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THE ROLE OF THE AMYGDALA IN LEARNING AND MEMORY

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RESUMO

A amígdala, uma das principais estruturas do sistema límbico, tem sido relacionada com muitas funções, incluindo a aprendizagem e a memória. No que diz respeito à memória de longa duração, o papel da amígdala pode ser classificado dentro de duas visões gerais: 1) a amígdala é o sítio onde ocorrem associações de um estímulo com o reforçamento, e pode servir como área onde essas alterações neurais são armazenadas (a visão de armazenamento da memória); 2) uma visão alternativa é de que a amígdala não é um sítio de armazenamento da memória mas, ao contrário, serve para modular o processo de armazenamento da memória localizado em outras áreas cerebrais (a visão de modulação da memória). Nesta revisão nos propomos examinar as evidências experimentais relativas a cada uma dessas teorias.

UNITERMOS: Aprendizagem, memória, amígdala, modulação, emoção.

ABSTRACT

The amygdala, one of the principal structures of the limbic system, has been implicated in many functions, including learning and memory. In terms of long-term memory, the role of the amygdala can be classified into two general views: 1) the amygdala is a site where association of a stimulus with a reinforcement occurs, and might serve as the site of neuronal changes underlying stimulus-affect associations (the memory-storage view); 2) an alternative view is that amygdala is not a site of memory storage but, rather, serves to modulate memory storage processing located in other brain areas (the memory-modulation view). This review in an attempt to examine the experimental evidence bearing on each of these two theories.

KEY WORDS: Learning, memory, amygdala, modulation, emotion.

Introduction

Together with the findings by Kluver and Bucy (1938) of "psychic blindness" and other associated symptoms following bilateral removal of the temporal lobes in monkeys, the famous case of the amnesic patient H.M. with bilateral medial temporal lesions reported by Scoville and Milner (1957) gave rise to the decade-long quest for understanding the role of the amygdala as well as the hippocampus in learning and memory. In addition to a presumed role in learning and memory, the amygdaloid complex exerts a distinct influence on the emotions and behavior. Neurophysiological investigations indicate that, although the amygdala is not the source of emotions, this brain region appears to have a regulatory effect on states of fear, anger, and aggression as well as endocrinological and autonomic facets of such responses (see Goddard, 1964a). Thus, the influence of the amygdala on learning and memory seems to be inseparable from its role in emotional and motivational spheres. However, the effects of the amygdala manipulations not directly related to learning and memory will not be considered in this paper. Instead, the primary goal of this paper is to look for the possibility of neuronal changes, or more boldly, "memory traces" in the amygdala.

Clinical Studies

Patients with long-lasting, severe psychomotor epilepsy may receive treatment in the form of an amygdalectomy. This operation is performed on the basis of the

knowledge that the amygdala has a low threshold for developing seizure activity (Sarter and Markowitsch, 1985). Despite the obvious methodological problems in making inferences from the data obtained in patients who suffered from epilepsy or who had severe behavioral disorders prior to amygdalectomy, studies with these patients before, during and after the operation have generated many interesting, sometimes conflicting, data. Although amygdalectomy produces various behavioral changes such as decreased aggressiveness, disappearance of motor excitability and hypersexuality (Mempel *et al.*, 1980; Narabayashi, 1980), I will mainly focus on the effects of amygdala manipulations on learning and memory processes.

Lesion Studies in Humans

A general impression one may get from the literature on the effect of amygdalectomy is that the amygdala does not seem to be critically involved in learning and memory. With regard to general intellectual function and short-term memory, there seems to be an agreement that amygdalectomy does not have any effect (e.g., Hitchcock *et al.*, 1973; Milner, 1968), but with respect to the effects of amygdalectomy on learning and memory, there are conflicting reports. Some researchers have reported a detrimental effect of amygdalectomy on the patient's learning ability and memory, others found no effect, while still others have described improved learning efficiency (Scoville and Milner, 1957; Narabayashi, 1980; Nadig and Wieser, 1987).

In their report of the case H.M. and other patients who underwent temporal lobectomies, Scoville and Milner (1957) wrote, "whenever the hippocampus and hippocampal gyrus were damaged bilaterally in these operations some memory deficit was found, but not otherwise". They also noted that a case with bilateral excision of the uncus which removed only the amygdaloid and peri-amygdaloid areas showed "excellent memory function". Jurko and Andy (1977) have reported that stereotaxic lesions of either one or both amygdalae did not impair verbal learning ability as measured by a paired-associated test. Andy *et al.* (1975) also reported that a patient who had undergone three separate operations to remove the amygdala and its surrounding areas showed impaired memory initially but progressive improvement over a period of one year to the level of clinically insignificant impairment. The authors attributed the temporary deficit in memory to the extension of the lesion into the entorhinal cortex in the third operation. Narabayashi (1980) did not find memory loss after bilateral medial amygdalectomy.

Most of the studies to date (including those mentioned above) did not perform formal memory testing on the subjects, but instead, relied on, e.g., the surgeon's impression concerning the patient's memory function. However, Luczywek and Mempel

(1980) applied formal memory tests to 55 patients, 45 out of which had undergone unilateral amygdalectomy and the rest of which had received bilateral amygdalectomy and/or anterior hippocampectomy. (The authors did not separate these groups in their description of the test results). Surprisingly, it was found that the preoperatively disturbed short-term memory and word memory of the patients improved after the operation. Also, Chitanondh (1966) reported a case with unilateral amygdalectomy in which the performance in a word association test improved after the operation. Likewise, Nadig and Wieser (1987) reported that after unilateral "selective amygdalohippocampectomy", the learning and memory performance of the patients in a paired-associate learning test improved in the contralateral (nonoperated) hemisphere. They interpreted this result as due to the reduced "noise" from the unilateral epileptogenic focus in the amygdala and hippocampus. It should be noted that these 3 studies included mostly patients with unilateral amygdalectomy so that the remaining amygdala might have been functioning well. However, Naughton and Cairns (1972) have reported 4 cases with bilateral amygdalectomy in which the patients' performance in the Memory-for-Design Test of Graham and Kendall seems to have improved after the operation, although the authors did not specifically discuss this.

A more systematic analysis of cognitive changes after unilateral amygdalectomy was conducted by Andersen (1978). Preoperatively, the patients did worse than normals in learning word pairs and visual gestalts, short-term and delayed memory tests. After the operation, their performance in short-term memory tests (digit span, immediate reproduction of visual gestalts) and word pair delayed memory test did not change much, whereas the performance in other delayed memory tests (picture recognition, visual gestalts) were impaired. Interestingly, there was a significant improvement in story recall in right amygdalectomy patients. In the light of the fact that the speech area is usually in the left hemisphere, this result seems to be consistent with Nadig and Wieser's (1987) interpretation that amygdalectomy improves performance by reducing "noise" from the epileptic discharging focus. Siegfried and Ben-Shmuel (1973) also reported an anedoctic case with loss of long- and short-term memory after bilateral amygdalectomy.

Although most of the studies reviewed above show negative results, existing data are insufficient to conclude that the amygdala makes no contribution to memory. Most of all, the effects of amygdalectomy on the specific aspects of memory which we might expect the amygdala to contribute to, e.g., emotional attributes of stimuli, have not been tested (see Halgren, 1981). Besides, combined lesions of the amygdala and the hippocampus in monkeys have been found to induce a greater deficit in recognition memory than that produced by lesions of either structure alone (Mishkin, 1978). Also, Jurko and Andy (1977) reported that combined lesions of the left amygdala and the medial thalamus (centre median) in human reduced learning while either lesion alone did not. These results suggest that the effects of amygdalectomy on learning and memory may be very subtle and involve interaction with other structures.

