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The Amygdala, Arousal and Memory: From Lesions to Neuroimaging

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Abstract

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Emotional events are better remembered than neutral events. But what are the mechanisms behind this memory enhancing effect? It seems that they depend on the arousal level at the moment we experience the event to be remembered.

The first study of the present thesis mapped the brain areas that changed their activity in a highly arousing situation in subjects with snake or spider phobia. Looking at pictures of their feared object engaged the amygdala, situated in the medial temporal lobe. This area has previously been demonstrated to be necessary for fear reactions. Here, the novel question was what other brain areas the amygdala engages when the brain is in a state of high arousal. Results suggest that the amygdala recruits other limbic and cortical areas known to be involved in motor behavior and object recognition. In contrast, when subjects watched fear-relevant but non-phobic pictures, amygdala activity was negatively correlated to the anterior cingulate cortex suggesting cortical inhibition.

The final two studies aimed at explaining the physiological brain mechanisms behind arousal enhancement of memory. In the first one, epileptic patients with medial temporal lobe resections including the amygdala were compared to healthy controls on a recognition memory task where the pictures to be remembered varied in arousal intensities. Results suggested that the anterior medial temporal lobe including the amygdala is necessary for arousal enhancement of memory because the enhancement effect was abolished in resected patients.

The last study related inter-individual differences in bodily arousal to amygdala-parahippocampal interaction. Results suggest that the beneficial effects of emotion on memory depend on arousal regulating mechanisms of the amygdala that in turn affects parahippocampal activity.

Collectively, results suggest that the amygdala is regulating changes in arousal states of the brain and body during distressful situations. Further, arousal in turn determines memory strength through gating amygdala influences on the parahippocampal cortex. Thus, the amygdala is a node both in a fear and a memory network and arousal influences the amygdala to prepare for action and to enhance memory. This seems evolutionary sound.

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List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I Åhs, F., Pissioti, A., Michelgård, Å., Frans, Ö., Furmark, T., Appel, L., Fredrikson, M. (2008) Disentangling the web of fear: amygdala reactivity and functional connectivity in spider and snake phobia. *in press*.
- II Åhs, F., Kumlien, E., Fredrikson, M. (2009) Arousal enhanced memory retention is abolished following medial temporal lobe resections.
- III Åhs, F., Michelgård, Å., Pissioti, A., Appel, L., Frans, Ö., Furmark, T., Fredrikson, M. (2009) Arousal gates amygdala interaction with the parahippocampal cortex during encoding of phobic pictures.

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Abbreviations

ACC	Anterior cingulate cortex
BA	Brodmann's area
EMG	Electro-myogram
fMRI	Functional MRI
GABA	Gamma-aminobutyric acid
LTP	Long term potentiation
MRI	Magnetic resonance imaging
MTL	Medial temporal lobe
PET	Positron emission tomography
PTSD	Post traumatic stress disorder
rCBF	Regional cerebral blood flow
ROI	Region of interest

Introduction

A major factor influencing memory is emotion. An event that evokes an emotion such as a first kiss from a person we like will stick stronger to our memory than a neutral event as for example what we had for dinner last Monday. It seems like memory will be enhanced if we feel excited or aroused. Situations that elicit negative emotion such as fear will also be better remembered. Understanding the impact of highly arousing events on memory might be valuable for understanding the development and maintenance of anxiety disorders.

States of arousal are associated with profound changes of activity in the brain and body. Hormones are released that affect brain mechanisms involved in memory, especially in the amygdala which is an evolutionary old part of the brain. The first study in this thesis will describe alterations in activity in the brain during a distressful event in subjects with spider or snake phobia. It primarily focuses on the amygdala and its interaction with other parts of the brain. The hypothesis was that amygdala activity would be suppressed by medial prefrontal activity during low-arousing stimuli and trigger fight or flight responses during a high-arousing condition.

The second study will describe how arousal enhanced memory is affected when the amygdala and surrounding tissues have been removed due to medically intractable epilepsy. This experimental set-up gives the opportunity to test whether the amygdala is necessary for arousal induced memory enhancement. Finally, the third study tests the hypothesis that the amygdala regulates the motivational state that in turn regulates memory related processes in the parahippocampal cortex and the hippocampus. Preceding the empirical studies, an introductory part will describe relevant areas of research.

Emotion

Everyone has a concept of emotion, but giving an operational definition is hard. However, a few main points can be made. Emotions can be positive or negative and can vary in intensity. They are usually brief, lasting seconds to minutes, in contrast to mood which is more enduring. It is worth noting that emotions are linked to changes in arousal.

Theories of emotion: Categories or dimensions

A still ongoing debate in psychology is whether emotions are distinct from each other and best are described as categories or whether all emotions can be described with a few underlying dimensions. The idea of emotions as discrete categories dates back to Darwin (Darwin 1872) who described a few basic human emotions that were claimed to be universal across cultures. The categorical view has also had advocates in more recent years (Ekman 1992). The basic emotions generally include happiness, sadness, anger, fear and disgust (Calder et al. 2001). The other line of thought describes emotion along the dimensions of arousal and valence (Russel, 1980). The arousal dimension describes how exciting a stimulus is whereas the valence dimension relates to its hedonic value. From a neuroscience standpoint, it can be argued that the categorical view of emotion is valuable because injuries to certain brain areas can cause problems with the identification of a specific emotion but not a dimension such as arousal or valence (Calder et al. 2001). However, when it comes to emotional memories it seems that valence and arousal exert their influence through different areas of the brain (Kensinger and Corkin 2004; Lewis et al. 2007). Valence and arousal dimensions can also be directly related to the behavioral dimensions of direction and vigor (Lang et al. 1990). This behavioral distinction has also been argued for from an evolutionary standpoint (Ohman and Mineka 2001). The dimensional account is further favored by being more economical and has been extensively used to understand emotional memory (McGaugh 2004) which is why the theoretical constructs of arousal and valence will be used throughout this thesis.

The aroused brain

A distinction can be made between general arousal governed by intrinsic mechanisms such as homeostasis and sleep/wake cycles and alterations of arousal driven by extrinsic factors (Garey et al. 2003). Systems of the brain concerned with changing the arousal state in response to external stimuli may be specific to certain types of situations. Most likely, the general arousal systems such as the reticular formation in the midbrain (Moruzzi and Magoun 1949; Kinomura et al. 1996) and the hypothalamus (Stellar 1954) interact with these specific systems.

The effects of arousal on the brain and body are fast and generalized (Pfaff et al. 2008). An example: Crossing a grave yard on the way home one night something suddenly makes a flapping sound on a tomb close by. Before realizing what caused the sound, the body startles and then freezes. After realizing it was a bird that caused the sound, the walk can continue. This illustrates that arousal can act at a pre-attentive level changing the brain state and regulates large classes of behavioral responses. We can thus know that something is relevant to us and calls for an action before we have detected exactly what it is. Experimental evidence comes from a study of detection of angry faces among neutral faces, where socially anxious individuals show shorter response latencies than non-socially anxious individuals after their social fear was experimentally enhanced (Juth et al. 2005). Emotionally arousing stimuli have an advantage when competing for the attentional resources of the brain (Bishop 2008).

Arousal is associated with increased levels of the neurotransmitters norepinephrine (Valentino and Van Bockstaele 2008) and acetylcholine (Jones 2008) and also increased levels of certain hormones such as corticotrophin-releasing factor (Winsky-Sommerer et al. 2005) and orexin/hypocretin (de Lecea et al. 1998). These neuromodulating substances have a widespread and diffuse action on the brain and can directly regulate bodily hormonal systems as in the case of corticotropin releasing factor (Schmidt and Thews 1983). Genetical manipulations of hormone-activated transcription factors can therefore affect the general arousal state (Garey et al. 2003). Arousal also has more local effects in the brain. A brain area often associated with arousal responses during fear is the amygdala (LeDoux 2003).

The amygdala

Anatomical organization

The amygdala is a collection of groups of neurons (nuclei) located deep within the anterior MTL. The nuclei of the amygdala are traditionally divided into an evolutionary older part associated with the olfactory system, the cortico-medial region, and an evolutionary more recent division

associated with the neocortex, the basolateral region (LeDoux 2007). The basolateral region consists of the lateral and basal nuclei while the cortico-medial part includes the central and medial nuclei. In between the basolateral and cortico-medial part are intercalated cells thought to be important in inhibitory processes (Royer et al. 1999).

Connectivity

The lateral amygdala is the major input area and receives afferents from all sensory systems. Sensory inputs come from thalamic and cortical areas. Cortical sensory inputs arise from association areas rather than primary sensory cortices and provide the amygdala with elaborate representation of the outside world. Thalamic inputs are cruder but involve fewer synapses from the sensory source and are faster.

The central nucleus is the major output region of the amygdala regulating emotional and physiological responses while the basal nucleus projects to striatal regions important for motor learning. The amygdala has dense projection to the orbitofrontal (Dolan 2007) and medial prefrontal cortex (Hoover and Vertes 2007), both important in emotion regulation. Neurons in the central nucleus of the amygdala can be inhibited by the GABA-ergic intercalated cells situated in between the central and basal nucleus (Royer et al. 1999). Intercalated cells are triggered by inputs from the basolateral nucleus. Inputs from other brain areas to the basolateral amygdala can thereby inhibit output from the central nucleus.

Behavioral functions

Klüver and Bucy first reported profound changes in fearful and sexual behavior following temporal lobe damage in monkeys (Klüver and Bucy 1937). It was later demonstrated that removal of the amygdala was the cause of these behavioral alterations (Weiskrantz 1956). Since then, a large number of studies have used Pavlovian fear conditioning to examine the contribution of the amygdala to fear behaviors and fear learning. During fear conditioning a neutral stimulus is paired with a painful shock that affects brain circuitry and elicits autonomic responses. Just after a few pairings, the previously neutral stimulus will now by itself elicit these responses. Such studies have shown that the basolateral nucleus of the amygdala is crucial in conditioning the neutral cue on the shock (see Maren 2001). Evidence of the involvement of the human amygdala in emotional behavior comes from patients with lesions to the amygdala and from neuroimaging studies.

Neuroimaging studies of human fear conditioning comparing a cue paired with electric shock to a non-paired cue have shown bilateral (Furmark et al. 1997; Buchel et al. 1999; Armony and Dolan 2002; Dunsmoor et al. 2007), right (Buchel et al. 1998; LaBar et al. 1998; Armony and Dolan 2001; Critchley et al. 2002; Gottfried and Dolan 2004; Knight et al. 2004; Phelps et al. 2004; Tabbert et al. 2006; Milad et al. 2007) or left sided amygdala

activation (Morris et al. 1998; Morris et al. 2001; Phelps et al. 2001; Morris and Dolan 2004; Glascher and Buchel 2005; Tabbert et al. 2005). Previous studies of delay fear conditioning in patients with unilateral lesions to the MTL including the amygdala (LaBar et al. 1995; Peper et al. 2001; Weike et al. 2005) reported reduced conditioned skin conductance responses when compared to a control group. Weike et al. (2005) also observed reduced startle potentiation to the paired cue in MTL-resected patients with epilepsy.

Clinically it is valuable to understand how conditioned fear can be unlearned. If amygdala is involved in learning, how is it involved in unlearning? Recent data suggest that selective lesions to the intercalated neurons interfere with extinction of fear memories providing evidence of their necessary role in the inhibition of fear expression (Likhtik et al. 2008). It has been shown that the medial prefrontal cortex can inhibit amygdala dependent fear responses (Milad and Quirk 2002). Stimulation of the medial prefrontal cortex activates the intercalated neurons (Berretta et al. 2005) which provides a neurophysiological account of how this inhibition works. Neuroimaging results support an inhibitory role of the medial prefrontal cortex on amygdala activity in humans (Pezawas et al. 2005; Stein et al. 2007) and a relative lack of connectivity between these structures has been noted in subjects with specific phobia (Etkin and Wager 2007).

Neuroimaging techniques have also been used to investigate the involvement of the amygdala in fear responses triggered by fear provoking stimuli in patients with small animal phobia (fig. 1). In comparison to fear conditioning, these studies induce intense distress that is accompanied by amygdala activation (Dilger et al. 2003; Veltman et al. 2004; Schienle et al. 2005; Larson et al. 2006; Straube et al. 2006b; Goossens et al. 2007; Schienle et al. 2007). In conclusion, the human amygdala seems involved both in fear learning and in generating fear behavior.

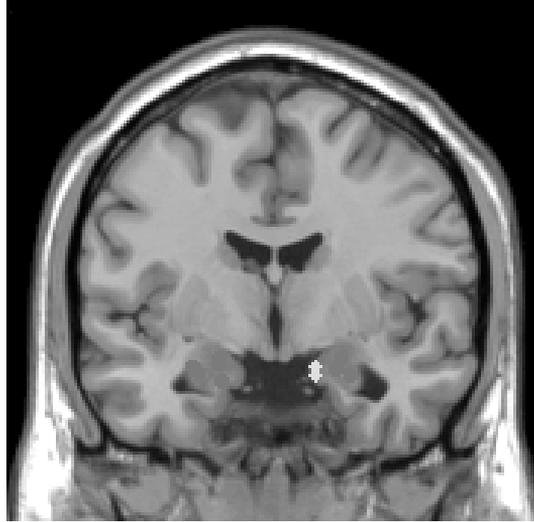


Figure 1. Fear activates the amygdala. Amygdala/periamygdaloid activations from six neuroimaging studies of small animal phobia (Dilger et al. 2003; Pissiota et al. 2003; Veltman et al. 2004; Schienle et al. 2005; Straube et al. 2006b; Goossens et al. 2007) are superimposed on a structural MR-image. Red=amygdala; Yellow=periamygdaloid area.

Quantifying the arousal state

In studies of emotion and memory, the state of arousal is most often implicitly inferred to have changed with an experimental manipulation. The arousal state can however be considered to be a continuous variable with a capacity to explain inter individual differences in biological responses when a well controlled experimental setting is kept constant. Changes in arousal state are associated with reliable alterations in respiration (Dampney et al. 2008), cardiac output (Fredrikson et al. 1990; Zimmerman and Frohlich 1990), muscle tension (Glombiewski et al. 2008), electrodermal activity and endocrinal response (Lightman 2008).

Measures of autonomic and hypothalamic pituitary adrenal-axis activity have been used to quantify arousal. An interesting biological marker of stress and arousal because of its modulatory role in memory formation is cortisol, which can be sampled from saliva (Kirschbaum and Hellhammer 1989). The cortisol response is however delayed following an arousing event which favors measures of autonomic activity that can be assessed *in situ*. A well validated measure of autonomic activity is electrodermal activity (see methods section for an introduction). Electrodermal activity has been correlated to arousal ratings of pictures (Bradley et al. 1992) and stress in a

wide variety of tasks. Other variables used to index arousal are heart rate, blood pressure and respiration (Pappenheimer et al. 2001).

The electromyogram (EMG) can be used to measure startle blink responses (see methods section for an introduction). Startle blink responses have been correlated to emotional valence but not arousal (Lang et al. 1990; Jansen and Frijda 1994) and can therefore be used as an emotional state measure that is segregated from arousal.

Recognition memory

Memories can be declarative or non-declarative (Tulving and Markowitsch 1998). Declarative memories are of the sort that can be reflected upon and be communicated such as: “I rode my pink bike through town”. The non-declarative counterpart in the previous example would be remembering *how* to ride the bike which is referred to as a procedural memory.

Recognition memory is a judgment of the prior occurrence of an object (see fig 2 for illustration of experimental set-up) and is thought to be a critical component of declarative memory (Winters et al. 2008). It is commonly studied by presenting words or pictures to subjects during an encoding phase. Then, during a retrieval phase where previously presented objects are mixed with foils, the subjects have to judge whether the objects presented have previously been seen or not.

Two regions that have been implicated in recognition memory are the hippocampus and the perirhinal cortex. The latter is situated in the parahippocampal cortex. Importantly, lesions to the amygdala does not directly impair recognition memory (Mishkin 1978) but rather arousal enhancement of memory as will be discussed in next section.

On a neural level, memory is thought to depend on long term potentiation (LTP). LTP was first described by Bliss and Lømo (1973) and involves changes in the synaptic efficacy between two nerve cells so that a presynaptic cell can invoke an axonal response in a post-synaptic cell after, but not before LTP. The discovery of LTP was a major breakthrough in memory research because it allowed scientists to study the details of memory formation *in vitro*. The effects of neuroactive compounds can then be directly examined in preparations to formulate hypothesis that can be tested *in vivo*.

Hippocampus and the perirhinal cortex in recognition

The hippocampus has been of central interest for researchers in human memory since the seminal study of Henry Gustav Molaison (H.M.) by Scoville and Milner (1957). H.M. suffered severe memory impairment following bilateral removal of the anterior MTL regions in an attempt to reduce epileptic seizures. Several later studies of patients with well

documented lesions restricted to the hippocampus have confirmed the importance of this structure in human recognition memory (Wais et al. 2006; Bayley et al. 2008)



Figure 2. Illustration of the procedure used to test recognition memory in study II and III. During encoding, subjects passively view pictures. During retrieval, subjects have to judge whether they have seen the picture before.

A failure to correctly encode sensory stimuli is consequently associated with less hippocampal activity (Stevens et al. 2008). Recent neuroimaging data also suggest that failure to encode may be due to increased activity in the default network, or baseline activity, of the brain (Shrager et al. 2008; Stevens et al. 2008). Activation of the default network of the brain has been interpreted as “mind wandering”, which could interfere with attentional processes necessary for memory encoding.

In the late 1970's, studies in monkeys indicated that lesions to the amygdala or the hippocampus was not interfering with recognition memory (Mishkin 1978). Only if both structures were destroyed could a severe impairment be noticed. Later research however showed that the technique used to remove both structures also damaged the perirhinal cortex. The perirhinal cortex is as before mentioned situated in the parahippocampal gyrus. Removal of the perirhinal cortex by itself while sparing the amygdala and the hippocampus in turn interfered with recognition (Zola-Morgan et al. 1989). Attempts have been made to functionally segregate the perirhinal cortex and the hippocampus in memory formation. An ongoing debate

concerns whether the perirhinal cortex is necessary for familiarity with a stimulus and the hippocampus for the recollection of a stimulus (Sauvage et al. 2008) or whether they are equally involved in both processes (Wais et al. 2009).

Arousal enhances memory

One of the earliest researchers to observe that strong emotions can generate long-lasting memories of arousing events was Colgrove (1899). He noted that people could describe vivid details from the day Abraham Lincoln was killed even though three decades had passed since the assassination. Memories for shocking events of national importance have later been referred to as flashbulb memories (Brown and Kulik 1977). A few years after Colgrove's report, Yerkes and Dodson (1908) studied the effect of different shock intensities on learning rates during a discriminatory avoidance task in mice. They found that if the discrimination was easy, stronger shocks led to faster learning rates. During more complex discrimination, learning rates first increased at moderate shock intensities but then decreased with intense shock levels. Therefore the effect of emotion on learning seems to be dependent both on task difficulty and arousal level (see fig. 3).

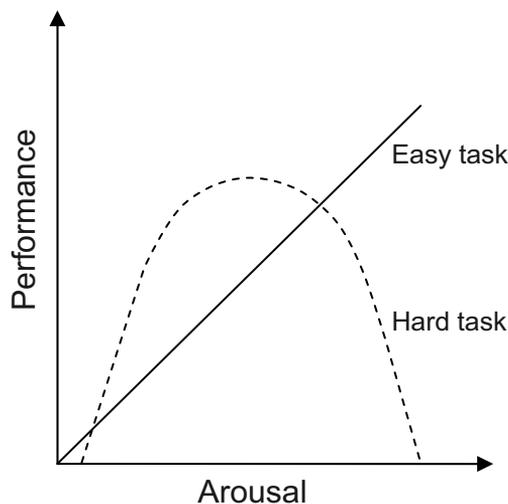


Figure 3. Illustration of the Yerkes-Dodson's law.

How the distinction between an “easy” and a “complex” task should be framed is a matter of debate. However, it seems fair to call the judgment of pictures of clearly different motives as “old” or “new” an easy task, implicating that increasing arousal would lead to increased performance.

Arousal enhanced memory: amygdala interactions

Two hypotheses explaining how emotion can enhance memory have recently been proposed. The first one is often referred to as the modulation hypothesis (McGaugh 2004) and the second the temporal dynamics hypothesis (Diamond et al. 2007). On a systems level, both hypotheses are stating that processes residing in the amygdala modulate hippocampal activity and therefore predict that removal of this structure will interfere with arousal enhanced memory; a proposition tested in study II of the present thesis. Although these hypotheses cannot be directly tested in humans with present state of the art technology, they provide valuable models for understanding arousal enhanced memory.

The modulation hypothesis

There are two main arguments based on results from previous research that the amygdala modulates other brain areas during memory formation. First, electrical stimulation of the amygdala can lead either to memory enhancement or impairment depending on stimulation intensity and learning conditions (Gold et al. 1975). If memory would depend on amygdala plasticity only, it would have been expected that the intensity of stimulation would modulate memory in the same direction under all circumstances. Second, post-training lesions to the stria terminalis, which is a main projection area of the amygdala, block memory enhancing effects of amygdala stimulation (Liang and McGaugh 1983).

Later research has concentrated on finding the receptor systems within the amygdala that are associated with memory modulation. The noradrenergic system is a major candidate (for reviews see McGaugh 2004; van Stegeren 2008). A main finding has been that β -adrenergic receptors in amygdala neurons seem to mediate the effects of arousal on memory because antagonists reduce or totally block this effect. Consequently, β -adrenergic agonists can enhance the modulatory effects. Drugs affecting memory through other receptors, such as GABA, opioid and α -adrenergic receptors are all dependent on a functioning β -adrenergic receptor system. Cortisol that is released by the adrenal gland during stressful experiences can have beneficial effects on memory (Cahill et al. 2003). The effects of cortisol are also mediated by β -adrenergic receptors. Cholinergic muscarinic receptors that also are of importance for arousal enhancement of memory (McGaugh

2004) seem however to influence memory independently of β -adrenergic receptors (McGaugh 2004).

The temporal dynamics hypothesis

The temporal dynamics model has been proposed by Diamond and colleagues (2007) and bears resemblance to another recent idea (Joels et al. 2006). Instead of concentrating on the receptor systems within the amygdala that modulate memory in other brain areas, this theory is based on evidence from neurophysiological research demonstrating that amygdala activity may influence properties of hippocampal neurons facilitating long term potentiation (LTP). It also attacks the question how high arousal can improve performance during simple tasks and decrease performance during more complex tasks (Yerkes and Dodson 1908), a question that has been left open by McGaugh's modulation hypothesis (McGaugh 2004).

Amygdala is engaged during arousing conditions and facilitates LTP in the hippocampus for a duration of a few minutes after the arousing event has occurred. During that time period, memories will be more easily encoded. However, that time window is followed by a recession where new memories are more likely to be forgotten. Diamond et al. (2007) further hypothesize that the decline in performance on complex tasks during states of high arousal is dependent on the degree of prefrontal cortex engagement. High states of arousal seem to impair prefrontal functioning which could explain declining memory performance.

Neuroimaging studies

Hypothesis regarding the influence of arousal on memory have until recently been based on animal research. Initial neuroimaging of human subjects showed that when the encoding material is arousing, the amygdala is engaged as shown by correlations between recognition memory and amygdala activity at encoding (Cahill et al. 1996; Hamann et al. 1999; Canli et al. 2000). Increased functional connectivity between the amygdala and the hippocampus with surrounding cortices has also been associated with emotional as compared to neutral encoding (Kilpatrick and Cahill 2003; Dolcos et al. 2004). These neuroimaging studies support amygdala modulation of other MTL memory systems during arousing conditions as proposed by McGaugh et al. (2004) and Diamond et al. (2007).

Methods

The studies included in the present thesis used both central and peripheral measures of nervous activity. These measures are described below.

Brain activity: Regional cerebral blood flow

Positron emission tomography (PET), functional magnetic resonance imaging, electroencephalography and magnetoencephalography are *in vivo* measures of brain activity that are commonly used. In study I and III of the present thesis, PET was used to measure regional cerebral blood flow (rCBF). A PET-scanner can measure the coincidence of two gamma-rays that are emitted when a positron from a decaying radioligand collide with a photon. By injecting radioactive ^{15}O -water into the blood stream, it is thus possible to reconstruct 3D-images of the blood flow within the brain.

The activity captured by ^{15}O -water PET most probably reflects synaptic activity rather than spiking activity as shown by Logothetis et al. (2001). The majority of the efferent synapses of neurons are to be found on neighbouring neurons rather than on distant neurons (Logothetis et al. 2001). Regional CBF then is a mixture of activity in local neurons and afferent input from distant neurons, most probably reflecting more of local interconnections than distant inputs. It is therefore reasonable to interpret an activation of certain voxels in a PET volume as increased local field potentials in that area. This also seems to be true of deactivations as suggested by a recent study (Shmuel et al. 2006).

The integration of activity between brain areas is often referred to as functional connectivity. Functional connectivity is inferred by using correlational methods and is a measure of how well activity in one brain area can be predicted from activity in another brain area. However, it does not give information on the direction of the influence (Friston 1994). It is often of interest to know all other brain areas that co-vary in activity with a specific region of interest (ROI). This can give information of functional networks that work in a co-operative manner.

Peripheral measures of central nervous activity

Peripheral measures of central nervous activity in the study of fear and anxiety capitalizes on the fact that emotion triggers the autonomic nervous system associated with defensive responses such as increased emotional sweating and heart rate, reflex facilitation as well as pupil dilation. These defensive responses may support behaviors enhancing chances of survival in dangerous environments (Ohman and Mineka 2001). Autonomic responses can therefore be thought of as phylogenetically old and as such depend on brain structures that were developed early in the course of evolution. The startle blink reflex (Davis 2006) and electrodermal activity (Boucsein 1992) have often been used as autonomic indices of fear. One advantage of these measures is that they are related to the constructs arousal and valence and that they can be measured in humans as well as other species (Davis 2006). Both startle and electrodermal activity were used as emotional state indices in study III of the present thesis and deserve a shorter introduction.

The startle reflex: a psychophysiological index of valence

Studies of electrical changes in the human skin began over a hundred years ago (see Pappenheimer et al. 2001 for a review) and many of the principles revealed then are still of importance in psychophysiological research today. A Russian scientist named Tarchanoff discovered that by applying electrodes to the human skin changes in the electrical potential could be measured. This principle is used for registering electromyography (EMG) often used to monitor muscular activity indicative of startle. The startle response is a fast reflexive response that is elicited by loud noises or tactile stimuli (Blumenthal et al. 2005). Previous studies have shown that stimulus valence modulates the startle response (Lang et al. 1990; Jansen and Frijda 1994). Stimuli with negative valence increase startle magnitudes relative to neutral stimuli, whereas positively valenced stimuli attenuates the startle response. Affective ratings have also been correlated to startle responses (Buchanan et al. 2004) indicating that there is a linear relationship between the startle response and the experienced valence of stimuli. The auditory startle response is known to be mediated by synapses in the cochlear root neurons, the nucleus reticularis pontis caudalis and motor neurons in the facial motor nucleus (Davis 2006). Both lesion studies (Funayama et al. 2001; Buchanan et al. 2004; Kettle et al. 2006) and a neuroimaging study in humans (Pissiota et al. 2003) concur with animal studies (Rosen and Davis 1988; Sananes and Davis 1992) that have shown that modulation of startle is associated with amygdala activity. The modulatory effect of the amygdala is held to take place at neurons in the pontis caudalis (Davis 2006).

Electrodermal activity: a psychophysiological index of arousal

Féré (Pappenheimer et al. 2001) discovered that the skin became a better conductor when external stimuli were presented than during rest. This has to do with the fact that sweat glands are activated and ions in the sweat in turn alter the conductivity of the skin. Sweat glands are of two kinds: eccrine and apocrine. Apocrine sweat glands are found primarily in the armpits and genital areas whereas eccrine sweat glands are distributed all over the body with the highest density in the palms and the soles of the feet. The eccrine sweat glands have mostly been of interest to psychophysiologicalists. Their main function is thermoregulation but it is held that the hand and feet glands also might facilitate grasping behavior. All eccrine glands are believed to be involved in emotionally induced sweating, but measurements thereof usually is restricted to hands and feet because of the greater density of eccrine sweat glands in those areas as compared to the rest of the body.

Electrodermal activity can be measured as tonic skin conductance level or phasic shifts in skin conductance reflecting stimulus characteristics. When activation of the electrodermal system is studied as responses to emotional stimuli like pictures, it is usually the phasic response that is measured. Phasic responses can be measured time locked to the presentation of stimuli or as fluctuations during a whole block of stimulus presentations. The regulation of electrodermal activity depends on efferents from the sympathetic division of the autonomic nervous system. Notably, there is no para-sympathetic innervation of eccrine sweat glands. The central nervous control of electrodermal activity is complicated. Three relatively independent neural systems have been delineated (Pappenheimer et al. 2001). The first one involves the hypothalamus and the limbic system. Direct electrical stimulation of the human amygdala (Lanteaume et al. 2007) has been demonstrated to evoke electrodermal responses and fear conditioned electrodermal activity has been correlated to amygdala activity (Furmark et al. 1997). The second level of control involves cortical and basal ganglia influences and the third one involves the reticular formation and brainstem. The reticular formation is a brain area that since long has been implicated in regulation of arousal states (Moruzzi and Magoun 1949).

Aim

The general aim was to study medial temporal lobe mechanisms underlying the memory enhancing effects of arousal. Bodily arousal can be induced by an emotionally salient stimulus. Because previous results strongly suggest amygdala involvement in fear induced arousal, but little is known about the functional networks in which the amygdala is engaged, the first goal was to study amygdala connectivity in phobic fear. It is well recognized that the amygdala is modulating other memory related brain areas during arousing conditions. To establish whether the amygdala was necessary for arousal enhancement of memory, recognition for pictures varying in arousal was tested in patients with resections to the anterior MTL compared to controls. A final goal was to study if amygdala mechanisms generating bodily arousal also activate the parahippocampal cortex to facilitate memory encoding.

Specific research questions

1. Is amygdala activation during a highly arousing state associated with increased functional connectivity with other limbic and motor areas (study I)?
2. Is amygdala activity inversely related to activity in the anterior cingulate cortex during processing of fear relevant stimuli that do not instigate high levels of arousal (study I)?
3. Is the amygdala necessary for arousal enhancement of memory (study II)?
4. Is amygdala activity during encoding specifically associated with recognition memory during intense arousal but not during low arousal (study III)?
5. Is amygdala modulation of the parahippocampal cortex dependent on the bodily state of arousal (study III)?

