SPM) demonstrating left amygdala activity during the emotional processing of faces versus the processing of neutral faces. An uncorrected p-value of 0.05 was used as the contrast for the threshold. Views of the brain are shown for orthogonal slices with the cross-hair placed at the left amygdala voxel ($x = -21$, $y = -3$, $z = -15$). The significant areas of activation are displayed on a mean structural MRI.
An fMRI Study of Amygdala Activation

**Emotional Faces > Neutral Faces**

\[ x = -21, \ y = -3, \ z = -15 \]

Z-Value
Figure Caption

Figure 4. A statistical parametric map demonstrating a lack of amygdala activation during the emotional processing of pictures versus the presentation of neutral pictures. An uncorrected p-value of 0.01 was used as the threshold for the contrast. Views of the brain are shown for orthogonal slices with the cross-hair placed at the left amygdala voxel (x = -21, y = -3, z = -15). The significant areas of activation are displayed on a mean structural MRI.
Emotional Pictures > Neutral Pictures

x = -21, y = -3, z = -15
Appendix A

Screening Form
Screening and Information Form for PET

Completed by: __________________________ Date: __________

Name: ____________________ Sex: ___ Age: ___

Date of Birth: ________ Marital Status: Single Married Divorced Other: __________

Address: ____________________________________________

______________________________________________________

Telephone: Home: ________ Work: ________ Best: ________

Race: (Circle)

Caucasian Asian-Oriental Asian-Nonoriental Black Native Other: ________

Primary Language: English/Other Languages in addition to Primary: ________

Highest Level of Education: ________ Years of Education: ________

Current Main Occupation and for How Long: ____________________________

Previous Main Occupation and for How Long: ____________________________

Handedness:

1) Subjectively: Left Either Right

2) Write a Letter: Left Either Right

3) Throw a Ball: Left Either Right

4) Play Racquet Games: Left Either Right

5) Hold a Match: Left Either Right

6) Hold Scissors: Left Either Right

7) Hold Hammer: Left Either Right

8) Hold Tooth-Brush: Left Either Right
Visual Health: Excellent Good Fair Poor
Optical Correction: Distance only Near only Both None
Eye Disease: Cataract Glaucoma Age Related Maculopathy Other
If other, please specify
Last Eye Exam: < 1 year ago 1-3 years ago > 3 years ago
Last new eyeglass prescription: < 1 year ago 1-3 years ago >3 years ago

Medical History:
1) Are you taking any medications currently? If yes, list and duration. (For women, oral contraceptive pills?)

2) Are you currently seeing a doctor regularly for any medical problems? If yes, why and duration.

3) In the past, did you take any medications regularly? If yes, list and duration. (For women, oral contraceptive pills?)

4) In the past, did you see a doctor regularly for any medical problem? If yes, when, why and duration.

5) Have you ever been hospitalized: seriously illness or surgery? If yes, when, why, and duration.

6) In the last 3 years, have you undergone any medical diagnostic procedures that have involved radiation (i.e. medical or dental x-rays, etc.)? If yes, what, when and why?
7) For females - Is there a chance that you may be pregnant? Have you had your period within the last 6 to 8 weeks? If there is a chance that you are pregnant, you should not undergo the scan.

I understand that the scans may pose a potential risk if I am currently pregnant, and I confirm that I am not pregnant at this time.

Subject's Name: ____________________  Date: ________________

Subject's Signature: ____________________

Witness's Name: ____________________  Date: ________________

Witness's Signature: ____________________

Neurologic History:

1) Have you ever had seizures/fits/epilepsy? If yes, when, how many, any medications, for how long.

2) Have you ever had a serious head injury which resulted in a loss of consciousness or hospital visit? If yes, how long was the loss of consciousness, what investigations, what outcome.

Psychological History

1) Have you ever sought counseling for any psychological help (i.e. seen a psychiatrist, psychologist etc.) If yes, under what circumstances? When? How long? And where?

Substance Use

1) Have you ever taken any medications to help you will energy, sleep, nervousness or mood.
2) Have you ever used any other substances such as marijuana, hash, cocaine, LSD, any uppers, downers in the past 3 years (When, Max use/month, times for month)?

3) What are your drinking habits like? Note Frequency and type.