Stimulation Studies in Humans

Electrical stimulation of the amygdala in humans evokes not only changes in autonomic and motor behavior, but also a rich variety of mental phenomena (see Halgren, 1981; Sarter and Markowitsch, 1985). These "psychic" or "experiential" phenomena evoked by temporal lobe stimulation can be classified into 3 main categories: perceptual, mnemonic, and emotional. The amygdala is predominantly involved in all 3 main categories (Gloor *et al.*, 1981). Of special interest here is the second category, i.e., evocation of memory "flashbacks". Chapman *et al.* (1967) reported that stimulation of the left amygdala of an epileptic patient elicited resurrection (or re-experience) of an event from his past which had been forgotten completely. Many other instances of evocations of past events were reported by Gloor (1986) and Halgren *et al.* (1978). Most of the mental phenomena evoked by amygdala stimulation are expressions of emotional tension (Halgren, 1981). For example, the retrieved event of the patient studied by Chapman *et al.* (1967) had a strong personal emotional meaning to him. Such an association of affect with an experiential phenomenon related to perception and memory is common (Gloor *et al.*, 1982).

What is the basis of evocation of past experience by amygdala stimulation? Does the amygdala stimulation induce memory "flashbacks" by activating memory traces in the amygdala? Or, does the stimulated amygdala activate, in turn, other brain regions to induce the recollections? Answers to these questions will have theoretical significance for theories of the role of the amygdala in learning and memory because some argue that at least some form of memory trace is formed in the amygdala after learning, while other researchers think differently. (This controversy will be considered in later sections).

Gloor and his colleagues (1981, 1982, 1986) have shown that the most of the memorial experiences were elicited from amygdaloid rather than from hippocampal or parahippocampal gyral stimulation. And, in more than half of the cases (26 out of 44), such responses to amygdala stimulation were not associated with an afterdischarge (Gloor *et al.*, 1982). In another study, the percent of memory recall among all experiential responses evoked by amygdala stimulation was 17% (12/70 responses), and the percent of memory recall without afterdischarge was 67% (8/12) (Gloor *et al.*, 1981). Thus, Gloor (1986) contends that the anatomical substrate for eliciting experiential phenomena is limbic and not neocortical.

However, more extensive evidence seems to favor the position that amygdala stimulation seldom evokes a re-experiencing phenomenon, unless it also evokes an afterdischarge. Chapman *et al.* (1967) noted that the re-experiencing phenomenon seemed dependent on the capacity of the amygdala stimulation to evoke patterns of synchronous waves in the ipsilateral hippocampus, and that direct stimulation of the hippocampal sites uniformly failed to evoke the re-experiencing phenomenon. The

authors pointed out that the stimulation-evoked re-experiencing phenomenon was observed only in epileptic patients. Regarding this point, Rasmussen (discussion to Chapman *et al.*, 1967) reported that stimulation of the temporal cortex did not produce hallucinatory responses or re-experiencing phenomena unless the temporal lobe had been sensitized in some way by recurring epileptiform discharges within it. Rasmussen (1967) also reported that, in over 300 epileptic patients, almost without exception, when stimulation of the amygdala or hippocampus had produced psychic phenomena, there had been significant alteration of the electrical activity of the temporal lobe. He contended that these complex hallucinatory or re-experiencing phenomena evoked by stimulation of the temporal lobe should be regarded as representing activation of extensive neuronal circuits involving the temporal cortex as well as the medial temporal region. Halgren *et al.* (1978) found that mental phenomena were much more likely to occur in response to stimulation of the hippocampus or amygdala which also evoked afterdischarges: in the amygdala, 41.3% of the stimulation evoking an afterdischarge also evoked these phenomena whereas 10.7% of the stimulation whithout afterdischarge did so. Furthermore, repeated stimulation of the same site in the same patient with the same or more intense parameters could evoke very different experiences without concomitant differences in electrographic effects. Therefore, Halgren (1981) argues that amygdala stimulation activates distant normal tissue as the critical step in evoking re-experiencing phenomena. He also contends that amygdala stimulation does not evoke hallucinations by activating the specific neural substrate for a particular experience, partly because the content of the mental phenomena is influenced by the ongoing psychodynamic context around the patient (e.g., Rayport and Ferguson, 1974) and partly because the afterdischarges seldom spread to the neocortex which is presumed to store the kind of memories that are evoked by the stimulation. These two observations seem to raise questions as to whether the reported "revived memories" are really memories, as opposed to the patient's creation or interpretation of the present situation. In a recent study with 3 epileptic patients, Halgren and Wilson (1985) unilaterally stimulated the amygdala, hippocampus and parahippocampal gyrus simultaneously during the recall phase of paired associates learning. Delayed (60 sec) recall was severely impaired if, and only if, an unilateral afterdischarge was evoked. Immediate recall or mental arithmetic were not affected even when afterdischarges were evoked. The authors argue that afterdischarges may be necessary to impair the performance because the critical site disrupted is not the medial temporal lobe, but rather in a site where the afterdischarges have propagated.

Thus, although the controversy is not settled completely, activation of the amygdala alone seems to rarely elicit re-experiencing phenomena. This tentative conclusion suggests that the amygdala is not the storage site of long-term memory which seems to be retrieved by the electrical stimulation, and is in agreement with the case of the temporal lobectomy patient H.M.

Anatomy of the Amygdala

The functions of the amygdala are suggested by its anatomical connections with other brain structures, the functions of which are better known in the present. But inferring specific functions of the amygdala from its anatomical connections is not a simple matter. According to Goddard (1972), on the input side, although every sensory modality has a pathway into the amygdala, the pathways are indirect. Thus, the information which arrives at the amygdala is abstract, almost abstruse. Recently, however, a direct sensory projection from the medial geniculate nucleus on the amygdala was reported (LeDoux *et al.*, 1985). On the output side, the amygdala is equally remote from the external world so that it is generally believed that no response is lost when the amygdala has been removed. This is not exactly the case, however, according to Richardson (1973). Thus, in this paper I have reviewed the amygdala anatomy literature from a functional viewpoint, that is, in terms of the information the amygdala deals with, at the expense of a detailed and systematic description of the anatomy.

What Kind of Information does the Amygdala Receive?

The amygdala is an heterogeneous complex with many subdivisions. It has been traditionally divided into the corticomedial and basolateral groups (De Olmos *et al.*, 1985), the former being phylogenetically old and composed of the medial, ACe, and cortical nuclei, and the latter being evolutionarily recent and composed of the lateral, basolateral (BL), and basomedial nuclei, primarily.

Cortical inputs to the amygdala have been most extensively studied in the monkey. Nearly all areas of the temporal lobe and major parts of the frontal lobe send projections to the amygdala. Thus, the amygdala receives inputs from all 5 sensory modalities through sensory association areas (except olfaction); for example, the inferotemporal cortex (vision), the superior temporal cortex (hearing), the insular cortex (taste and possibly tactile sensation), olfactory bulb and primary olfactory cortex (olfaction) (Whitlock and Nauta, 1956; Herzog and Van Hoensen, 1976; Aggleton *et al.*, 1980; Russchen, 1986; Turner *et al.*, 1980; Van Hoesen, 1981). Each sensory system achieves influence over a restricted sector of the amygdala by means of separate, modality-specific projections (Turner *et al.*, 1980), and the lateral nucleus is a major site of sensory convergence from all 5 modalities (Van Hoesen, 1981). The amygdala is also innervated by the orbital frontal and anterior cingulate cortex, temporal pole, insula, and subcallosal gyrus, all of which appear to play some role in autonomic modulation such as regulation of respiration and blood pressure (Aggleton *et al.*, 1980).

In the rat, in contrast, neocortical inputs are very limited or non-existent (Veening, 1978; Ottersen, 1982). As in the monkey, however, the rat amygdala receives projections from meso- and allocortical areas; the insular; perirhinal, entorhinal, pyriform, medial frontal cortices, and the hippocampus, etc (see Russchen, 1986). Thus, the sensory related cortical inputs to the amygdala are comprised of cascades of cortico-cortical connections that reach meso- and allocortical areas in the rhinal sulcus which in turn distributes to the amygdala (Turner and Zimmer, 1984; Ottersen, 1982).

In both species, the amygdala does not receive inputs from the primary sensory cortices (except for olfaction), but those cortical areas which do send fibers to the lateral and/or BL nuclei of the amygdala have been shown to receive convergent multisensory pathways (Krettek and Price, 1977a). The fact that these sensory-amygdaloid pathways involve a number of intervening cortical synapses implies that the sensory information reaching the amygdala is of a highly processed, complex nature (Turner, 1981). Gloor (1978) conjectured that complex perceptual patterns are most likely present in the BL amygdala because it represents one of the last (i.e., highest) stages of polysensory processing in the primate brain.

The amygdala also receives prominent inputs from the basal forebrain, diencephalon, midbrain, and lower brainstem. The thalamic projections to the amygdala are confined to the "non-specific" nuclei such as the midline and intralaminar nuclei (Aggleton *et al.*, 1980; Turner, 1981). The BL nucleus in the rat receives inputs from the dorsomedial thalamus (Kretek and Price, 1977c) which is implicated in the memory deficit of the Korsakov syndrome patients (Parkin, 1984). The BL nucleus is also innervated by the ventral pallidum, globus pallidus, and substantia innominata (Ottersen, 1981b). The hypothalamus and the lower brainstem autonomic nuclei mainly project to the ACe and medial nuclei, and the parabrachial nucleus is by far the most prominent source of the lower brainstem afferents (Ottersen, 1981b). The ACe nucleus is the most important termination area of the thalamic afferents and the afferents from the lower brainstem autonomic nuclei in the rat (Ottersen, 1981b) and the hypothalamic afferents in the monkey (specially, the ventromedial nuclei) (Amaral *et al.*, 1982). It is important to note that the amygdala appears to receive sensory information directly from subcortical sites: These are direct inputs from the medial division of the medial geniculate nucleus (auditory), the parabrachial nucleus and the nucleus of the solitary tract (taste, cardiopulmonary, and visceral information), and the periaqueductal gray (LeDoux *et al.*, 1985; Cechetto, 1987; Aggleton *et al.*, 1980).

Thus, it is suggested that the amygdala stands as an interface between hypothalamic and brainstem structures (and the visceral and autonomic functions associated with them) on the one hand, and much of the cerebral cortex (and associated cognitive functions) on the other hand (Amaral and Price, 1984), and that the internal environment of the body

receives equal representation with the outside world in the amygdala (Goddard, 1972). This characteristic of the amygdala anatomy has led to many basically comparable proposals concerning the function of the amygdala: That is, it has been suggested that the amygdala is involved in linking information about the sensory aspects of the stimuli processed by the neocortex with the fundamental motivational drive mechanisms and emotions, or in attaching some affective or motivational significance to the percept formed in the neocortex (Gloor, 1960; Geschwind, 1965; Aggleton *et al.*, 1980; Mishkin and Aggleton, 1981; Amaral and Price, 1984; Russchen, 1986).

How does the Amygdala Influence the Rest of the Brain?

One of general features of the amygdaloid efferents is that the basolateral group mainly projects to the cortex and related structures such as the substantia innominata, striatum, and dorsomedial thalamus whereas the corticomedial group (especially the ACe nucleus) mainly projects to the visceral structures in the hypothalamus and brainstem (Price, 1986), although the ACe may also influence the cortex indirectly via the nucleus basalis of Meynert (discussed below).

The BL nucleus in the rat has a widespread projection to the anterior half of the cortex (Sripanidkulchai *et al.*, 1984). It sends the most prominent projections to the medial frontal, temporal, and cingulate cortices and the dorsomedial thalamus (Krettek and Price, 1977a, 1977b; Amaral and Price, 1984; McDonald, 1987). The lateral nucleus projects to areas around the rhinal sulcus (Krettek and Price, 1977b). The amygdala may also influence virtually all parts of the cerebral cortex via the nucleus basalis of Meynert (Price, 1981) which receives prominent amygdala projections, especially from the basal and ACe nuclei (Krettek and Price, 1978 *et al.*, 1979). The BL also innervates the striatum, which may provide an access route to the somatic motor system (Kelley *et al.*, 1982).

Although the BL nucleus lightly projects to the lateral hypothalamus (LH), the predominant projection to the LH and all of the projections to the midbrain, pons and medulla autonomic centers (e.g., the central gray, parabrachial nucleus, etc.) arise from the ACe nucleus (see Price, 1981). The medial nucleus projects, among other structures, to the ventromedial hypothalamus (Krettek and Price, 1978) which can influence the pituitary (Price, 1981).

This gross separation of the amygdaloid efferents suggests the double nature of the amygdala. On the one hand, the amygdala can influence cognitive functions, either by their extensive direct cortical projections or through structures such as the nucleus basalis or the dorsomedial thalamus. On the other hand, the amygdala can affect visceral function through the direct projections to the hypothalamus and brainstem autonomic

nuclei (Price, 1986). Considering the intraamygdala connections, virtually all of the other amygdaloid nuclei project to the ACe and medial nuclei (Price, 1986) and the ACe is the only amygdaloid nucleus that truly collects all types of input that reach the amygdala (Russchen, 1986) because it receives visceral, taste, and cardiopulmonary information directly from the brainstem and other sensory information through the lateral and BL amygdaloid nuclei. Therefore, the ACe provides a way station for the majority of amygdalopetal structures to exert and influence on autonomic functions (Russchen, 1986).

Once, the amygdala was thought to be devoid of projections to the primary sensory and motor cortices (e.g., Kretek and Price, 1977b). Recently, however, the BL nucleus was found to project to the primary motor, somatosensory, and gustatory cortices in the rat (Sripanidkulchai *et al.*, 1984). In the monkey amygdala projects to the somatosensory, striate and prestriate areas (Amaral and Price, 1984). So, the amygdala appears to project to a greater number of cortical areas than those from which it receives projections (Amaral, 1986). This suggests that the amygdala can influence very early stages of sensory information processing. It is tempting to make another pure speculation from this suggestion. That is, based on a highly processed, rather complete percept received from the neocortex (Turner, 1981; Gloor, 1978) along with its non-sensory consequences received from the subcortical structures, the amygdala might be able to modulate, or change, the perception of the stimulus in a way that the features of the stimuli which is critical and relevant in the context can be preferentially selected and perceived.

Finally, the relationship of the amygdala with the hippocampus deserves mention. The lateral nucleus projects to the perirhinal and entorhinal cortices which provide most inputs to the hippocampus. The BL nucleus projects to the subiculum which is the major output system of the hippocampus in the rat (Kretek and Price, 1977b). The subicular and entorhinal cortices send projections to the medial basal and lateral amygdaloid nuclei in the monkey (Rosene and Van Hoesen, 1977; Aggleton, 1986). Thus, it can be concluded that the amygdala can influence and be influenced by the hippocampus, a structure which has been implicated in the consolidation of a long-term memory (Milner, 1966).

Neuronal Activity of the Amygdala in the Context of Learning and Memory

In an unusual "conditioning" experiment where a white noise ("CS") was on during a 2 hr immobilization period in rats, Henke (1983) found that some units in the central amygdaloid nucleus showed "conditioned" firing rate change to the auditory "CS" subsequently presented alone during the initial 15 min period of a 30 min test session. In addition, during the second 15 min period, responding returned almost to the baseline (unrestrained) rate. That is, the responses appeared to "extinguish". Units found outside the central nucleus did not show significant activity change. The rats that had shown significant unit-activity changes during the immobilization paired with the white noise escaped faster than the controls at the presentation of the white noise in behavioral testing. Unfortunately, the time course of the multiple unit-activity changes during the immobilization period (which would be comparable to a conditioning period according to the author) was not reported.

In more conventional classical conditioning situation, Ben-Ari and Le Gal La Salle (1972) found that the about 30% of the amygdala units recorded, the association of CS and UCS produced changes in response to the CS. Using a Pavlovian heart rate (bradycardia) conditioning paradigm in rabbits, Applegate *et al.* (1982) showed that several different patterns of multiple-unity activity in the amygdala central nucleus developed to the tone CS during the course of the conditioning procedure. In two cases, the increases in multiple unit response were significantly correlated with the development of the conditioned bradycardia response. In a better controlled Pavlovian differential bradycardia conditioning, Pascoe and Kapp (1985) first identified central amygdala neurons projecting to the lower brainstem by antidromic activation and observed differential single-unit activity to the CS+ and CS- in many of those neurons. It was also found that the responses of some units to a fear-arousing CS were correlated with the magnitudes of concomitant conditioned bradycardia responses. Based on these results and other anatomical data, the authors suggested that the amygdala central nucleus may function in the motoric expression of the conditioned bradycardia responses. However, such correlations between the activity of central amygdala neurons and the magnitudes of CRs were seen in neurons that could not be identified as projecting to the brainstem. And it should be noted that whereas behaviorally, there were no conditioned bradycardia responses to the CS-, a change in activity associated with the CS- was apparent in most of the neurons which displayed differential responses to the CS+ and CS- although the magnitudes of the change were smaller than those to the CS+. For example, the activity changes of the type-1 neurons were 50% and 86% in response to the CS- and CS+, respectively. In addition, in the Applegate *et al.* (1982) study, the change remained significant during behavioral extinction. Thus, the activity of central amygdala neurons does not exactly predict the behavioral motor responses. These findings weaken the hypothesis suggesting that the amygdala is involved in the motoric expression of

conditioned responses. In summary, the findings from electrophysiological studies certainly suggest that neuronal changes induced by learning can occur in the amygdaloid complex.

LESION STUDIES

Avoidance Learning

Almost all studies of the effects of amygdaloid lesions on avoidance learning have demonstrated a deficit of some type, although there is little agreement among investigators concerning the nature of this deficit (Goddard, 1964). Perhaps the most consistent effect of amygdaloid lesions is the impairment of acquisition of conditioned avoidance responses. Brady et al. (1954), Horvath (1963), Ursin (1965), and Zielinski *et al.* (1983) reported that in cats, amygdaloid lesions retarded the acquisition of an active avoidance response. Robinson (1963), Werka et al. (1978) reported similar findings in research with rats. King (1958) found that amygdalectomized rats were not impaired in the rate of acquisition, but did show significantly longer response latencies in a shuttle-box avoidance task. Kellicutt and Schwartzbaum (1963) and Spevack et al. (1975) observed deficits in the conditioned emotional responses (CER) in rats with amygdala lesions. Amygdala lesions are reported to impair acquisition of inhibitory (passive) avoidance responses in cats, rats and mice (Ursin, 1963; Pellegrino, 1968; Nagel and Kemble, 1976; Russo et al., 1976; Slotnick, 1973). Amygdala lesions also retard acquisition of active avoidance and CER in monkeys (Weiskrantz, 1956).

However, this seemingly most consistent body of data is not without conflicting results. Sometimes acquisition of an active avoidance response is not affected by the amygdala lesion (Kemble and Tapp, 1968). Moreover, surprisingly, Grossman (1972) and Grossman *et al.* (1975) reported that small lesions in each of the 6 major nuclei (cortical, medial, central, intercalated, lateral, and basolateral) of the amygdala facilitated learning of active avoidance behavior whereas inhibitory avoidance behavior was impaired in rats with lesions in the central, intercalated, and basolateral nuclei. These researchers suggested that the deficit in avoidance learning seen after extensive amygdala lesions may be due to cortical (particularly pyriform cortex) damage rather than destruction of components of the amygdala itself. However, this interpretation conflicts with evidence indicating that lesions restricted to the central nucleus disrupt both active and inhibitory avoidance learning in rats (Werka *et al.*, 1978). Werka *et al.* (1978) attributed the discrepancy between these studies to the high degree of difficulty of the task used in Grossman and his colleagues (1972; 1975). Another explanation is suggested by

Kemble and Beckman (1969) who found that amygdalectomized rats escaped faster than controls rats in a shuttle-box escape task. The authors noted that the normal rats rapidly developed a reluctance to enter a chamber where they had been previously shocked whereas amygdalectomized rats did not. Because the shuttle-box was composed of two similar compartments, it was suggested that the shorter escape latencies of the amygdalectomized rats reflect, in part at least, a failure to inhibit approach responses to the opposite compartment (i.e., inhibitory avoidance deficit). In this connection, taking into consideration the fact that amygdala-lesioned rats showed deficits in active avoidance in an apparatus with two dissimilar "danger" and "safe" compartments (Robinson, 1963; McNew and Thompson, 1966), Kemble and Beckman suggested that this dissimilary reduced or eliminated any inhibitory avoidance component in the active avoidance task, resulting in the better performance of the control rats. This kind of reasoning may explain the findings of Grossman *et al.* (1975) since they used a shuttle-box with two similar compartments.

Lesions of the amygdala may or may not affect the retention of a postoperatively acquired avoidance response. Werka et al. (1978) reported that rats with the central or basolateral amygdaloid lesions produced prior to training needed more trials in subsequent retraining (i.e., retention test) of active avoidance responses than controls even though they were trained to the acquisition criterion previously. In contrast, Weiskrantz (1956) and Jellestad and Cabrera (1986) found that amygdala lesions produced prior to training did not affect the retention of active avoidance behavior once it was learned to a criterion.

Investigations using lesions to examine the functional role of the amygdala have always been complicated by the fact that fibers pass through this area. In all the studies reviewed above, the lesions were produced by electrocoagulation, a lesion technique which destroys not only neurons in the lesioned area, but also fibers of passage as well as neurons in other brain regions due to retrograde degeneration. Therefore, the behavioral changes cannot be attributed to amygdala neurons alone (Jellestad and Cabrera, 1986). In a series of experiments, Jellestad and the associates (1985; 1986; 1986) compared the effects of the conventional lesion with those of the ibotenic acid lesion which selectively destroys cell groups without damaging extrinsic terminals and axons of passage (Kohler and Schwarcz, 1983). Both ibotenic acid and radio frequency lesions of the basolateral and central nuclei of the amygdala were found to impair inhibitory avoidance learning in rats (Jellestad and Bakke, 1985). In a subsequent study, ibotenic acid lesion confined to the central amygdaloid nucleus impaired inhibitory avoidance learning, but electrolytic lesion of the same nucleus resulted in a more pronounced deficit (Jellestad et al., 1986). In contrast, ibotenic acid lesions of the basolateral and central amygdaloid nuclei did not disrupt active avoidance learning whereas radio frequency lesions of the same nuclei did (Jellestad and Cabrera, 1986). Thus, at least for the central nucleus of the amygdala, the effects of the conventional lesions seem to be largely attributable to the intrinsic neurons of the nucleus.

While many studies have tried to identify specific functions with specific amygdaloid nuclei, the findings have, as yet, led to no consensus. Ursin (1965) found that the acquisition of an active avoidance response was impaired by lesions of the lateral nucleus or the ventral amygdalofugal fibers which had been identified as a "flight zone" (Ursin and Kaada, 1960) while passive avoidance learning was disrupted by lesions involving the medial nucleus or the stria terminalis. Horvath (1963) reported that basolateral amygdaloid lesions produced a severe deficit in a 2-way active avoidance task, but smaller deficits in 1-way active,and passive avoidance tasks. On the other hand, Werka et al. (1978) found that lesions of the central nucleus produced more pronounced deficit in 1-way active avoidance than the basolateral nucleus lesion whereas forced extinction was affected more by the latter than the former. The authors suggested that the basolateral nucleus might be more specifically involved in passive avoidance behavior. In contrast, Jellestad et al. (1986) reported that ibotenic acid lesions of the central nucleus disrupted passive avoidance learning, while ibotenic acid lesions of the lateral and basolateral lesions did not affect 1-way active avoidance learning. Ursin (1965) reported finding no direct relationship between the amygdaloid substrates for active and passive avoidance. Zielinski et al. (1983) showed that the acquisition of active avoidance responses was disrupted by lesions of either central or lateral nucleus in cats. Overall, in spite of the lack of agreement among studies, the role of the central nucleus in the inhibitory avoidance learning seems to be the most robust and consistent findings of this research.

In order to infer the functions of the amygdala in learning and memory from the results of studies using pretraining lesions, it is important to ensure that the lesion does not prevent the subject from receiving the relevant information, i.e., the conditional and unconditional stimuli. In a carefully conducted psychophysical experiment with rats, Goldstein (1968) found that lesions of the amygdala, particularly the basolateral portion, increased the thresholds for peripheral electric shock. A positive response for shock was defined as any movement of the animal at the moment of shock onset. But it should be noted that at the higher end of the shock intensity used in this study, the rats with amygdala lesions showed normal responses. Thus, as long as the intensity of the shock is high enough, the amygdalectomized animals do not seem to be impaired in perceiving painful stimuli. In contrast, Bagshaw and Pribram (1968) showed that amygdalectomized monkeys had a lowered threshold for electric shock (as measured by the GSR) and failed to respond differentially to various shock levels. Grijalva et al. (1986) did not find any differences between control and amygdalectomized rats in tail-flick or hot-plate tests. In addition, Kemble and Beckman (1969) reported that amygdalectomized rats escaped more rapidly than control rats in a shuttle-box at 3 intensities of electric shock. Therefore, it seems clear that increased pain threshold cannot account for all the deficits in avoidance learning exhibited by animals with the amygdaloid lesions.

Since the deficits in inhibitory avoidance learning by amygdala-lesioned animals

constitute the making of punished responses, some investigators have proposed that amygdala-lesioned animals are unable to inhibit punished or nonreinforced responses (Pellegrino, 1968; Kellicut and Schwartzbaum, 1963; Shibata *et al.*, 1986). Although the response inhibition hypothesis nicely explains the effects of the amygdala lesions on the inhibitory avoidance and CER, it gives difficulty accounting for the deficits in active avoidance produced by amygdalectomy (Spevack *et al.*, 1975). Besides, the view does not seem to really constitute "theory" or explanation because one may argue that it is only a re-description of the phenomena.

In addition to the effects on learning and memory, lesions of the amygdala have a variety of effects on emotional/motivational conditions of the organism. Increased open-field activity has been reported after large electrolytic lesions of the amygdala (e.g., Bresnahan *et al.*, 1976; White and Weingarten, 1976). Such activity increments have commonly been interpreted as indications of reduced fear in animals (Jellestad and Cabrera, 1986). Blanchard and Blanchard (1972) observed reduced freezing to both conditioned and unconditioned threat stimuli in amygdala-lesioned rats. Since lesions restricted to the central, but not the basolateral, nucleus of the amygdala in rats produced increased activity on all parameters studied in an open-field test, Werka et al. (1978) proposed a fear-reduction hypothesis for the deleterious effects of the central nucleus lesion on the active avoidance learning. The hypothesis that amygdalectomy impairs avoidance learning by decreasing fear arousal has been proposed by other investigators as well (Slotnick, 1973; Spevack *et al.*, 1975).

Approach Learning

Although the majority of the studies investigating functions of the amygdala have used aversively-motivated tasks, there are considerable data suggesting involvement of the amygdala in appetitively-motivated tasks too. In contrast to the effects typically seen in the acquisition phase of aversive tasks, the effects of the amygdala lesion in appetitive tasks are usually manifest when the stimulus-reinforcement relationship is changed, as in reversal tests, or when the magnitude of the reinforcement is changed as in a behavioral contrast paradigm.

In rats, cats and monkeys, simple visual discrimination learning is not affected by amygdala lesions (Pellegrino, 1968; Ursin, 1965; Horel *et al.*, 1975). Also, odor discrimination learning is not disrupted by anterior amygdala lesions in rats (Slotnick, 1985). However, if a successive discrimination paradigm is introduced, the amygdala-lesioned animals show impaired performance. Peinado-Manzano (1988) reported that learning a go-no-go visual discrimination in a free operant feeding situation was disrupted by lesions of the central or lateral amygdaloid nuclei in rats. These animals

were impaired to a greater degree in reversal learning of the task. On the contrary, in a remarkably similar task, Pellegrino (1968) found that lesions of the basolateral amygdala in rats did not affect the acquisition and reversal of the discrimination. Whereas Peinado-Manzano (1988) measured the rats' performance using the sessions to 3 learning criteria, Pellegrino (1968) did not train the animals to a criterion and used for analysis the number of errors made during the no-go period. This difference may explain the discrepancy. Because none of the amygdala-lesioned reached the second and third (i.e., higher) levels of the original learning criteria or any levels of the reversal learning criteria, Peinado-Manzano (1988) contended that they did not make a durable association of stimuli with reinforcement.

Schwartzbaum and Poulos (1965) found that in monkeys, amygdalectomy seriously interfered with performance on learning-set problems and visual discrimination reversals. Jones and Mishkin (1972) reported that lesion of the temporal pole and amygdala disrupted the acquisition of an discrimination and its serial reversals. In the data analysis, the course of reversal learning was divided into 3 stages: stage I represented retention of the old response; stage II indicated that the animal was responding at a chance level; stage III was the period of responding above chance level to a new positive object, but before the attainment of criterion, indicating formation of new stimulus-reinforcement associations. Monkeys with lesions of the temporal pole and amygdala made most of their errors in the stage II and III while monkeys with lesions of the orbitofrontal cortex or the hippocampus showed different patterns of error scores. Based on this analysis, the authors contended that the temporal pole and amygdala region plays a role in the formation of stimulus-reinforcement (or affective) associations. In the following study with a similar task, the lesion was confined to the amygdala or nuclei of the amygdala. While monkeys with lesions in the lateral or basolateral amygdaloid nuclei or anterior temporal white matter showed normal performance in learning an object discrimination and its 11 serial reversals, monkeys with total amygdalectomy were impaired in the reversal learning (Aggleton and Passingham, 1981). It was suggested that the impairments on objects reversal learning correlated with the extent of amygdala damage. After analyzing error scores of a monkey with large lesion of the dorsal amygdala according to the method of Jones and Mishkin (1972), the authors contended that this monkey failed to relearn the new contingency, thus producing a large preponderance of stage II errors. It was also noted that only those animals that were hypoemotional showed a deficit in the reversal learning. In addition, Spiegler and Mishkin (1981) reported that in monkeys, lesions of the amygdala impaired one-trial learning of object-reward associations. In this task, in order to respond correctly, the animal had to remember the reward value of the object on the basis of single acquisition trial in which the object had been either baited or unbaited with food.

Amygdaloid lesions in rats attenuate the response-rate increase or decrease following quantitative increases or decreases, respectively, in the magnitude of reward

(Goomas and Steele, 1980). Common examples are behavioral contrast, frustation effect, collapse effect, pattern-running, etc., which are discussed below.

A bar-press operant conditioning task can be run with multicomponent reiforcement schedules. If the reinforcement frequency in one component schedule is changed whereas that in the other component schedule remains unchanged, the subject's responding in the unchanged component schedule is altered (behavioral contrast) (Reynolds, 1961; Pear and Wilkie, 1970). For example, switching one component of a multiple variable-interval schedule to extinction produces response rate increases in the unchanged component (Reynolds,1961). This behavioral contrast is not obtained with amygdalectomized rats (Henke, 1972, 1973, 1979; Henke *et al.*, 1972). In these experiments, amygdala lesions did not affect the initial acquisition of the bar-press response or extinction. Lesion of the stria terminalis did not prevent the behavioral contrast effect (Henke, 1979). It is important to point out that the response rates were clearly differentiated in the reinforced and nonreinforced components for both the amygdala-lesioned and control groups. Thus, the amygdala lesions did not impair the discrimination between the two reinforcement contingencies (Henke *et al.*, 1972).

Assuming that the increased responding in behavioral contrast experiments represents by-products of emotional responses, e.g., frustration, elicited by nonreinforcement during the extinction component (Scull *et al.*, 1970), Henke and his colleagues (1972, 1977, 1979) argued that amygdala lesions affect the behavioral contrast by preventing the occurrence of emotional states induced by non-reinforcement. That is, amygdala-lesioned animals are deficient in forming affective responses to changed reinforcement conditions (Henke, 1972). This contention is supported by the well-documented fact that reduced emotionality, usually described as placidity, is commonly found after amygdala lesions (see Goddard, 1964). It is also supported by the finding that amygdaloid lesions virtually eliminated the frustation effect in a double runway (Henke and Maxwell, 1973). The frustation effect refers to the following phenomenon: After a large number of continuous reinforcements in the first goal box of a "double runway", rats run faster in the second alley on trials in which reinforcement is omitted from the first goal box than they do on trials in which reinforcement is given (Amsel and Roussel, 1952). The increased vigor of responses, as measured by running speed, in the second alley following nonreinforcement (i.e., the frustation effect) is prevented by amygdaloid lesions (Henke and Maxwell, 1973; Henke, 1977).

In a single runway, the amygdala-lesioned rats were less responsive, in comparison with controls, to changes in the magnitude of the reinforcement (Kemble and Beckman, 1970). In this study, the latencies to reach the goal box were about the same in the amygdala-lesioned group regardless of the number of food pellets in the goal box whereas the control group showed significantly longer latencies in the trials with 1 pellet than in the trials with 5 or 10 pellets. Similarly, amygdalectomized monkeys in a bar-press task

were consistently less responsive, but by no means insensitive, to increased or decreased amounts of rewards, provided the rewards were not omitted entirely (Schwartzbaum, 1960a). This effect could not be accounted for by increased hunger drive, as migth be inferred from the hyperphagic effects of the lesion. However, Schwartzbaum (1960b) also reported that in an experiment studying the transient increase in responding following a signal which predicted that the next reward would be unusually large, amygdalectomized monkeys showed appropriate response changes.

If reinforced and nonreinforced trials are alternated in a runway, running speed on reinforced-trials becomes increasingly faster than that on nonreinforced-trials as training continues, an effect termed pattern running (Bloom and Capaldi, 1961). Amygdala lesions were found to retard the appearance of single-alternation pattern running in rats. But, once the lesioned rats exhibited pattern running, there was no difference between the lesioned and control groups (Goomas, 1982).

When two groups of rats are administered either a large or a small magnitude of reward in a runway, the large-reward group runs faster to the goal box with the small-reward group catching up later in the training (the collapse effect) (Goomas *et al.* 1980). The collapse effect occurred significantly earlier in training in amygdala-lesioned groups than in control groups, and performance decrement produced by introducing 60-sec delay of reinforcement in the goal box was smaller in the lesioned groups than in the control groups (Goomas and Steele, 1980). These findings suggest that relative to the control animals, rats with amygdala lesions were less responsive to original reinforcement contingencies as well as to changes in reinforcement contingencies.

Aggleton and Passingham (1982) showed that amygdalectomy in monkeys did not alter the appreciation of at least one class of positive rewards, food. Thus, the amygdalectomized animals could recognize the reward value of the food. Horel *et al.* (1975) reported that amygdala lesions do not disrupt discrimination of food from non-food in monkeys. As noted above, there is evidence that amygdala-lesioned rats do not respond differently to different levels of electric shocks (e.g., Bagshaw and Pribram, 1968). These studies show that amygdalectomized animals can react normally to primary reinforcers. In the majority of studies reporting insensitivity or reduced sensitivity to changes in magnitude of reward in amygdala-lesioned animals, there are external stimuli to be associated with rewards, or the animal has to rely on internal cues to respond correctly to get rewards in the absence of external signals. Thus, the reduced sensitivity to changes in reinforcement may be because they do not know what the external stimuli associated with rewards mean or not have internal cues associated with the rewards. This reasoning would imply that it is the stimulus-reinforcement association that is disrupted by amygdala lesions. Although the study by Schwartzbaum (1960b) is directly opposed to this hypothesis, it seems to be one of the few reports in this respect.

Posttraining Lesion Studies

McGaugh (1966) has argued that time-dependent processes of consolidation are involved in memory storage. Thus, if a treatment is given shortly after learning, its effect is interpreted as being not on the acquisition of the task, but on the storage or consolidation of the memory, which is measured by the retention performance some time after the treatment. If a brain structure is a site of memory storage, destruction of that structure at any time after learning should abolish the memory and the related behavior. Therefore, findings about the post-training lesions are central to the issue of whether the amygdala is a site of memory storage. There are very few studies aimed specifically at examination of the role of the amygdala in consolidation or retention of memory as opposed to memory acquisition. Some of the studies discussed above also examined the effects of amygdala lesions made after learning. Most of the studies reviewed below reported effects of amygdala lesions on acquisition, but effects of posttraining lesions on retention vary among different studies. Brady *et al.* (1954) reported that amygdala lesions had no effect on retention of active avoidance responses in cats. The authors interpreted their results on the grounds that only the acquisition, and not the maintenance, of avoidance behavior is affected by amygdala lesions. However, Horvath (1963) observed that basolateral amygdaloid lesions produced a severe deficit in retention of an active avoidance response in cats. Also, Goldstein (1965) found that amygdalectomized rats lost their classically conditioned fear responses following the lesions which were performed one day after learning. More recently, in an operant task with a reinforcement conflict schedule where two periods of rewarded and punished bar-presses were continuously alternated, Shibata *et al.* (1985) showed that posttraining lesion of the central amygdaloid nucleus in rats impaired retention of behavioral suppression of the punished responses and prevented reacquisition of the same behavior. In classical conditioning of blood pressure and respiratory responses with cats, reversible lesion by cooling of the central amygdaloid nucleus attenuated or abolished the conditioned autonomic responses to CS, which returned after rewarming the nucleus (Zhang *et al.* 1986).

In approach learning, there are also conflicting findings. In an 8-arm radial maze on a task in which memory for magnitude of reinforcement was tested, posttraining lesions of the central amygdala in rats produced a marked deficit at the 5-and 15-min delays, but no deficit at the 5-sec delay, whereas lesions of the basolateral amygdala had no effect (Kesner *et al.*, 1989). In contrast, ibotenic acid lesions of the central or basolateral amygdala impaired the acquisition of an operant go-on-go visual discrimination task, but not the retention of the same task acquired before the lesion (Peinado-Manzano, 1988).

There seems to be only one study which varied the time between training and amygdala lesion. In one-trial inhibitory avoidance task with rats, Liang *et al.* (1982) showed that amygdala lesions made 2 days, but not 10 days after training impaired the

retention. This finding indicates that for long-term retention of the avoidance behavior, the amygdala is necessary shortly after training, but not when sufficiently long time has passed following training. Thus, the amygdala seems to affect time-dependent processes involved in memory storage (i.e., consolidation) and not the long term memory itself. The authors suggested that the amygdala lesions affect retention by modulating memory storage processing elsewhere in the brain rather than by disrupting memory traces in the amygdala. But the possibility that memory could be stored in the amygdala temporarily was not ruled out, as the authors admitted.

Horvath (1963) pointed out that before the amygdalectomy, the animals in Brady *et al.* (1954) received 100 more trials after they reached acquisition criterion whereas the animals in his study were not overtrained. According to Horvath, if overtraining can prevent the retention deficit by posttraining amygdala lesion, it suggests that the amygdala is involved primarily in acquisition processes and may not be related to processes of long-term memory storage. This suggestion was supported by the finding of Thatcher and Kimble (1966) that all overtrained rats exhibited normal retention of active avoidance responses following lesions of basolateral amygdala performed one day after training while retention was impaired in 3 out of 4 rats that had reached acquisition criterion but not been overtrained. Also, Fonberg *et al.* (1962) showed that amygdalectomized dogs fully retained an overtrained avoidance response, but completely lost a defensive leg-flexion that had not been overtrained. Goddard (1964) interpreted the findings of these studies and majority of other lesion studies as suggesting that one of the major functions of the amygdala is the consolidation of the association of a neutral stimulus with an aversive stimulus.

Recently, we (Parent *et al.* 1992) investigated the effect of variations in the amount of preoperative training on the retention deficits produced by posttraining lesions of the amygdala. Rats received 1, 10 or 20 training trials in a footshock-motivated escape task 7 days prior to receiving N-methyl-D-aspartic acid lesions of the amygdala. Inhibitory avoidance retention performance, which was measured 4 days postoperatively, indicated that increased training improved retention in lesioned animals as well as in control animals. These findings suggest that the amygdala is not a critical site for the long term neural plasticity underlying stimulus-affect associations that are based on extensive training.

In the viewpoint of memory consolidation, assuming that overtraining results in faster consolidation of memory, the findings that overtrained active avoidance responses were not affected by 1-day posttraining lesions of the amygdala (Thatcher and Kimble, 1966) but non-overtraining inhibitory avoidance responses were impaired by 2-day posttraining lesions of the amygdala (Liang *et al.*, 1982) support the view that the amygdala is not the storage site of memory, but is important for the time-dependent memory storage processes. This interpretation can be supported by the following

observation: In those studies reporting impaired retention by posttraining amygdala lesions, the animals were not overtrained, and the lesions were usually made within 1 day after training. For example, in Zhang *et al.* (1986), the cooling of the amygdala was done shortly after only 30 CS-UCS pairings. Also, after extensive training (100 consecutive correct responses) in an active avoidance task, electrical stimulation of the amygdala with intensities high enough to inhibit ongoing food intake failed to impair avoidance reactions tests in cats (Fonberg and Delgado, 1961).

The view that the amygdala is important for the time-dependent processes involved in memory storage occurring after training (Liang *et al.*, 1982) is further supported by posttraining electrical stimulation studies reviewed below.

Electrical Stimulation Studies

Goddard (1964b) suggests that electrical stimulation of the amygdala acts a functional (reversible) lesion by scrambling the otherwise orderly traffic of impulses through the amygdala. So, the chief advantage of using electrical brain stimulation (EBS) to influence learning and memory is that the animal is normal at all times other than the experimental period, thus preventing a gradual reorganization of neural activity which is supposed to occur following a permanent lesion. However, the exact mode of action of EBS is not clear. EBS can act by disrupting ongoing neural activity within the vicinity of the stimulating electrodes, by activating interconnected neural regions remote from the stimulation site, or by altering neural activity throughout the whole brain (Kesner, 1982). Furthermore, there are instances that EBS facilitates retention (e.g., Bloch, 1970). Thus, although only studies using EBS with subseizure intensities are discussed in this section, one cannot argue that the neural unit affected by EBS represents the location of the engram. However, one may do so by comparing the effects of EBS of different brain structures on different tasks.

Pellegrino (1965) showed that noncontingent, continuous stimulation of the basolateral amygdala impaired the acquisition of a passive avoidance response. Similarly, in a carefully controlled study, Goddard (1964) found that continuous stimulation of the amygdala prevented the acquisition of 2-way active avoidance behavior, and retarded that acquisition of a conditioned emotional response (CER). Explanation of these results in terms of cortical arousal by the amygdala stimulation was ruled out. Stimulation during the CS only did not affect the CER whereas the general activity remained normal, from which it was concluded that amygdala stimulation did not act directly on fear. In contrast, stimulation begun immediately after the US retarded the acquisition of the CER. Thus, Goddard concluded that amygdala stimulation seemed to disrupt the consolidation of a CER.

In a similar consolidation paradigm, immediate posttraining electrical stimulation of the amygdala was found to disrupt long-term retention of inhibitory avoidance, active avoidance, and taste-aversion learning (Gold *et al.*, 1973; Handwerker *et al.*, 1975; Kesner and Conner, 1974; Gold *et al.*, 1977; Cross and Goodman, 1982; Sternberg and Gold, 1981; Liang and McGaugh, 1983; Kesner *et al.*, 1975). Posttraining amygdala stimulation may not only impair, but also facilitate memory. Gold *et al.* (1975) showed that amygdala stimulation impaired retention of high footshock training, but facilitated retention of low footshock training in an inhibitory avoidance task. This finding is not easily accounted for if the localized electrical stimulation directly interfered with memory storage processing itself occurring in the amygdala. Specifically, it is difficult to understand how the electrical stimulation can enhance, not impair, memory stored in the stimulated region. Since it is reasonable to assume that EBS affects neurons in ways which never occur with naturally triggered volleys of nerve impulses, one mode of EBS action is likely to disrupt ongoing neural activity through scrambling of normal firing patterns, while indirectly facilitating on inhibiting neural activity in interconnected structures (Doty, 1969; Kesner, 1982). Thus, "any excitatory effect on mnemonic processes is probably a function of changes in interconnected neural systems" (Kesner, 1982). Therefore, the memory-enhancing effect of posttraining amygdala stimulation indicates that the strength of the memory stored in the brain structures connected with the amygdala is influencied by amygdala stimulation. Also, the amnestic effect of posttraining amygdala stimulation on avoidance responses was found to be attenuated by lesions of the stria terminalis which is a major input-output pathway of the amygdala (Liang and McGaugh, 1983), which confirms a major prediction from the above interpretation. Lesions of the stria terminalis did not significantly affect retention in the unstimulated rats. Together with the findings of posttraining lesion study of the amygdala by Liang *et al.* (1982) and Parent *et al.* (1992), these results support the view that the amygdala modulates memory storage processing by influencing brain function elsewhere rather than by affecting the memory storage localized within the amygdala. It is further supported by finding that an opiate antagonist naloxone administered into the bed nucleus of the stria terminalis after learning prevented retrograde amnesia produced by posttraining stimulation of the amygdala (Liang *et al.*, 1983).

However, Kesner and his colleagues have obtained results suggesting that some form of memory trace may be stored in the amygdala. Kesner (1980) has proposed that any specific memory is composed of a set of features or attributes that are specific and unique for each experience, and postulated that the amygdala is involved in the processing of aversive emotional attributes whereas the hippocampus processes spatial or environmental attributes (Baker *et al.*, 1981). Posttraining stimulation of the amygdala or hippocampus impaired retention of an inhibitory avoidance response in both groups, after which a footshock reminder cue reinstated the memory in the hippocampus-stimulated, but not in the amygdala-stimulated groups (Baker *et al.*, 1981). Conversely,

in the same inhibitory avoidance task, providing an environmental reminder cue prevented retention deficit in the amygdala-stimulated, but not in the hippocampus-stimulated rats (Kesner and Hardy, 1983). These results seem to suggest that memory for the aversive footshock, but not the spatial environment, is stored in the amygdala and disturbed by the stimulation. The finding that posttraining injection of a protein synthesis inhibitor cycloheximide into the amygdala, but not into the internal capsule or frontal cortex, disrupted retention of inhibitory avoidance training (Berman *et al.*, 1978) is consistent with this idea. Accordingly, Kesner (1982) suggested that it is possible that amygdala stimulation affects mnemonic function by altering the efficacy of protein synthesis.

Although Berman and Kesner (1976) initially showed that posttraining amygdala stimulation did not affect retention of an appetitive task in water-deprived rats, in another task involving large vs. small magnitude of reward, amygdala stimulation was found to disrupt rat's memory for the large reward, but not for the small reward (Kesner and Hardy, 1982). Thus, the authors contended that the amygdala processes both positive and negative emotional attributes of a specific memory, providing the reinforcement inputs elicits a strong emotional reaction. It is plausible that most positive reinforcement, for example, water or pellets of food, does not evoke strong emotion, which results in the lack of effects of amygdala manipulations. This is supported by the finding that in an instrumental conditioning in the same apparatus, shock motivated rats showed significant increases of heart rate and blood pressure to the CS whereas food-motivated rats did not (Drewett and Zbrozyna, 1985).

These two lines of research seem to be difficult to be reconciled with each other, but they are not necessarily exclusive. Although the evidence suggests that one function of the amygdala is to modulate the strength of memory stored in other brain regions, the evidence does not rule out the possibility that certain forms of short-term memory can be stored within the amygdala. The differential posttraining lesion effect of Liang *et al.* (1982) seems to imply that a temporary neuronal change in the amygdala may be necessary for the modulatory effects on the specific memory to occur. To modulate the memory of the particular experience only and not the others, i.e., to ensure the specificity of the modulatory influence, there should be a neuronal change specifically connected with the particular experience. Otherwise, memories of every experience which occurs while the amygdala is active (e.g., for 2 days) will be modulated, and this does not seem to happen. Thus, the finding of Liang *et al.* (1982) seems to suggest that short-term neuronal change may be produced in the amygdala by training.