Paper I: Disentangling the web of fear: amygdala reactivity and functional connectivity in spider and snake phobia

Aim and background

Specific animal phobia as for example spider and snake phobia is characterized by excessive and unreasonable fear, escape and avoidance behaviors (American Psychiatric Association 1994). It is therefore a suitable model to study neural responses during highly arousing conditions in an experimental environment, because high levels of distress can be obtained by showing subjects pictures of the feared animal. The primary aim of study I was to study functional connectivity of the amygdala during the phobic and non-phobic state. From previous studies, increased activity in the amygdala (Dilger et al. 2003; Pissiota et al. 2003; Veltman et al. 2004; Schienle et al. 2005; Straube et al. 2006b; Goossens et al. 2007) and the insula (Dilger et al. 2003; Straube et al. 2006a; Goossens et al. 2007) was expected. Recent neuroimaging reports had also observed a negative functional coupling between the amygdala and the ACC during overt presentation of mildly emotion inducing pictures (Pezawas et al. 2005; Stein et al. 2007). Therefore, it was hypothesized that this negative functional coupling would be found during the presentation of the non-phobic but fear-relevant slides. It was also expected that this coupling would be non-existent during the phobic state as indicated by a previous meta-analysis (Etkin and Wager 2007).

Methods

Sixteen right handed women with either snake (n=8) or spider phobia (n=8) but not both participated in the study. The study was approved by the local ethics committee of Uppsala University and subjects signed informed consent. RCBF was measured using ¹⁵O-water PET while subjects viewed phobic or non-phobic slides intermittently presented on a computer screen to reduce the probability of amygdala habituation (Wright et al. 2001). Following PET-scanning subjects rated experienced distress using a visual analog scale (range 1-100).

Results

Subjects rated the phobic slide presentation as more distressful than the non-phobic presentation. This was paralleled by increased right amygdala rCBF. Difference scores of amygdala rCBF reflecting phobia induced activity were positively correlated with difference scores in distress ratings. Increases in the insula did not reach statistical significance. Exploratory whole brain analyses revealed increases in neuronal activity in a cluster in the extrastriate visual cortex, (BA18) extending into the fusiform area (BA37), as well as in circumscribed parts of the prefrontal (BA10) and temporal cortices (BA22).

There were extended decreases in a cluster in the prefrontal cortex encompassing BA47 and BA46. A cluster in BA10 and the medial orbital gyrus (BA11) also showed attenuated activity during symptom provocation. In addition, reduced activity was noted in the primary somatosensory (BA3) and the primary auditory cortices (BA41) as well as in the parietal cortex (BA40).

Exploration of amygdala functional connectivity during the phobic state revealed a functional network including the left BA34/amygdala, left fusiform gyrus (BA37), and a cluster with a peak voxel in the precentral gyrus, extending into the right motor cortex (BA 4, see fig. 4). As predicted, a negative correlation was also found between the right amygdala and the ACC during the non-phobic but not during the phobic condition (fig 5).

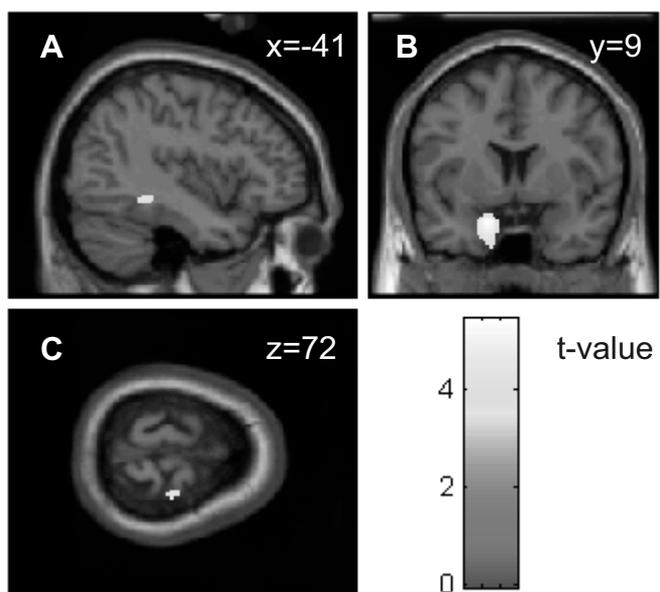


Figure 4. Voxels co-varying with right amygdala activity during phobic stimulation. A) Sagittal section showing cluster situated in the left fusiform gyrus. B) Coronal section showing cluster situated in left amygdaloid region. C) Transverse section showing cluster situated in the right motor cortex. All voxels thresholded at $p < 0.001$.



Figure 5. Negative functional connectivity between the right amygdala and the supra-genual ACC during fear-relevant but non-phobic picture viewing. $x=16$.

Discussion

The present study demonstrates that symptom provocation in individuals with specific phobia results in amygdala activation concurrent with a decoupling of the amygdala and the anterior cingulate. Other frontal areas implicated in emotion regulation decreased in activity. Together with the finding that amygdala is functionally coupled to the fusiform gyrus involved in visual object recognition, this could imply that top-down processing is abolished in favor of stimulus driven bottom-up processing during the phobic reaction. In conjunction with the observation that the right amygdala is functionally connected to the left amygdaloid area and the motor cortex this could be interpreted as visually induced fight/flight preparedness.

Paper II: Arousal enhanced memory retention is abolished following temporal lobe resection

Aim and background

Previous studies have implicated reduced emotional enhancement of memory following MTL resections (Buchanan et al. 2001; Edith Frank and Tomaz 2003; Adolphs et al. 2005), but no distinction has previously been made between the arousal and valence dimensions of the encoding material. The aim of the present study was to examine recognition memory for non-arousing, moderately and highly arousing pictures while keeping the mean valence level constant. Because subjects had unilateral resections of the anterior MTL, the study design also permitted conclusions to be drawn as to whether the right or left MTL is more involved in arousal enhancement of memory.

Response latencies during the recognition test were also examined. Delayed response latencies have previously been reported to conditioned stimuli in fear conditioning paradigms (Armony and Dolan 2001) and latencies were therefore expected to increase with increased stimulus arousal. Moreover, we hypothesized that this effect would only be present in controls if it was dependent on the anterior MTL.

Methods

Nineteen subjects with uni-lateral resections to the left (10 women) and 14 to the right (8 women) anterior medial temporal lobe due to medically intractable epilepsy were compared to 16 controls (8 women) on a recognition memory task. The whole or most of the amygdala was removed together with the anterior hippocampus. Subjects were presented with 126 pictures and then immediately after tested for recognition of 64 of the previously presented pictures blended with 64 foils in a yes/no forced choice paradigm. Recognition memory was scored as proportion correct responses for the 10 pictures with the lowest normative arousal ratings (scale 1-9, mean arousal=2.7), the 10 pictures centered on the median normative arousal ratings (mean arousal =4.5) and the 10 pictures with the highest normative arousal ratings (mean arousal =6.4). The valence level was constant across

arousal categories (mean valence =5.5). The response latencies for correct responses were also compared between patients and controls.

Results

The number of correct responses did not differ between resected patients and controls for low arousing pictures. Recognition of medium and high arousing pictures was better for controls and showed a linear trend for arousal enhanced memory in the control group only (fig. 6). Controls also showed slower response latencies with increasing arousal, which was not the case for patients. No differences in recognition or response latencies between patients with right and left sided resections were found.