4) Was there ever a period of time in your life when you drank too much? Has drinking ever caused problems for you? Has anyone ever objected to your drinking? Has anyone else ever though that alcohol was a problem for you?
Appendix B

Information Sheet and Consent Form
INFORMATION SHEET
Investigation of the Processing of Facial Expressions and Pictures
Investigators: ML Keightley, Dr CL Grady

Nature and the Purpose of this Study

This study will investigate parts of the brain that are important for perception of faces and pictures in normal healthy humans. You will be asked to view a series of faces and pictures and may be asked to make decisions about them. Some of the images may be unpleasant. During performance of these tasks, brain activity will be monitored using a method known as functional Magnetic Resonance Imaging or fMRI. At the time of the MRI scan, we also will ask you to complete some paper and pencil tests that measure verbal and memory abilities.

MRI Scan

For the MRI scan you and the investigators will go Sunnybrook Health Science Centre. The MRI technique uses magnets and radiowaves to construct a picture of the brain on a computer. Before the scan begins, you will be asked to remove any magnetic metals that you may be wearing. For the procedure, you will be asked to lie on a padded bed that will be moved into a tunnel-like machine for the MRI scan of your brain. Since you will be inside the machine during the scan, and a screen will be in place for viewing the visual images, you may not be able to see the technicians operating the machine or the investigators. However, there is an intercom system that will allow you to talk with them at any time. If you feel uncomfortable during the scan and you wish to discontinue the procedure, you will be taken out of the machine at your request.
The scans take approximately 1.5 to 2 hours. During this time you will be presented with a variety of visual tasks. You should try to remain as still as possible during the scan. Movement will not be dangerous to you in any way, but would blur the picture of your brain. You will hear moderately loud knocking or beeping during the scan when the MRI machine is in operation. Although you may find this to be unsettling, the machine cannot hurt you in any way.

Risks of an MRI scan

The MRI scan is not associated with any known risks to your health and there is no evidence that there will be either short-term or long-term side effects. However, it is the policy of the hospital that if you are a woman of child-bearing age, that you not be pregnant at the time of the MRI scan. Prior to the MRI you will be required to fill out a questionnaire to ensure that there are no contraindications for performing the study. The only absolute requirements for the MRI scan are that you

1) do **NOT** have an implanted cardiac pacemaker
2) do **NOT** have any metal implants, pieces of shrapnel, aneurysm clips, or wires in your head.

Participation in the Study

Your participation is voluntary. You may refuse to participate in the study at any point in time. The study will not benefit you specifically, but knowledge will be gained that may benefit others. Each individual's results are confidential. Neither your identity nor any personal information will be
available to anyone other than the investigators. No personal information will be disclosed in any resulting publication or presentation. If you are interested, we would be happy to provide you with the final results of the study when they appear in press. If any unexpected medical findings should arise from the results of the procedures involved in this project, we will recommend that you have a follow-up health assessment and we will provide all relevant information to the physician that you specify.

If you have any further questions about this, please feel free to call Michelle Keightley at 785-2500 ext. 3516, or Dr. Grady at 785-2500 ext. 3525.
CONSENT FORM
Investigation of the Processing of Facial Expressions and Pictures
Investigators: ML Keightley, Dr CL Grady

I have read the attached information form, and I understand the purpose of my participation, the procedures involved and the potential risks to myself, as stated in the attached information sheet. All my questions have been answered to my satisfaction. I understand that I can ask further questions during any stage of the study.

My Rights
I understand that my participation in the study is voluntary. I may withdraw from the study at any point in time. I am aware that the study will not benefit me specifically, but knowledge will be gained that will benefit others.

It has been explained to me that the results of the study are confidential. Neither my identity nor any personal information will be available to anyone other than the investigators. No personal information will be disclosed in any resulting publication or presentation. I have been given a copy of this consent form and the attached information sheet.

I will be reimbursed for the time of my participation and for travel expenses.

If I am a woman of child-bearing age, I confirm that I am not or could not be pregnant at the time of the MRI scan.

The study and its consequences have been explained to me by:
If I have any further questions I may call Michelle Keightley at 785-2500 ext. 3516 or Dr. Grady at 785-2500 ext. 3525.

Participant:
Name: ____________________________
Signature: _________________________

Witness:
Name: ____________________________
Signature: _________________________

Date: