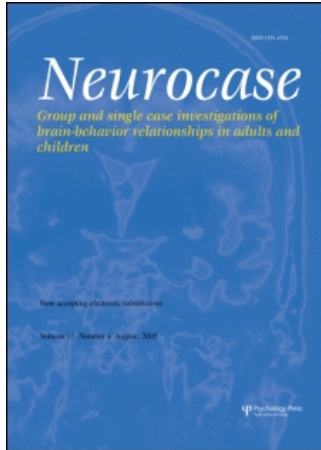


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Publisher: Psychology Press
Informa Ltd Registered in England and Wales Registered Number: 1072954
Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Neurocase

Publication details, including instructions for authors and subscription information:
<http://www.informaworld.com/smpp/title~content=t713658146>

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Online Publication Date: 01 November 1998

To cite this Article: Phelps, Elizabeth A., Labar, Kevin S., Anderson, Adam K., O'Connor, Kevin J., Fulbright, Robert K. and Spencer, Dennis D. (1998) 'Specifying the Contributions of the Human Amygdala to Emotional Memory: A Case Study', *Neurocase*, 4:6, 527 — 540

To link to this article: DOI: 10.1080/13554799808410645
URL: <http://dx.doi.org/10.1080/13554799808410645>

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Specifying the Contributions of the Human Amygdala to Emotional Memory: A Case Study

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Abstract

We examined emotional memory in patient SP, a 54-year-old woman with bilateral damage to the amygdala. Consistent with previous case studies, SP showed deficits on tests of fear conditioning and recognition memory for arousing stimuli. SP's performance on several emotional episodic memory tasks was examined. We found that bilateral damage to the amygdala only leads to deficits on a subset of emotional episodic memory tasks. Specifically, the amygdala does not seem to be involved when episodic memory performance benefits from the valence of the stimuli. However, when episodic memory benefits from arousal, damage to the amygdala leads to a deficit in performance. Based on our results, we postulate that the amygdala is not involved when emotion enhances episodic memory primarily by contributing an organizing principle such as a schema or category. We expect the effects of amygdala damage to be limited to memory tasks affected by the neuromodulatory changes that occur with arousal. The effects of arousal on episodic memory would be most apparent in the rate of forgetting for arousing stimuli, the recall of arousing stimuli that have a weak central theme, and the recognition of details or events associated with arousing stimuli.

Introduction

The importance of the medial temporal lobe structures in human memory has been known since the initial reports of the famous amnesic patient HM. Most studies examining the role of the medial temporal lobe in memory have focused on the hippocampus and associated cortices as key structures. However, recent research with non-human animals has suggested another medial temporal lobe structure, the amygdala, may have a unique role in mnemonic processing. Specifically, it has been suggested that the amygdala may be critical for the modulation of memory with emotion, or emotional memory. In humans, it has been difficult to determine if selective emotional memory deficits exist following bilateral damage to the amygdala because these lesions rarely occur in the absence of extensive medial temporal lobe damage and associated episodic memory impairments. However, there have been a few reported cases of patients who have bilateral amygdala lesions and relatively spared episodic memory (Tranel and Hyman, 1990; Babinsky *et al.*, 1993; Markowitsch *et al.*, 1994). In the present paper, we introduce an additional case, patient SP. We examine her abilities on several memory tasks where normal performance is influenced by emotion.

Memory performance following bilateral amygdala damage, in the absence of a severe episodic memory impairment, has been examined in three previous cases. All of these cases suffer from a rare dermatological disease known as Urbach–Wiethe syndrome or lipid proteinosis. About half of the patients diagnosed with this syndrome exhibit intracranial calcification primarily in the amygdala and hippocampal gyri (Lever and Schaumburg-Lever, 1990). The first reported case of memory assessed in one of these patients was SM-046 (Tranel and Hyman, 1990). Her emotional memory was tested using a version of a fear conditioning paradigm (Bechara *et al.*, 1995). Most of the research on non-human animals examining the role of the amygdala in emotional memory has used fear conditioning paradigms (see LeDoux, 1996). In this paradigm a neutral event, such as a tone, is paired with an aversive event, such as a foot shock. After a few pairings, normal animals start to exhibit fear responses to the previously neutral tone when presented alone. Animals with amygdala lesions never learn the aversive properties of the tone. Similar to non-human animals with amygdala lesions, SM-046 did not demonstrate conditioned fear, as measured by skin conductance responses (SCR) to the neutral stimulus that

was paired with the aversive stimulus. However, she did show a normal SCR to the aversive stimulus, suggesting the deficit is one of learning the aversive properties of stimuli, as opposed to responding to aversive stimuli.

This result suggests a preservation of the role of the amygdala across species. However, aside from altering the physiological response to neutral stimuli that signal aversive events, as in fear conditioning, there are several other ways in which emotion may influence memory in humans. For instance, most people can recall memories for emotional events that seem especially vivid or enduring. This type of memory for events, often referred to as episodic memory, is the most widely studied type of memory in humans and may be particularly important in human experience (Wheeler *et al.*, 1997). It has been demonstrated that emotion can influence performance on episodic memory tasks, primarily by enhancing memory for emotional events (Christianson, 1992). Performance on episodic memory tasks that are influenced by emotion has been examined in a brother (BP) and sister (CP) who showed bilateral mineralization of the amygdaloid complex associated with Urbach–Wiethe syndrome (Babinsky *et al.*, 1993; Markowitsch *et al.*, 1994). Recall and recognition memory performance were assessed in CP and BP for emotional and neutral stimuli using two tasks (Markowitsch *et al.*, 1994). The first was a verbal cued recall task in which the subjects had to recall emotional and neutral words at four retention intervals. On this task, BP exhibited impaired memory for the emotional words compared to neutral words, especially after a delay. CP showed equivalent performance for emotional and neutral words across all delays. The second task assessed recognition of emotional pictures. On this task, CP exhibited impaired recognition for emotional pictures compared to neutral pictures, whereas BP had a normal pattern of performance.

In another study, recognition memory for an emotional story was examined in patient BP. Using a paradigm adapted from Heuer and Reisberg (1990), Cahill and colleagues (1995) asked normal controls and BP to view a narrated story that consisted of 12 slides. The story was divided into three parts. The early and late sections were relatively neutral in emotional content, whereas the content of the middle section was somewhat arousing. Normal subjects demonstrate enhanced recognition of the middle section of the story compared to the early and late neutral sections. Patient BP failed to show enhanced recognition of the middle, arousing section of the story. However, she also had below average recognition of the late, neutral portion, indicating a more global memory impairment for the story. The same study was later conducted with patient SM-046, who had a similar deficit in recognizing the arousing portion of the story (Adolphs *et al.*, 1997).

Aside from the three cases presented above, there have been a few other reported cases of patients with bilateral amygdala damage in the absence of severe episodic memory deficits (e.g. Lee *et al.*, 1989, Young *et al.*, 1995).

However, these patients have primarily been studied in tasks examining evaluation of emotional stimuli or emotional reactions. Emotional memory performance has been examined in patients with partial damage to the amygdala (LaBar *et al.*, 1995; Phelps *et al.*, 1997) and patients with bilateral amygdala damage who also have extensive temporal lobe damage and an episodic memory impairment (Hamann *et al.*, 1997). These studies, combined with the case studies mentioned above, result in two preliminary conclusions about the role of the amygdala in emotional memory. First, the amygdala seems to be critical for normal performance on fear conditioning tasks (Bechara *et al.*, 1995; LaBar *et al.*, 1995). Second, the amygdala may only be partially involved in the memory enhancing effects of emotion on episodic tasks. Although patients with amygdala damage sometimes exhibit deficits on these tasks (Cahill *et al.*, 1995; Adolphs *et al.*, 1997), they also show normal enhanced memory involving emotion in other circumstances (Markowitsch *et al.*, 1994; Phelps *et al.*, 1997).

In the present study, we introduce another case with bilateral damage to the amygdala who has intact episodic memory. Unlike the previous cases presented, this patient did not suffer from Urbach–Wiethe syndrome. Her brain injury was the result of surgery for epilepsy combined with gliosis of the amygdala. We examined her performance on a variety of emotional memory tasks, including fear conditioning and four tests of episodic memory influenced by emotion. By examining several episodic memory tasks, we could begin to identify some of variables that characterize situations where the amygdala plays a role in emotional memory.

Patient report: case SP

Medical history

SP is a 54-year-old, right-handed female with a history of epilepsy. SP's first indication of any neurological impairment occurred at 3–4 years of age. She was later diagnosed with epilepsy. As she reached middle age, her epilepsy became more severe and at the age of 48 years she was considered for surgical treatment of medically intractable complex partial seizures of right medial temporal lobe origin (see Spencer and Spencer, 1985). Although extensive pre-operative testing determined that the seizure origin was the right medial temporal lobe, MR images prior to surgery also revealed a lesion of the left amygdala. A biopsy of the left amygdala was performed prior to surgery and revealed reactive gliosis or scar tissue. The aetiology is unknown. Given the severity of her epilepsy, SP chose to proceed with surgery and underwent *en bloc* right anteromedial temporal lobe resection. The surgical procedure involved an approximate 3.5 cm resection of the anterior middle and inferior temporal gyri, allowing access to the temporal horn of the lateral ventricle. This was followed by a severing of the

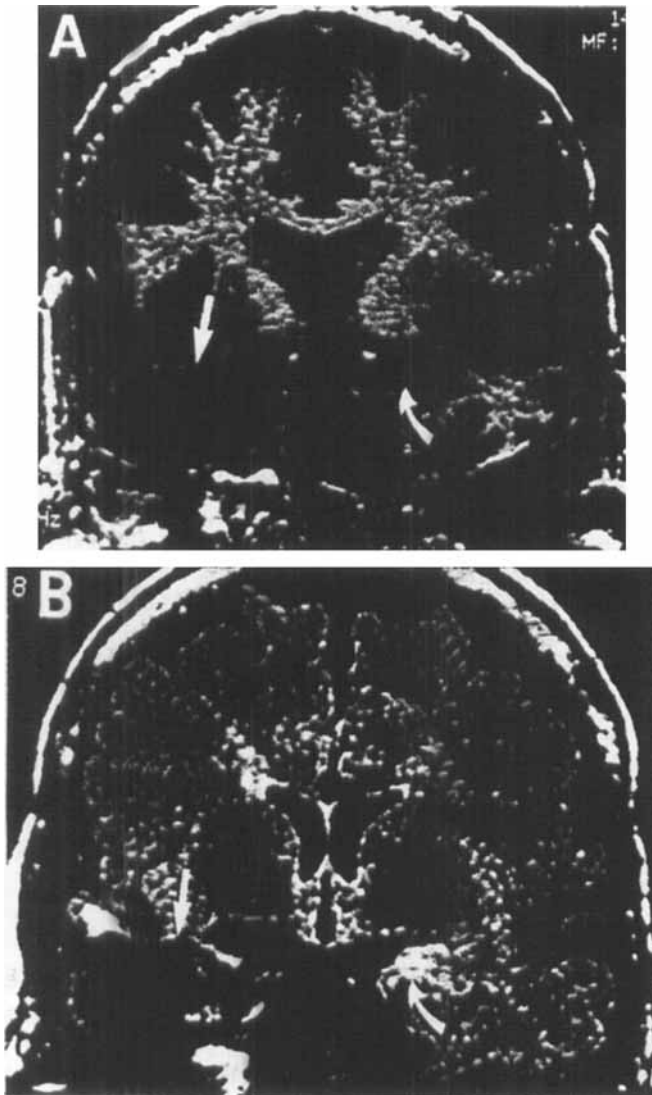


Fig. 1. Coronal T1-weighted (A) and fluid-attenuated inversion recovery (FLAIR) T2-weighted (B) images at the level of the amygdala. There is abnormal signal intensity in the left amygdala secondary to gliosis (curved arrows). There is some indication of the left amygdala abnormality in the standard T1 image (A), but it is clearly apparent in the more sensitive FLAIR imaging sequence (B). The absence of the right amygdala secondary to surgery (straight arrows) is also portrayed. The right hemisphere is depicted on the left side of each image.

occipito-temporal fasciculus and subsequent removal of the amygdala and all of the hippocampus, parahippocampus, and projection fibres to their posterior extent. At the time of surgery, a second biopsy was taken from a different region of the left amygdala. This second biopsy also revealed reactive gliosis. Post-surgery MR scans, presented in Fig. 1, reveal abnormal signals throughout the left amygdala and the right anteromedial temporal lobe resection. On T2-weighted images, the subject also had two or three small foci of signal hyperintensity in the periventricular and subcortical white matter. These are commonly seen in many patients of this age, and are probably due to a

combination of blood flow and other age-related changes in the white matter. Epilepsy patients, for reasons not well understood, can also have an increased incidence of these white matter foci.

Neuropsychological profile

There were no significant differences in SP's neuropsychological profile before and after surgery. Her IQ was average (Wechsler Adult Intelligence Scale-Revised: verbal – 104, performance – 107, full scale – 106). She did not demonstrate any naming deficits (Boston Naming score – 56) and her reading recognition and comprehension scores were equivalent to her education level (12.9). On tests of visual perception, SP performed somewhat below average on some (Benton Line Orientation – 19; Hooper Visual Organization – 21) and slightly above average on others (Benton Face Recognition – 48). On tests of executive control, SP performed in the normal range (Trails A and B – 32 and 74 s; FAS verbal fluency test – 49 words; Wisconsin Card Sort – 6 categories). Two tests were conducted to assess her memory performance, the Selective Reminding Test and the Wechsler Memory Scale-Revised (WMS-R). Her performance on the verbal Selective Reminding Test was average (recall – 119). An unpublished visual analogue to the Selective Reminding Test that was designed by the Yale Neuropsychology Service was also administered. On this visual memory test, SP performed slightly above average. SP also performed in the slightly above average range on all subtests of the WMS-R. Her general memory quotient was 110 (all WMS-R scores reported are index scores). Her verbal memory subscale score was 110. Her visual memory subscale was 108. Her delayed recall score was 114. SP's performance on the neuropsychological tests assessing memory reveal intact episodic memory performance. SP's episodic memory performance appears to be intact in spite of the removal of her right hippocampus and associated cortices. It has previously been reported that epileptic patients with damage to the right medial temporal lobe often display subtle visual memory impairments (Jones-Gotman, 1986). However, several recent studies have shown that these deficits are only apparent in a small range of tasks (Loring *et al.*, 1989) and in patients for whom seizures or initial temporal lobe injury occurred later in development (Seidenberg *et al.*, 1997). Patients with earlier onsets of seizures or right temporal lobe injury, such as SP, appear to be intact on most tests of visual memory (Lee *et al.* 1989; Cohen *et al.*, 1990).

Personality and personal information

SP is a funny, likeable woman with a relatively unremarkable personal history. She is a high school graduate who attended some college courses. She is divorced and has grown children. She previously ran a successful business,

but stopped working when her seizures became frequent. The right anteromedial temporal lobe resection was highly successful in controlling SP's epilepsy. She no longer suffers from seizures, is on reduced medication, and has started working part-time. In her spare time, SP likes to write poetry and paint. In an effort to assess SP's emotional reactions, she was given the Positive and Negative Affect Scale (Watson *et al.*, 1988). This scale lists 20 common emotional states (10 positive and 10 negative, e.g. guilty, inspired, scared, happy) and asks the respondent to indicate the extent to which he or she felt that way in the past year on a scale of 1 (very little) to 5 (extremely). SP's score for positive and negative emotions was similar to 27 normal controls (positive – SP 33, control mean = 37.6, SD = 6.1; negative – SP 24, control mean = 24.9, SD = 8.2). Compared to control subjects, SP did not report extreme scores (i.e. > 2 SD from the control mean) for any individual emotional state. Particular emotional states that might be of interest given the presumed role of the amygdala in fear, anxiety and aggression (Lee *et al.*, 1989; LeDoux, 1996) are afraid, nervous, jittery and hostile. Compared to control means and standard deviations, SP rated herself as more afraid ($z = 1.74$), less nervous ($z = -1.74$), less jittery ($z = -1.18$) and more hostile ($z = 0.95$). This indication of relatively average emotional responses by SP is consistent with our own observations. She appeared to have normal emotional responses and had never been inappropriate with us. SP could be described as more expressive and friendly than most other subjects who are tested in our laboratory. However, SP has also been repeatedly tested in our laboratory and is more familiar with us than other subjects.

Experiment 1

The predominant task used to examine the amygdala's role in emotional memory in non-human animals is fear conditioning. In this task, a neutral stimulus (the conditioned stimulus – CS) acquires aversive properties through repeated pairings with an aversive stimulus (the unconditioned stimulus – US). Memory is assessed by measuring if an arousal reaction, which is a normal response to the US (the unconditioned response – UR), is eventually elicited by the previously neutral CS. This acquired fear response is the conditioned response (CR). In humans, the most commonly used measure for this paradigm is SCR, an autonomic nervous system response to arousing stimuli. Two previous patient studies have suggested a role for the human amygdala in fear conditioning as measured by SCR. As mentioned above, Bechara *et al.* (1995) demonstrated impaired fear conditioning in a patient with bilateral amygdala damage. In addition, LaBar *et al.* (1995) found impaired fear conditioning in a group of patients with unilateral damage to the amygdala. In this experiment, we tested a similar paradigm in patient SP.

Method

Subjects

The control subjects for Experiment 1 were two normal control subjects who were matched for sex, age and level of education. All subjects gave informed consent and were paid for their participation.

Apparatus

A visual CS was displayed on a computer screen. The US was an electric shock delivered transcutaneously over the subjects' median nerve of their dominant arm by a stimulating bar electrode (30 mm electrode spacing; Nicolet Instruments, Madison, WI, USA). The electrode lead was secured using a Velcro strap around the subject's forearm. The shock was generated by a Grass Instruments (Quincy, MA, USA) SD-9 stimulator.

Physiological measures of conditioning (SCRs) were recorded via 8 mm Ag–AgCl electrodes attached to the middle phalanges of the second and fourth digits of the non-dominant hand (BIOPAC Systems, Santa Barbara, CA, USA). Lafayette Instruments (Lafayette, IN, USA) electrode gel was used as an electrolytic conductor. Physiological responses were amplified using a BIOPAC Systems skin conductance amplifier at a gain of 10 $\mu\text{mho/V}$ and sampled at 250 Hz on a computer running AcqKnowledge software (BIOPAC Systems). Subsequent data processing and analysis were performed using the same AcqKnowledge software package.

Procedure

The CS was a blue square that was presented 10 times throughout the study (CS duration = 10 s, inter-trial interval = 17–20 s). The conditioning paradigm consisted of three phases: habituation, acquisition, and extinction. The number of trials in each phase was three, four and three, respectively. In the acquisition trials, the US (shock, 200 ms duration, 50 pulses/s) coterminated with the CS presentation. Subjects were first informed that we were assessing physiological reactions to stimuli, and the recording and shock electrodes were attached. Two to three test shocks were delivered to adjust the voltage level to each subject's tolerance. Subjects were then instructed to choose a shock level that was aversive but not painful. All subjects chose a US intensity level of 28 V.

Subjects were instructed that the task involved passive viewing of visual stimuli and that they should try to notice a pattern between image presentation and electric stimulation. SCR data for each trial were collected during a 26-s interval beginning 4 s prior to CS onset.

Scoring SCR

Before scoring, the recorded SCR waveforms were low-pass filtered using a Blackman window (cut-off frequency = 31 Hz) and were smoothed over three successive data points. The SCR responses to the CS were measured

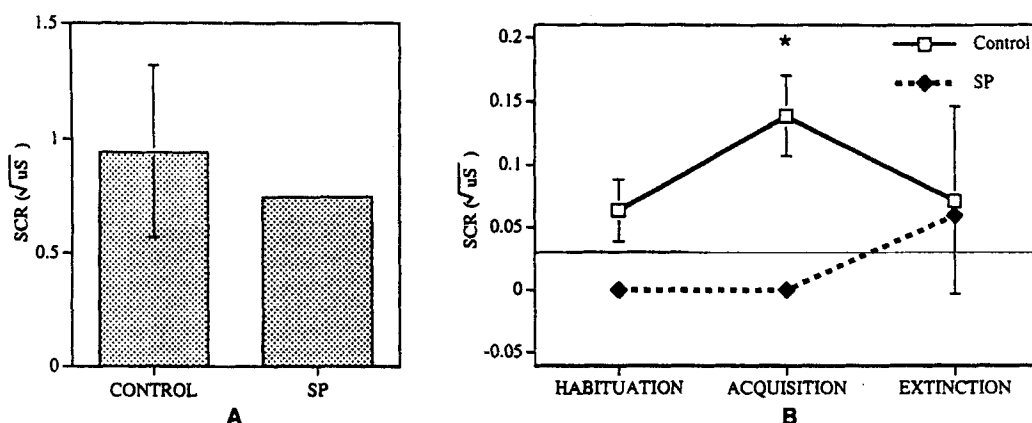


Fig. 2. (a) Mean unconditioned response (UR) during simple fear conditioning. SCRs for controls and patient SP are collapsed across four acquisition trials. (b) Mean SCR to the CS collapsed across trials for habituation, acquisition and extinction. Asterisk indicates that SP's conditioned response (SCR to the CS during acquisition) fell more than 2 SD below the control mean. Error bars represent SEM.

as the conditioned response or CR. SCRs were scored in accordance with conventional criteria by calculating the base to peak deflection amplitude in the 1–4 s window after CS onset (Lockhart, 1966). SCRs to the US were also scored in a similar manner as a measure of the subject's unconditioned response or UR. A minimal deflection criterion of $0.02 \mu\text{Siemen}$ (μS) was set for inclusion into the analysis. SCRs were square-root transformed prior to statistical analysis in order to reduce skewness.

Results

As can be seen in Fig. 2a, SP and matched controls showed a similar UR to the shock. However, as illustrated in Fig. 2b, SP showed no differential response to the CS across habituation, acquisition and extinction trials, indicating that she did not acquire the CR. The matched controls demonstrated an increased SCR to the CS during acquisition compared to habituation and extinction, indicating acquisition of the CR. When questioned after testing, all subjects, including SP, began to expect the shock at the end of the CS after the first acquisition trial until the beginning of extinction, indicating awareness of the CS–US contingency.

Discussion

SP failed to demonstrate any conditioned response, indicating a deficit in fear conditioning. This deficit was apparent in spite of her normal unconditioned response to the shock and her awareness that the conditioned stimulus predicted the unconditioned stimulus after the first acquisition trial. This suggests that the amygdala mediates a form of implicit, autonomic memory, which signals the acquired aversive properties of the conditioned stimulus. This implicit, autonomic memory is separate from an episodic memory system, as indicated by SP's ability to report the relation between the conditioned and uncon-

ditioned stimuli. These results are consistent with previous reports of fear conditioning in patients with amygdala damage (Bechara et al, 1995; LaBar et al., 1995) and animal models of amygdala function (LeDoux, 1996).

The results of Experiment 1 indicate that SP performed as expected on a task known to be sensitive to amygdala damage. However, in human experience we often learn about the aversive properties of neutral events by means other than direct experience of the neutral and aversive stimuli in conjunction. For example, most people will avoid touching an item, such as a plate, if they have been told it is hot. They do not have to touch the stimulus to have an awareness of the aversive properties of the stimulus. This information is learned using an episodic memory system. Previous research has shown that emotion can influence episodic memory, primarily by enhancing performance. In the following experiments, we examine whether the amygdala plays a role in the enhanced episodic memory observed for emotional stimuli by assessing SP's performance on these tasks.

Experiment 2

When examining episodic memory for emotional stimuli, it is useful to consider some of the factors that influence the emotional response to a stimulus. For example, subjects may have a very different emotional reaction when reading a story with an interesting or touching plot compared to seeing a violent film with graphic images. Two variables that have been postulated to contribute to our emotional reactions are valence and arousal (Russell and Bullock, 1985). Valence represents the emotional meaning of a stimulus, or rather the degree to which it is considered positive or negative. Arousal corresponds to the magnitude or intensity of an arousal response elicited by a stimulus. Both valence and arousal might influence episodic memory performance, but the neural mechanisms underlying these influences may differ. Experiments 2 and 3 examine

enhanced episodic memory observed for stimuli with an emotional valence that do not elicit an arousal response, as measured by SCR or subjective ratings. Experiments 4 and 5 examine enhanced episodic memory observed for arousing stimuli. By examining SP's performance compared to normal controls, we can get an indication of the role of the amygdala in these types of tasks. Experiment 2 examines recall for emotional words. Both Experiments 2 and 3 are based on a recently published study examining the effect of valence on recall in patients who have received unilateral temporal lobectomy, but do not have the additional amygdala damage found in SP (Phelps *et al.*, 1997).

Method

Subjects

SP's recall was examined and her performance is compared to 23 normal control subjects similar in age. Data from the control subjects are the same as those reported in Phelps *et al.* (1997). All subjects gave informed consent and were paid for their participation.

Materials

A list of 27 words, nine each of three categories – positive (e.g. lucky), negative (e.g. victim) and neutral (e.g. stamp) were used. This list was taken from Phelps *et al.* (1997), where it was reported that the emotional words, although they differ from neutral words in valence, do not differ in arousal as measured by SCR.

Procedure

Subjects were told that they would see a list of words and were asked to rate the words for affect on a scale of 1 (negative) to 5 (positive). Each word was presented on the computer screen for 4 s. Subjects were asked to respond with the rating after the word was removed from the screen. A new word was presented every 14 ± 2 s. Order of word presentation was randomized across subjects. Subjects were given a surprise recall test for the words ~ 1 min after the last word was presented. In order to obtain a reliable measurement from SP, this task was administered twice separated by a period of ~ 4 years. The second time SP performed the task, the procedure was identical except the inter-trial interval was shortened from 14 ± 2 s to 2 s.

Results

SP's ratings for the affective words were similar to controls (SP versus controls – positive: 4.05 versus 4.21; neutral: 3.11 versus 3.21; negative: 1.92 versus 1.87). SP's mean overall recall score was slightly better than the mean for controls (9.5 versus 7.5). The difference in overall recall could be due to a few factors. First, SP performed slightly better on the second recall test (10 words versus nine words). Although it is unlikely SP remembered the word list from 4 years earlier, it is possible that the shortened

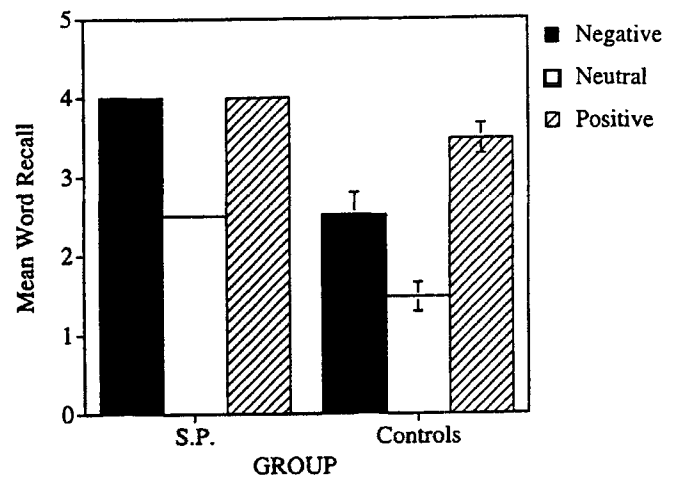


Fig. 3. Mean number of negative, neutral, and positive words recalled for normal controls and patient SP. Error bars represent SEM.

inter-trial interval on the second list aided recall. Additionally, SP's familiarity with memory experiments may have led her intentionally to encode stimuli, even though she was not told that her memory would be assessed. This strategy, relative to the naive controls, may have given her a marginal advantage.

Figure 3 presents SP's and control subjects' recall for positive, negative and neutral words. Even though SP had slightly higher overall recall, her pattern of performance is similar to controls. All subjects, including SP, showed enhanced recall for the positive and negative words compared to neutral words. SP's recall for positive, negative and neutral words was in the normal range (SP's standard score compared to controls' mean and SD: positive $z = 0.51$; neutral $z = 1.07$; negative $z = 1.01$).

Discussion

SP's memory performance is similar to control subjects and indicates normal enhanced memory for valenced words. These results are consistent with a previous study showing normal performance on this task in patients with unilateral temporal lobectomy who do not have additional amygdala damage (Phelps *et al.*, 1997). SP's enhanced memory for emotional words suggests that the amygdala is not necessarily involved in all situations where emotion influences episodic memory. In particular, the amygdala does not seem to be necessary for the enhanced memory observed for words that have an emotional valence, but do not elicit an arousal response as measured by SCR. It could be that arousal is necessary to observe any effect of amygdala damage on an episodic memory task. However, another possibility is that the amygdala's primary role in episodic memory is similar to its role in fear conditioning. That is, the amygdala may be uniquely involved in attaching emotional significance to neutral stimuli, as opposed to enhancing memory for emotional stimuli. This hypothesis is tested in Experiment 3.

Experiment 3

A study by Banaji (1986) found that episodic memory for neutral stimuli in emotional contexts is enhanced. In this study, words that are neutral in valence are embedded in sentences that depict hypothetical events which are positive, negative or neutral in emotional valence. On a later recall test, subjects remember more of the neutral words embedded in emotional sentences than words embedded in neutral sentences. A recent study in our laboratory (Phelps *et al.*, 1997) found that patients with unilateral temporal lobectomy, without additional amygdala damage, show normal enhanced recall for neutral words embedded in emotional sentences. In Experiment 3, we examine if bilateral amygdala damage will lead to a deficit in the superior recall observed for neutral stimuli embedded in an emotional context.

Method

Subjects

SP's recall was examined and her performance is compared to 28 normal control subjects similar in age. Data from the control subjects are the same as those reported in Phelps *et al.* (1997). All subjects gave informed consent and were paid for their participation.

Materials

A list of 30 nouns that are neutral in emotional valence were taken from a list of affective word norms (Belleza *et al.*, 1986). This is same list used in our previous study (Phelps *et al.*, 1997). The words were written on index cards and were randomly assigned an emotional valence (10 positive, 10 negative, and 10 neutral) that was indicated by a symbol on the card (+, -, 0).

Procedure

Subjects were given the stack of index cards and were told to write a sentence on each card that included the assigned word. They were told the sentence should depict a hypothetical, autobiographical event that is consistent with the assigned valence. For example, if a subject was given the word *chair* and the valence of negative, s/he might write the sentence, 'When I sat on the *chair* it broke and I hurt my back.' After the subjects finished writing all the sentences, they conversed with the experimenter for ~5 min. The subjects were then given a surprise recall test for the assigned neutral words. In order to obtain a reliable measurement from SP, the task was administered twice separated by a period of ~4 years.

Results

As shown in Fig. 4, we were somewhat successful in replicating the original Banaji (1986) study. Control subjects demonstrated superior recall for the neutral words

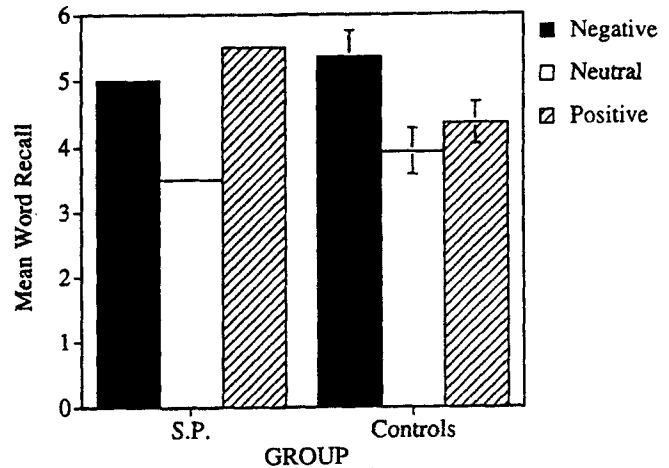


Fig. 4. Mean number of neutral words recalled embedded in negative, neutral, and positive sentences for normal controls and patient SP. Error bars represent SEM.

embedded in negative sentences compared to neutral words embedded in neutral sentences. There was also a numerical trend showing enhanced recall for neutral words embedded in positive sentences compared to those in neutral sentences; however, this failed to reach significance (see Phelps *et al.*, 1997). SP's performance on this task did not differ from control subjects. Her recall of words embedded in neutral and negative sentences was essentially equivalent to control subjects (SP's standard score based on controls' mean and SD: neutral $z = -0.23$; negative $z = -0.17$). Her mean recall of neutral words embedded in positive sentences was slightly better than control subjects ($z = 0.67$).

Discussion

SP's memory performance is similar to control subjects and indicates normal enhanced recall for words in an emotional sentence context. These results are consistent with a previous study showing normal performance on this task in patients with unilateral temporal lobectomy who do not have additional amygdala damage. Both of these studies suggest that the amygdala is not involved in the enhanced memory observed for neutral words embedded in emotional sentences. Arousal did not seem to play a role in this study. Although the subjects' sentences described events that could be arousing if they actually occurred, subjects did not appear to be aroused by the act of generating the emotional sentences. A subset of the subjects were asked about their emotional reactions while generating sentences and these subjects did not report being aroused by writing the emotional sentences. The result of Experiment 3, when combined with Experiment 2, suggests that the amygdala may not be involved in situations where the valence of the stimuli leads to enhanced episodic memory performance.

It is possible that the effects of valence on episodic memory could be explained by other variables that are

manipulated along with valence and are known to affect episodic memory performance. For instance, in both Experiments 2 and 3 the emotional character of the stimuli adds a schema or category that may aid recall. Previous research has shown that factors that help organize stimuli can enhance memory performance. In a study conducted in our laboratory, we found that effects of valence on memory can be eliminated by varying the inter-item associations (Phelps and LaBar, 1997). It is unlikely that a subcortical structure such as the amygdala would play a role in situations where valence enhances memory by affecting the organization of memory. However, arousal responses lead to a host of physiological changes that may have different effects on memory. Several studies have demonstrated that arousal can improve episodic memory (see Christianson, 1992). It has been suggested that arousal may be critical for activating an amygdala-based memory system (LeDoux, 1996). In Experiments 4 and 5, we examine SP's performance on tasks where arousal enhances episodic memory in order to determine what role the amygdala might have in these tasks.

Experiment 4

It is well established that the hippocampus is a critical structure in episodic memory performance. Patients with extensive damage to the hippocampus and associated cortices have severe impairments on episodic memory tasks. Therefore, if the amygdala is going to play a role in the enhanced episodic memory observed with emotion, it must somehow be involved in modulating the hippocampal memory system. Such a role for the amygdala has been reported in studies with non-human animals (Packard *et al.*, 1994). McGaugh and colleagues have suggested that the neurohormonal changes that occur with arousal lead to enhanced hippocampal consolidation. They propose that this enhanced consolidation is mediated by the amygdala (McGaugh, 1992).

Consolidation is a process that occurs after initial encoding where a memory is slowly settled or 'fixed' in the mind (Nadel and Moscovitch, 1997). The extent to which an event can be remembered at a later date is not only a function of how well it was initially learned, but also how well it was consolidated. Since consolidation is a process that occurs over time, one might expect that any effect of enhanced consolidation would be reflected in the forgetting curve. Several behavioural studies have shown that arousal leads to a forgetting curve that is less steep (Heuer and Reisberg, 1990). In fact, some studies report enhanced memory over time for arousing stimuli (Kleinsmith and Kaplan, 1963). If the amygdala is involved in modulating hippocampal consolidation for arousing stimuli, we might expect to see a differential forgetting curve for arousing stimuli in SP as compared to control subjects. We examine this hypothesis in the present study.

Method

Subjects

SP and 23 normal control subjects (mean age = 40 years) participated in the arousal section of this study. The data for control subjects in this task are taken from LaBar and Phelps (1998). SP and four control subjects (mean age = 52.5 years) participated in the valence section of this study. All subjects gave informed consent and were paid for their participation.

Materials

There are two parts to this study: the arousal section and the valence section. For the arousal section, a list of 40 words and four filler words were used. The 40 words were divided into two types: neutral and taboo. The 20 neutral words were selected to be neutral in emotional valence from a master list of affective word norms (Belleza *et al.*, 1986). The taboo words consisted of profanities, sexually explicit words and words depicting social taboos (list available by e-mail request). The filler words were four neutral words added to the beginning and the end of the list to reduce serial position effects in recall.

For the valence section of this study, a list of 27 words was used; 18 emotional (e.g. bankrupt, riot) and nine neutral (e.g. door, water). These words were similar in frequency and valence ratings to the words used in Experiment 2. Ratings by pilot subjects found that the emotional words have an emotional valence, but that reading them does not elicit an arousal response based on subjective report.

Procedure

For the arousal section of this study, the subjects were shown the 40 neutral and taboo words (preceded and followed by two filler words) on a computer screen in a random order. Each word was presented for 4 s. There was a 14 ± 2 s interval between successive word presentations. During this interval, the subject was asked to rate the words for arousal on a scale from 1 (not at all arousing) to 4 (very arousing). Recall was assessed for the words immediately after the final word was presented and again after ~1 h delay. The hour between recall tests was filled with other non-verbal experiments. In order to obtain a reliable measurement from SP, the task was administered twice separated by a period of ~2 years.

For the valence section of this study, the 27 words were presented at the rate of one word every 4 s. Subjects were asked to rate the words for valence. After 1 h delay, subjects were given a surprise recall test for the words.

Results

SP's arousal ratings for the taboo and neutral words were similar to control subjects (SP's standard scores are based on controls' mean and SD – neutral rating: $z = -0.58$, SP

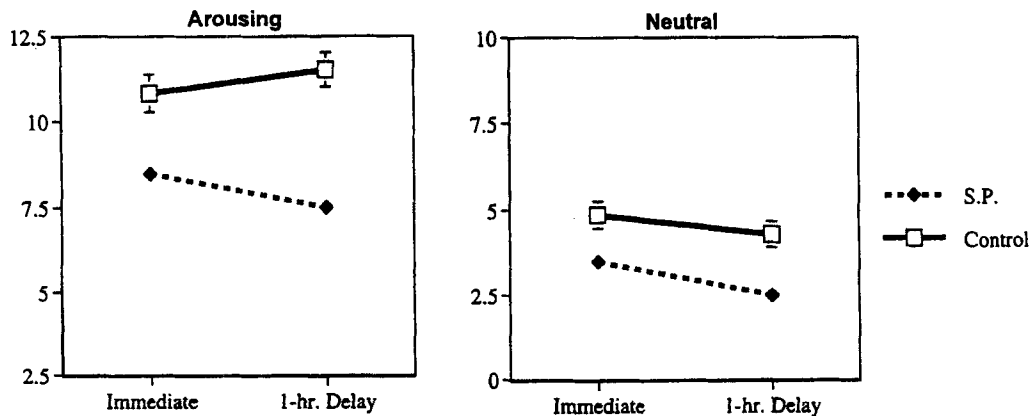


Fig. 5. Mean recall for taboo words and neutral words at immediate and delayed tests for controls and patient SP. Error bars represent SEM.

mean = 1.08 versus 1.36 for controls; taboo rating: $z = 0.58$, SP mean = 2.93 versus 2.54 for controls). Both SP and controls found the taboo words to be arousing. SP's overall recall was slightly worse than controls ($z = -0.88$, SP mean = 8.5 versus 10.83 for controls). As can be seen in Fig. 5, SP recalled more of the taboo words than the neutral words at both immediate test and delay test. At the immediate test, SP showed an advantage for the taboo words that was similar to control subjects. However, at the delay test, the recall advantage for taboo over neutral words significantly increased for control subjects compared to the immediate test, $t(22) = 2.73$, $P < 0.05$. For SP, there was no increase in the recall advantage for taboo words over time (mean recall standard scores for SP: neutral - immediate $z = -0.82$, delay $z = -0.99$; taboo - immediate $z = -1.01$, delay $z = -1.87$).

For the emotional valence list, both SP and controls found the words equally emotional (SP's standard score, $z = -0.19$). Delayed recall for the emotional words was also similar for SP and controls (SP's recall three words versus mean = 3.25 for controls, $z = -0.26$).

Discussion

Although patient SP showed a recall advantage for taboo words compared to neutral words, this advantage did not increase over time, as it did for control subjects. At the delayed test, SP appeared somewhat impaired relative to controls. This result is consistent with a role for the amygdala as a modulator of hippocampal consolidation. The normal controls actually remembered more of the taboo words over time (compared to a decrease for neutral words) resulting in an exaggerated advantage for the taboo words. For SP, however, recall for both taboo and neutral words decreased over time and the forgetting curves were equivalent.

In contrast to the taboo words, SP and controls demonstrated similar delayed recall for words that have an emotional valence, but are not arousing. This similar performance for valenced words was also found when

recall was tested immediately in Experiment 2. These findings are consistent with previous studies suggesting that arousal is the primary factor necessary for the modulation of the forgetting curve observed with emotional stimuli (Kleinsmith and Kaplan, 1963; Berlyne *et al.*, 1965).

However, in spite of the divergent forgetting curves for SP and controls for taboo words, both SP and controls showed a recall advantage for the taboo words as compared to the neutral words at the immediate and delay test. This recall advantage could be due to a few factors. There are several qualities of emotional stimuli, which are not unique to emotion that might affect recall. For instance, the taboo words differed from the neutral words in inter-item similarity, distinctiveness, and category membership.

Although it is impossible to rule out the possibility that arousal contributed to SP's enhanced recall for taboo words on the immediate test, there are several other variables that could explain this effect. As shown in Experiments 2 and 3, we would expect SP to show a normal recall advantage for valenced words. In the present study, valence was not separated from arousal. The taboo words differ from the neutral words in emotional valence, as well as arousal. It could be that the overall advantage observed in SP for the taboo words on immediate test is due to the organizational effects of valence. However, as mentioned above, arousal also leads to a host of physiological changes that might affect memory in addition to the organizational effects of valence. Animal models would suggest that any effect of arousal on episodic memory would emerge with consolidation (McGaugh, 1992). If the primary role of the amygdala in episodic memory is modulating hippocampal consolidation, then any deficit in patients with amygdala damage would be most apparent when memory is tested after a delay. This interpretation is consistent with the results from Experiment 4.

Experiment 5

One difficulty with interpreting the results of Experiment 4 is that a number of variables that may affect episodic

memory when a stimulus is emotional, aside from arousal. The inter-item similarity and distinctiveness of the taboo words probably enhanced episodic memory for these words, in addition to arousal. In Experiment 4, we tried to separate the effects of arousal on episodic memory from the effects of organizational qualities of emotion by examining episodic memory performance over time. Given the neuromodulatory effects of arousal demonstrated in non-human animals (Packard *et al.*, 1994), we expected different forgetting curves for arousing and non-arousing stimuli, consistent with the results of Experiment 4.

Another way in which we might be able to separate the mnemonic impact of the organizational quality of emotion from arousal would be to examine different measures of episodic memory. It has been demonstrated that variables which help organize memory, benefit performance on recall tests more than recognition tests (Tulving, 1972). On recall tests, when there are no external cues available, subjects must rely on self-generated internal cues, such as schemas, to aid memory search. On tests of recognition, subjects are given memory cues, but must have an accurate representation of the event in order to answer correctly. If arousal leads to enhanced retention of all aspects of an event, we might expect this effect to be more apparent on tests of recognition that rely less on memory organization, than on tests of recall. If we assume the amygdala plays a role in the enhanced memory observed with arousal, then any deficit in patients with amygdala damage would be especially acute on tests of recognition. This hypothesis is examined in Experiment 5.

This study is adapted from a paradigm introduced by Heuer and Reisberg (1990) in which subjects showed enhanced recall and recognition for the arousing section of a story. A version of this paradigm was used by Cahill *et al.* (1995) and Adolphs *et al.* (1997) to assess the role of the amygdala in episodic memory of emotional stimuli. When they tested patients SM-046 and BP on this paradigm, they found an impairment on recognition for the arousing section of the story. In the present study, we examine both recall and recognition performance in patient SP and controls on a version of this emotionally arousing story.

Method

Subjects

SP and nine normal controls participated in this study. The normal controls were Yale undergraduates who were either paid for their participation or received course credit. All subjects gave informed consent.

Materials

A sequence of 12 photographic slides taken from a study conducted by Heuer and Reisberg (1990) were scanned in eight-bit colour and sized to 5 × 7.5 inches for presentation on a computer monitor. The story depicted in the slide sequence was designed to be divided into three

sections of four slides, with the first and last sections being relatively neutral in content, and the four critical middle slides presenting emotionally arousing material. The story depicted a mother taking her son to visit his father, a surgeon at a nearby hospital. The middle section depicts a car accident that is described to involve the son, who in turn is taken to the hospital where he is operated on by his father. This section includes graphic pictures of the surgical replacement of the boy's severed limbs. A transcript of the narrative is provided in Appendix 1. The slide sequence was accompanied by a spoken narrative adapted from Cahill *et al.* (1995) and Heuer and Reisberg (1990), which described the action in each scene. Narration was recorded with SoundEditPro software in a neutral tone of voice.

Procedure

Each picture stimulus was shown on a computer screen for 4250 ms and was presented 1750 ms prior to the onset of the voice over. Following the offset of each picture, an arousal Likert rating scale was presented on the screen. During encoding, subjects were told we were interested in their ratings of the arousing nature of each slide. Subjects were instructed to indicate their ratings by circling a number on a score sheet only when the rating scale appeared on the screen following stimulus offset. The rating scale was presented on the screen for 2500 ms. The next story element in the sequence was presented after an additional 1 s blank interval.

Following a 24-h delay, performance was assessed by recall and recognition measures of memory. Subjects were given 10 min to write about their memory for the picture and voice story elements in as much available detail as possible, in any order they wished. All subjects finished their reports in the allotted interval. Following their recall reports, we administered a pencil and paper version of a 72-item, four-alternative multiple choice questionnaire to assess their recognition memory for both the visual and auditory elements in each scene. There were six questions for each of the 12 presented scenes. Questions regarding each element were presented in order and subjects were asked to answer the questions in the order in which they were written. Subjects were given unlimited time to finish the recognition test.

Scoring

Scoring of the written recall narratives was performed by two judges blind to patient and control identity and to the predictions of the experiment. Judges were asked to rate how well they thought subjects recalled each story element on a scale from 1 to 7 (1, did not remember, and 7, sure they remembered). Inter-rater reliability was computed by correlating the judges' ratings of subjects' recall for each of the 12 story elements. When averaging across the correlation for each element, the rater agreement was found to be reasonably high ($r = 0.80$). Recall confidence scores were computed by averaging the two judges' ratings for

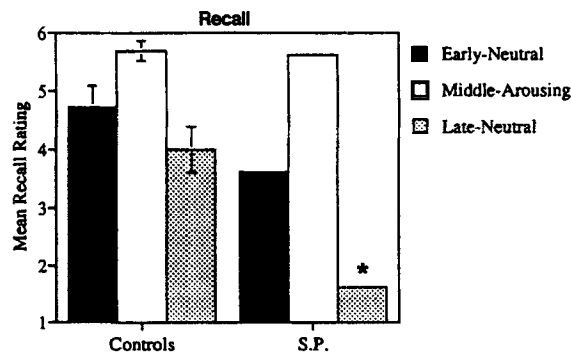


Fig. 6. (a) Mean confidence ratings of recall for early, middle and late story phases for controls and patient SP. The asterisk indicates that SP's performance fell 2 SD below the control mean. Error bars represent SEM.

each slide, and then averaging across the early, middle, and late story segments. Recognition scores were calculated by determining the percentage of correct items for each slide averaging across early, middle, and late sections.

Results

Both SP and controls rated the middle section of the story to be more arousing than the early and late sections (SP standard scores based on controls' mean and SD – early: $z = 1.24$, mean = 2.75 versus 2.03 for controls; middle: $z = 0.55$, mean = 6.25 versus 5.38 for controls; late: $z = 0.57$, mean = 3.25 versus 2.63 for controls). As can be seen in Fig. 6, control subjects showed significantly better recall for the middle-arousing section of the story relative to the early and late neutral sections [$F(2,16) = 7.63$, $P < 0.005$]. Follow-up t -tests confirmed that the arousing middle section was recalled more accurately than the early [$t(16) = -2.23$, $P < 0.05$], and later [$t(16) = 3.89$, $P < 0.002$] neutral phases. SP's recall for the story was similar to the control subjects. She showed intact recall for the early section ($z = -1.00$) as well as normal enhanced recall for the middle arousing section ($z = -0.13$). However, her recall of the late-neutral section was worse than controls ($z = -2.04$).

The results from the recognition test, shown in Fig. 7, yield a different pattern of performance. Control subjects showed significantly enhanced recognition for the middle-arousing and late-neutral sections of the story compared to the early-neutral section [$F(2,16) = 9.198$, $P = 0.002$]. t -Tests confirmed that the middle-arousing sections [$t(16) = -3.067$, $P = 0.007$] and late-neutral sections [$t(16) = -4.13$, $P < 0.001$] were recognized significantly more than early-neutral. SP recognition was intact for the early section ($z = -0.81$), was primarily impaired in the middle-arousing section ($z = -2.06$) and somewhat worse than controls in the late-neutral section ($z = -1.69$).

Discussion

SP's performance on the recognition portion of this task is similar to patient BP, who also showed an impairment

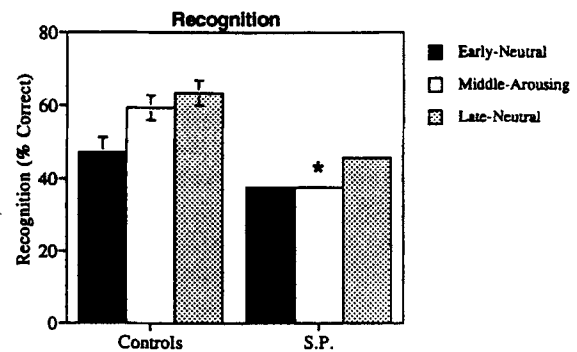


Fig. 7. Mean % correct identification on a multiple choice recognition test, for early, middle and late story phases for controls and patient SP. The asterisk indicates that SP's performance fell 2 SD below the control mean. Error bars represent SEM.

relative to controls in both the middle-arousing section and the late-neutral section (Cahill *et al.*, 1995). For SP, her recognition impairment was most severe in the middle arousing section. Patient SM-046 also showed an impairment relative to controls in recognition of the middle-arousing section, but this did not extend to the late-neutral section (Adolphs *et al.*, 1997). However, in the Cahill *et al.* (1995) and Adolphs *et al.* (1997) studies, the recognition enhancement in the control subjects was not apparent in the late-neutral portion of the story. This difference in the performance of control subjects may be due to the nature of the recognition questions. In the original Heuer and Reisberg (1990) study, they report that the memory enhancing effect of arousal extended to the late-neutral portion of the story when the recognition questions focused on the peripheral details of the scenes more than central events. The recognition questions used in the present study were mostly focused on details. In this way, our study may have differed from studies of Cahill *et al.* (1995) and Adolphs *et al.* (1997). Otherwise, the results for SP are consistent with the previous reported cases showing a deficit in recognition performance for arousing stimuli.

However, the results for SP on the recall test reveal intact enhanced recall for the middle-arousing section of the story. As mentioned earlier, recall is especially sensitive to the organizational properties of stimuli. It could be that the story line or schema was especially useful to SP in helping her organize her memory and cue her recall. The recall test measured whether or not the subjects remembered the central themes relevant to the story which were depicted in the slides. If a subject were to recall the story at all, he or she would most likely recall the central organizing themes, such as the visit to the father, the accident and surgery. However, SP was impaired in recalling the late-neutral section. The events that occurred in this section (the mother making a phone call or waiting for a bus) are details that are less central to the primary action of the story. If SP was relying more on the story plot to aid recall, as opposed to memories for the details of the slides, these are the types of events we might expect her to omit.

The results from this study combined with Experiments 2, 3 and 4 suggest that the amygdala's primary mnemonic role in episodic tasks may be the modulation of memory with arousal. The effect of arousal on episodic memory may be most apparent when memory is tested after a delay (Experiment 4) and recognition memory for details is assessed (Experiment 5). These are the types of situations where we might expect deficits in patients with amygdala damage, such as SP, to be most obvious.

General discussion

Case SP provides another opportunity to examine the role of the human amygdala in emotional memory. It is somewhat odd to study emotion in a case study, since emotion is one of the most variable human behaviours and it is difficult to generalize results from a single individual. However, when studying the role of the amygdala in emotional memory the case study approach is warranted because it is rare to find a patient with bilateral damage to the amygdala who does not have a severe episodic memory impairment. For this reason, evidence from additional cases, such as SP, is especially important. Although SP has a history of epilepsy and additional medial temporal lobe damage that may have affected her memory performance, our results are consistent with the findings of previously reported case studies of patients with bilateral amygdala damage. Like previous cases, SP is impaired on a test of fear conditioning and in the recognition of arousing stimuli.

In the present experiments, in addition to supporting previous results, we have also examined SP's performance on a wider range of emotional memory tasks. By examining SP's performance on a number of tasks, we are able to specify better the precise role of the amygdala in emotional memory. As previously reported, the amygdala is necessary for normal fear conditioning (Bechara *et al.*, 1995). However, the role of the amygdala in the enhanced episodic memory observed for emotional stimuli is more complex. The amygdala may play a role in some situations where emotion enhances episodic memory performance, but not others.

The results from patient SP suggest that the amygdala may not be involved in emotional memory tasks when valence enhances memory. Arousal seems to be necessary to engage an amygdala-based memory system (see LeDoux, 1996). In addition, the amygdala's impact on emotional, episodic memory may be less significant when memory is tested immediately, or a strong story line or theme contributes to recall. We suggest that these situations could be characterized as examples where emotion enhances episodic memory primarily by contributing an organizing principle such as a plot, schema, category or distinctive property. Based on our results with SP, we expect the effects of amygdala damage on episodic memory to be limited to situations where performance is affected by the

neuromodulatory changes that occur with arousal. The effects of arousal on memory may be most apparent in the rate of forgetting for arousing stimuli, the recall of arousing stimuli that have a weak central theme, and the recognition of details or events associated with arousing stimuli.

We are only beginning to understand the complex role that the human amygdala plays in emotional memory. It is clear that the amygdala makes significant contributions to normal emotional memory processing. However, it is also clear from this case study that there are effects of emotion on memory that do not rely on intact amygdala functioning. It is possible that patients with amygdala damage can rely on these other contributions of emotion to memory in order to help compensate for the deficits that accompany amygdala damage. Our ability to specify the role of neural systems that mediate difference aspects of emotional memory is dependent on our understanding of the relation between emotion and memory. As we begin to further specify the variables that mediate emotion's effect on memory, we will be able to achieve a clearer picture of the amygdala's unique contribution to memory.

Acknowledgements

We wish to thank SP for her patience and accessibility during participation in this research, and Daniel Reisberg and Friderike Heuer for permission to use their stimuli in Experiment 5. This work was supported by NIMH 50812 and McDonnell-Pew 97-26 to EAP.

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Received on 2 June, 1998; resubmitted on 27 July, 1998; accepted on 2 August, 1998

Appendix 1

Script for the story narrative in Experiment 5

1. Mother and son are leaving home in the morning.
2. She is taking him to visit his dad at work.
3. Father is chief surgeon at the nearby hospital.
4. They check before crossing busy Park Road.
5. While crossing the road, the boy was caught in a terrible accident.
6. The father's surgical team has been fighting to save his son.
7. Father was able to restore the son's severed limbs.
8. He is pleased that his son survived the surgery.
9. Mother leaves the hospital upset by what she saw.
10. Heading to call work, she passes a police station.
11. Mother asks her boss to get the day off.
12. She tries to hail a cab home at the number nine bus stop.

Specifying the contributions of the human amygdala to emotional memory: a case study

E. A. Phelps, K. S. LaBar, A. K. Anderson, K. J. O'Connor, R. K. Fulbright and D. D. Spencer

Abstract

We examined emotional memory in patient SP, a 54-year-old woman with bilateral damage to the amygdala. Consistent with previous case studies, SP showed deficits on tests of fear conditioning and recognition memory for arousing stimuli. SP's performance on several emotional episodic memory tasks was examined. We found that bilateral damage to the amygdala only leads to deficits on a subset of emotional episodic memory tasks. Specifically, the amygdala does not seem to be involved when episodic memory performance benefits from the valence of the stimuli. However, when episodic memory benefits from arousal, damage to the amygdala leads to a deficit in performance. Based on our results, we postulate that the amygdala is not involved when emotion enhances episodic memory primarily by contributing an organizing principle such as a schema or category. We expect the effects of amygdala damage to be limited to memory tasks affected by the neuromodulatory changes that occur with arousal. The effects of arousal on episodic memory would be most apparent in the rate of forgetting for arousing stimuli, the recall of arousing stimuli that have a weak central theme, and the recognition of details or events associated with arousing stimuli.

Journal

Neurocase 1998; 4: 527-40

Neurocase Reference Number:

O135

Primary diagnosis of interest

Epilepsy of right medial temporal lobe origin treated with right medial temporal lobe resection. Additional left amygdala lesion classified by biopsy as reactive gliosis

Author's designation of case

SP

Key theoretical issue

- Performance on several memory tasks is observed in a patient with rare bilateral amygdala damage. Previous research suggests that the amygdala is critical for the changes in memory performance that occur with emotion. This case demonstrates that emotion may influence human memory in a number of ways, only some of which are affected by amygdala damage

Key words: amygdala; medial temporal lobe epilepsy; emotion; memory; emotional memory; episodic memory; fear conditioning; arousal; valence

Scan, EEG and related measures

Magnetic resonance imaging: T1-weighted and fluid-attenuated inversion recovery (FLAIR) T2-weighted

Standardized assessment

WAIS, WMS, Wisconsin Card Sort, Boston Naming, FAS verbal fluency, Selective Reminding Test, Benton Line Orientation, Benton Face Recognition, Trails, Positive and Negative Affect Scale (PANAS)

Other assessment

Fear conditioning, episodic recall and recognition for emotional stimuli

Lesion location

- Right medial temporal lobe and left amygdala

Lesion type

Epilepsy-related medial temporal lobe resection and gliosis of unknown origin

Language

English