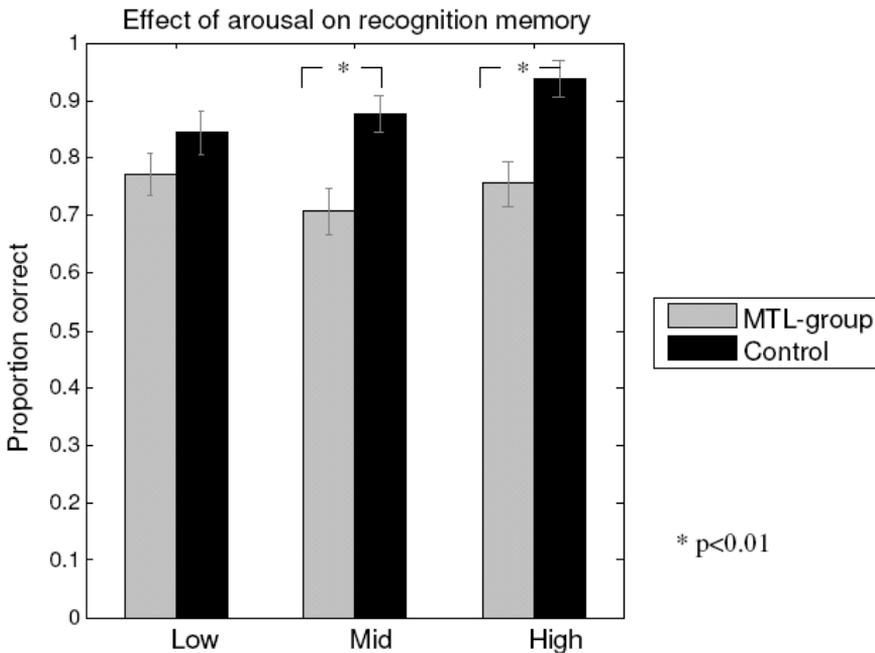


Figure 6. Memory performance measured as mean proportion correct recognition for non-arousing, moderately and highly arousing pictures in patients with resections to the medial temporal lobe (MTL-group) and non-operated healthy controls. Error bars show standard errors.

Discussion

Results suggest that the anterior MTL is necessary for arousal enhancement of memory. Further, response latencies for correctly recognized pictures increased with arousal. This might suggest that the emotion inducing properties of the stimuli were competing for the same neuronal resources as processes involved in memory. Because uni-lateral resections impair this competitive effect, results are consistent with the idea that both arousal enhanced memory and arousal induction are amygdala dependent. The null results from the comparison of right and left resected patients suggest that the left and right anterior temporal lobe might be equally important for arousal enhancement of memory. They further suggest that one intact MTL is not sufficient for arousal enhancement of memory to occur. Previous findings of laterality differences have been material specific. Subjects with an intact left MTL have shown an advantage over left resected in memorizing words (Buchanan et al. 2001; Burton et al. 2004) whereas no hemispherical specialization was seen for encoding of gist in images (Adolphs et al. 2005). It might be that encoding of pictures depends on visual cues and engage non-verbal memory processes independent of hemispherical specialization.

Paper III: Arousal gates amygdala interaction with the parahippocampal cortex during encoding of phobic pictures

Aim and background

The amygdala is modulating memory processes in other brain areas during states of enhanced arousal. Previous studies have shown enhanced amygdala recruitment during memory encoding of mildly arousing pictures and enhanced connectivity between the amygdala and the hippocampus and surrounding parahippocampal cortices. Here, highly arousing phobic stimuli served as encoding material. Understanding what mechanisms underlie arousal enhancement of memory is important in generating therapies for conditions of low memory performance as well as conditions where memory encoding during highly arousing conditions results in psychiatric problems like post traumatic stress disorder. The same stimuli can induce variable amounts of bodily arousal in different subjects and it was hypothesized that the induced state of arousal as indexed by electrodermal activity would mediate the influence of the amygdala on the parahippocampal cortex. The parahippocampal cortex would in turn predict recognition. In contrast, it was hypothesized that valence associated startle responsivity would be a psychophysiological emotional measure without any influence on amygdala-parahippocampal interaction. Correlations between the amygdala and the midbrain were also investigated, with the hypothesis that a stronger correlation would be present during phobic than non-phobic stimulation because of amygdala influences on general arousal mechanisms. The present study was a methodological advancement compared to previous studies in that identical encoding material served as arousing and non-arousing stimuli. The low arousing condition consisted of showing pictures of spiders to subjects with snake phobia and snakes to subjects with spider phobia with the opposite pattern of stimulation during the highly arousing condition, thus keeping visual input constant across conditions.

Methods

Sixteen right handed women with either snake (n=8) or spider phobia (n=8), but not both, participated in the study. These were the same subjects as in study I. Subjects passively viewed 50 phobic and 50 non-phobic pictures on two separate days while rCBF was measured with ^{15}O -water. Non-specific fluctuations of electrodermal activity indexing the arousal state and EMG of startle blink responses were recorded simultaneously with rCBF. Subjects were also asked to rate experienced distress during stimulus presentation on a visual analog scale (range 1-100). A surprise forced choice recognition test containing 36 previously shown pictures mixed with 12 foils for each condition (phobic/non-phobic) was given 1.5 hours post scanning. Recognition memory was indexed by d' (Macmillan and Creelman 2005) that is an unbiased measure of discrimination performance. A region of interest (ROI) approach including the amygdala, the hippocampus and the perirhinal cortex (BA35/36) was used for evaluation of rCBF data in the software SPM2 (see Friston et al. 1994 for description of statistical methods). The spatial location and extension of the ROI's is illustrated in figure 7. Mediation of amygdala-hippocampal interaction by electrodermal activity was tested using path analysis in Mplus 4 (Muthén and Muthén 2004).

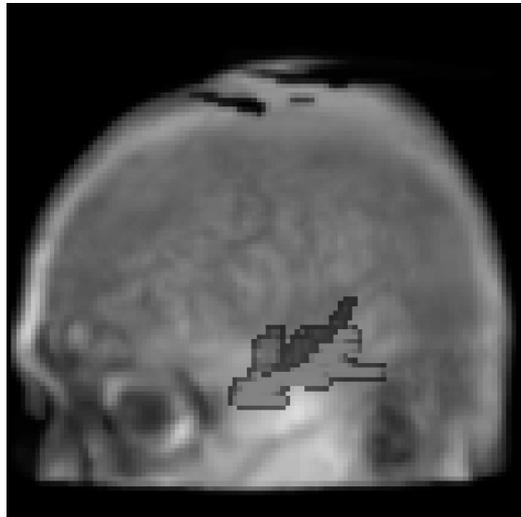


Figure 7. The amygdala (red), hippocampus (blue) and perirhinal cortex (green) in the left hemisphere rendered on an MRI-volume. These were the regions of interests used in study 3. The person is looking to the left.

Results

Highly arousing (phobic) cues were better remembered than low arousing (non-phobic) cues concomitant with increased electrodermal activity indexing arousal, startle responses reflecting valence and experienced distress. RCBF in bilateral amygdala and parahippocampal cortices was correlated to subsequent recognition memory during incidental encoding of highly arousing cues. Correlations to memory for low arousing cues were only observed in the left parahippocampal cortex. The degree of amygdala activation was a better predictor of electrodermal activity, startle and experienced distress during high than low arousing cues. The observed bilateral co-variation between recognition and parahippocampal activity was dependent on arousal but not startle (fig. 8). Electrodermal activity was mediating amygdala and the parahippocampal cortex connectivity (fig. 9). Further, the right amygdala showed a stronger co-variation with voxels in the midbrain during the phobic as compared to the non-phobic condition ($x,y,z=0,-20,-18$; $Z=3.46$; $p=0.024$ corrected for multiple comparisons, fig. 10). Activity in this midbrain cluster was also correlated to recognition memory for phobic pictures ($r=0.50$; $p=0.05$).

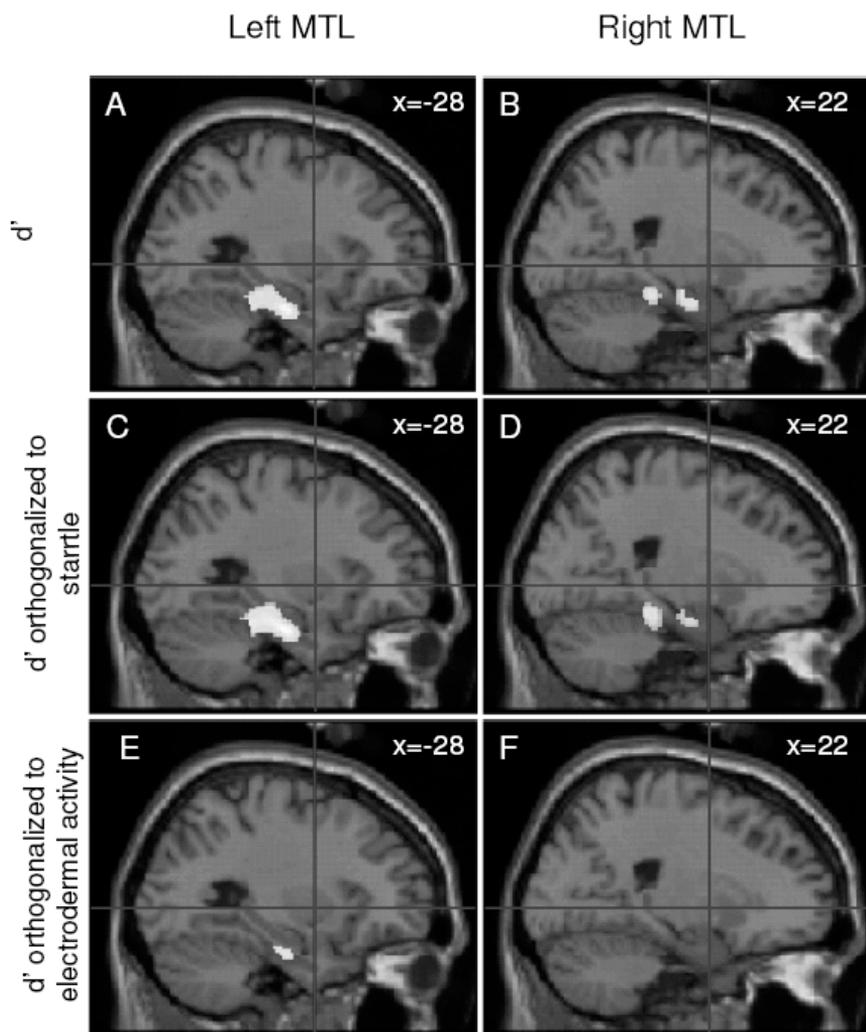


Figure 8. Co-variation between recognition memory (d') and parahippocampal rCBF during phobic stimuli presentation in A) the left and B) and right parahippocampal cortex. Co-variation when d' was orthogonalized to startle in C) the left and D) the right parahippocampal cortex. Co-variation when d' was orthogonalized to electrodermal activity in E) the left and F) the right parahippocampal cortex. Hair cross in $y=0, z=0$.

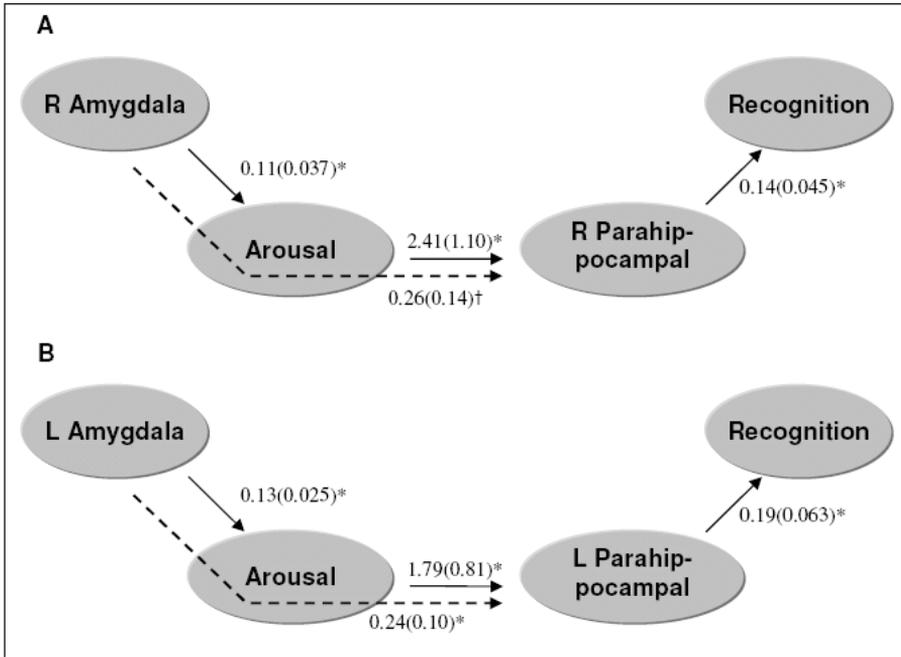


Figure 9. Path model testing if amygdala effects on parahippocampal rCBF during phobic cues are mediated by arousal as indexed by electrodermal activity. Arrows are labeled with unstandardized path coefficients and standard errors in parenthesis. Filled arrows represent direct effects and dashed arrows indirect effects. A) Indirect effects of amygdala on parahippocampal cortex mediated by electrodermal activity indexing arousal reached borderline significance in the right hemisphere. B) Indirect effects of amygdala on parahippocampal cortex mediated by arousal were significant in the left hemisphere. L=left; R=right; * $p < 0.05$; † $p = 0.051$.

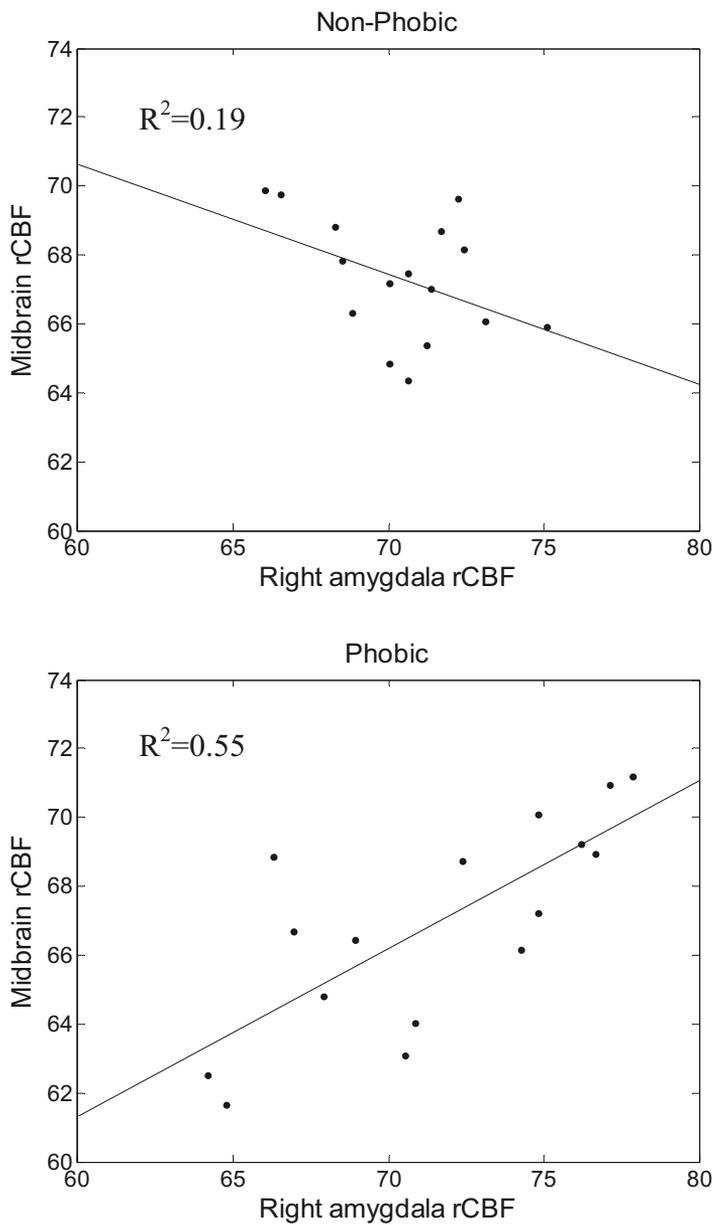


Figure 10. Scatter plots of right amygdala and midbrain rCBF. A) Non-phobic condition. B) Phobic condition. The mean value of voxels with a probability value less than 0.01 are plotted.

Discussion

Results suggest that highly arousing conditions enhance recognition memory. Arousal enhanced memory was paralleled by stronger recruitment of the MTL memory system. As predicted, the amygdala influence on the parahippocampal cortex was directly dependent on the arousal state as shown by the mediation analysis. From the same analysis, it was also shown that parahippocampal activity in turn predicted subsequent recognition.

According to the modulation hypothesis, amygdala influences memory by regulating activity in other brain areas which has been supported by a large body of evidence in animals (McGaugh 2004). Recent neuroimaging work also suggest that emotional enhancement of human memory is achieved by amygdala influencing the hippocampus and surrounding cortices (Kilpatrick and Cahill 2003; Dolcos et al. 2004). Consequently, pharmacological suppression of arousal by the anesthetic gas sevoflurane blocks emotional memory enhancement and also severely attenuates amygdala modulation of hippocampal activity (Alkire et al. 2008). Because anesthesia reduces arousal (Ledowski et al. 2006) these results might reflect a reciprocal relationship between brain systems involved in general arousal generation such as the reticular activation system, and brain areas involved in regulating arousal as a response to environmental threats, such as the amygdala. Interestingly, amygdala activity was more correlated to midbrain rCBF during phobic than non-phobic stimulation, an interaction that has previously been reported during encoding of mildly arousing pictures (Sterpenich et al. 2006). The midbrain cluster exhibiting this correlational pattern also showed a positive correlation to recognition memory. It is therefore likely that the arousal gating mechanism governing the influence of the amygdala on parahippocampal activity is co-dependent on amygdala-midbrain interactions. Future studies should delineate the difference in the temporal pattern of activation to arousing stimuli between the amygdala and general arousal systems in the midbrain to establish the directionality of this interaction. Collectively, the present findings and those of Alkire et al. (Alkire et al. 2008) suggest a direct relation between amygdala activity, arousal state and parahippocampal activity.

General discussion

The main findings will first be summarized and then followed by a general discussion of the results from studies I, II and III.

Main findings

The main findings of the present thesis are:

1. The amygdala is a node in a fear network involving other limbic areas and cortical motor and visual processing areas during intense levels of arousal. (Study I)
2. Under non-arousing conditions, the rostral ACC seems to suppress amygdala activity during processing of fear relevant stimuli. (Study I)
3. Amygdala activity co-varies with recognition memory during high but not low levels of arousal. (Study III)
4. The amygdala is necessary for arousal enhancement of recognition memory because patients with anterior MTL resections do not exhibit better memory for arousing as compared to non-arousing pictures. (Study II)
5. Arousal related electrodermal activity but not valence related startle mediates amygdala-parahippocampal connectivity. Parahippocampal activity in turn predicts recognition memory. (Study III)

Discussion

There is little doubt about the importance of the amygdala in fear behaviors and fear learning (LeDoux 1998). The present results suggest that in a fear provoking situation, the amygdala is involved in regulating the arousal state of the body. Arousal, in turn has been associated with the vigor with which a goal is pursued (Lang et al. 1990) and in the special case of fear, this could be interpreted as how much effort should be put into fight/flight actions. The results of study I suggest that the amygdala is a node

in a fear network supporting these behavioral demands. Motor areas are recruited during the fear state which might reflect motor-preparedness for avoidance behaviors, whereas the connectivity with object recognition areas in the fusiform gyrus could indicate a more stimulus driven bottom up mode of brain functioning directing attention to environmental threats.

Studies II and III investigated amygdala mechanisms involved in facilitation of memory by arousal. Results from study II suggest that the amygdala seems necessary for arousal enhancement of memory because the enhancing effects of arousing stimuli was abolished in patients where the anterior MTL had been uni-laterally removed due to medically intractable epilepsy. Interestingly, no difference was noted between patients with left and right resections. This response pattern converges with the mediation analysis in study III (fig. 9) where very similar correlations to recognition memory were observed in the two hemispheres. It could be argued that this regularity in the response of the two hemispheres could be due to the tight functional coupling between the right and left amygdala during the phobic state (study I, fig. 4) in turn explaining how resections to either hemisphere result in reduced memory facilitation by arousal (study II).

If a situation triggers arousal because of its emotional significance, cues that might predict a future similar event are relevant to memorize. Therefore, it could be hypothesized that the same brain areas as those in control of arousal also should facilitate memory. The results from study III support this hypothesis and suggest that amygdala generates bodily arousal that in turn gates amygdala influences on the parahippocampal cortex. Recognition memory for highly arousing stimuli in turn depends on the parahippocampal cortex. From an evolutionary modular view of the brain, neural arousal mechanisms might have evolved before neural mechanisms underlying recognition memory. From this point of view it is not unsound that neural processes generating arousal also influence memory.

It is likely that one or a few general systems in the brain generate arousal and that they are inter-connected with brain areas involved in more specific arousal modulation. Results from study III show that the amygdala is more functionally connected with the midbrain during high than low arousing stimulation. This connectivity is possibly associated with noradrenergic (Berridge 2008) and dopaminergic (Monti and Monti 2007) cell assemblies in the midbrain that also are involved in intrinsically governed forms of general arousal influencing for example awakening. Damage to the brainstem due to stroke have also been shown to attenuate physiological measures of arousal such as electrodermal activity (Linden and Berlit 1995). Therefore, the pathway through which the amygdala regulates arousal to extrinsic stimuli might pass through areas involved in intrinsic and general arousal regulation. Also, the observed amygdala-midbrain connectivity influences memory as shown by the positive correlation between recognition of phobic pictures and midbrain activity. This suggests that a

phylogenetically relatively old brain region is a key mediator in orchestrating the effect of arousal on memory.

During presentation of emotional faces a negative relationship has been observed between mPFC and amygdala activity (Kim et al. 2003). Such a negative relationship has been replicated in several studies using mildly emotional stimuli (Meyer-Lindenberg et al. 2005; Pezawas et al. 2005; Stein et al. 2007) and converges with animal literature showing reduced amygdala activity and fear responses to mPFC stimulation (Maren and Quirk 2004; Quirk et al. 2006). The negative correlation between amygdala and ACC activity in study I could therefore reflect an inhibition of amygdala activity. This inhibition could in turn attenuate amygdala enhancing effects on bodily arousal and the parahippocampal cortex, resulting in attenuated memory performance and arousal state, as shown in study III.

Limitations

Because we did not record electrodermal activity during the encoding of the IAPS pictures in the resected patients (Study II), we do not know whether the bodily arousal state also predicted memory performance in resected patients. Also, because the PET technology does not permit event related designs, we could not compare encoding activity in the MTL between remembered and non-remembered items. Further, only women participated in the PET-studies (I and III) and future studies could include men.

Future directions

Study I and III showed that specific phobia might be a powerful model for the study of arousal and arousal enhanced memory whereas the lesion study (II) allowed inference about the necessary involvement of the anterior MTL in arousal enhanced memory possible. Two hypothesis that should be tested in future studies came out from this thesis.

First, the present results suggest that MTL memory systems in the right and left hemisphere might work in concert, because 1) Resections to either hemisphere resulted in impaired arousal enhancement of memory. 2) A positive correlation between the amygdalae of the two hemispheres was observed in study I. 3) Path analysis showed a very similar pattern of influences between amygdala activity, arousal, parahippocampal activity and recognition memory in the left and right hemispheres. However, this hypothesis needs to be evaluated. An obvious next step would be to study brain activity in MTL resected patients during encoding and retrieval of

emotional material. This could show if the mediating effect of arousal on amygdala-hippocampal interaction remain in the intact hemisphere.

Second, we here showed that the interplay between amygdala activity and activity in the central arousing system of the midbrain might affect memory during intense distress. This observation predicts that damaging amygdala efferents to the midbrain should interfere with emotional memory and could be tested using animal models.

In summary, strong arousal influences the amygdala to prepare for action and to enhance memory.

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This thesis is a collaborative effort. I would like to thank my parents for always having supported me throughout my scientific work. I would also like to thank science for indirectly having brought me together with my wife, and my wife for giving me something else than science to love and admire.

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