Pavlovian Fear Conditioning

The extensive evidence that lesions of the amygdala attenuate the arousal of fear and impair the acquisition of a variety of aversively conditioned responses (e.g., Blanchard and Blanchard, 1972; Spevack *et al.*, 1975; Werka *et al.*, 1978) has led researchers to examine more explicity the contributions of the amygdala to fear-induced arousal and the involvement of fear in aversive conditioning. A popular paradigm in this line of research is Pavlovian conditioning of heart rate (HR, bradycardia) and/or blood pressure. Also, enhancement of startle reflex by fear-conditioned stimulus has been used to reveal the brain circuits involved in fear conditioning.

Both large and small pretraining lesions of the central nucleus of the amygdala produced a significant attenuation of the magnitude of the conditioned bradycardia response to a tone CS impaired with a shock UCS (Kapp *et al.*, 1979). No significant effects were observed on baseline HR or on the HR orienting response to a novel tone stimulus. But the lesions also produced a significant effect on the unconditioned HR response to the unconditioned stimulus. Adrenergic and opiate agonists and antagonists injected into the central nucleus region before conditioning also affected the magnitude of the conditioned bradycardia response (Gallagher *et al.*, 1980; Gallagher, 1981). Electrical stimulation of the central nucleus produced short-latency, vagally mediated bradycardia and depressor responses (Kapp *et al.*, 1982; Applegate *et al.*, 1983). Together with the neuroanatomical finding that the central nucleus project directly to the brainstem autonomic nuclei (Schwaber *et al.*, 1980; 1982), these results led Kapp and his colleagues to propose that the central nucleus may provide a substrate for the motoric expression of the conditioned bradycardia response, and perhaps other conditioned responses, during Pavlovian fear conditioning (Kapp *et al.*, 1984), which has already been discussed in the section of recording studies. But they did not preclude the possibility of the formation and/or the preservation of the association made between the CS and fear in the central nucleus.

While Kapp *et al.* (1979) used a simple pavlovian conditioning procedure in which one group of animals received a CS paired with a UCS and another group of animals received a CS unpaired with a UCS (pseudoconditioning procedure), Gentile *et al.* (1986a) employed a differential conditioning procedure in which the same animal received in the same training session a stimulus (CS+) paired with a UCS and another stimulus (CS-) presented alone. Lesions of the central nucleus produced immediately after training severely attenuated or abolished the HR CR in rabbits, but had no effect on HR baseline, orienting response, or HR unconditioned response to the UCS (Gentile *et al.*, 1986a). The latter finding seems to conflict with the impaired unconditioned response reported in Kapp *et al.* (1979). The findings of Gentile *et al.* (1986a) have been replicated by ibotenic acid lesions of the central nucleus made before training (Gentile *et al.*, 1986b).

In a similar differential pavlovian conditioning paradigm with tone CSs and a shock UCS in rabbits, Ryugo and Weiberger (1976, 1978) found that neurons in the magnocellular medial geniculate nucleus (mMGN) developed plasticity during acquisition of the conditioned response. The medial geniculate nucleus (MGN) projects to the amygdala central nucleus in rats and rabbits (LeDoux *et al.*, 1985; Kapp *et al.*, 1984; Jarrell *et al.*, 1985). Accordingly, pretraining lesions of nMGN were found to disrupt acquisition of differential HR CRs, but not to prevent the acquisition of bradycardia responses to the CSs (Jarrell *et al.*, 1985). Lesions of the nMGN produced at the end of conditioning session abolished the differential CRs when the animals were tested the next day (Jarrell *et al.*, 1987). This impairment was due to an increased response magnitude to the impaired tone (CS-), that is, the lesioned animals responded equally strongly to the CS- as well as to the CS+. Thus, whereas lesions of the central amygdala nucleus disrupt both the simple pavlovian HR conditioning using one CS paired with a UCS (Kapp *et al.*, 1979) and the differential pavlovian HR conditioning using CS+ and CS- (Gentile *et al.*, 1986), lesions of mMGN seems to impair differential pavlovian conditioning only and not the simple conditioning (Jarrel *et al.*, 1987). These results suggest that the amygdala adds something to the auditory information which it receives from the mMGN. The mNGM may send an enhanced signal for CS+ and a weakened signal for the CS- to the amygdala where emotional components (e.g., fear) are added to the signals. The view that the amygdala adds emotional components to the signals suggests that the sensory information from the CS may be associated with the aversive signals from the UCS in the amygdala central nucleus. Association of the CS and UCS would require neuronal changes to occur in the amygdala. Thus, neuronal changes induced by the conditioning may occur in the amygdala as well as in the structures preceding the amygdala (e.g., mMGN) in the information processing circuit.

Using conditioned emotional response (CER) paradigm with a tone CS and a footshock UCS, LeDoux and his colleagues measured mean arterial blood pressure, heart rate (tachycardia, increased HR), and the suppression of exploratory activity and drinking (i.e., freezing) during the presentation of the CS in freely behaving rats to find out "how afferent information acquires emotional coloration as sensory signals are transferred from station to station in the brain" (LeDoux *et al.*, 1983). The CER was abolished by lesions of the MGN, but not by lesions of the auditory cortex, which suggested that the structures responsible for this auditory fear conditioning are subcortical ones (LeDoux *et al.*, 1983). Subsequently, ibotenic acid lesions of intrinsic neurons in the amygdaloid field innervated by the MGN were found to disrupt the CER (Iwata *et al.*, 1986). In this study, amygdala lesions did not affect the non-associative heart rate increase (tachycardia) to the CS. More importantly, lesioning the amygdala on one side and the MGN on the contralateral side, thus disconnecting the two, abolished the CER (LeDoux *et al.*, 1986). Therefore, connections linking the two structures appear to be necessary for the establishment of associatively conditioned responses elicited by an acoustic stimulus

(LeDoux *et al.*, 1986). It was suggested that the amygdala (included in the striatal fiels as the authors described at that time) could play a role in the integration of information from the thalamus concerning the acoustic CS and the nociceptive UCS. Such integration is believed to constitute the neural basis of associative conditioning (LeDoux *et al.*, 1986). The central amygdaloid nucleus projects to the lateral hypothalamic area (LH), midbrain central gray (CG), and bed nucleus of the stria terminalis (BNST). Pretraining lesions of the LH and caudal CG disrupted the conditioned arterial pressure response and conditioned freezing, respectively, but lesions of the BNST had no effect (LeDoux *et al.*, 1988). Since lesions of the amygdala or earlier stations disrupt both behavioral and autonomic CRs, these findings suggest that the pathways for the CER diverge after the amygdala, with projections to the LH mediating autonomic changes and projections to the CG mediating behavioral changes (LeDoux *et al.*, 1988). Thus, the amygdala seems to be located in the center of sensory input and motor output pathways for the CER, the former being the MGN and earlier stations and the latter being the LH and CG and after.

In contrast to the approaches reviewed so far, Davis and his colleagues have used a simple reflex to find where in the brain the associative learning occurs. Specifically, in their paradigm of fear-potentiated startle (FPS), the magnitude of a startle reflex is increased when the startle-eliciting stimulus is presented in the presence of a cue (CS) that has previously been paired with a shock by a Pavlovian conditioning procedure. Thus, the FPS paradigm is similar to the CER paradigm in that associative learning modulates an ongoing behavior (Davis, 1986). If lesion of a structure blocks the modulatory effect of previous associative learning on the startle response, i.e. the FPS, then it suggests that the structure is involved in the associative learning circuit. Because potentiated startle appears to be a measure of fear, it was hypothesized that lesions of the amygdala should block the FPS (Davis, 1986). It was found that lesions of the central amygdaloid nucleus completely blocked the FPS without affecting the startle response itself (Hitchcock and Davis, 1986). Also, low-level electrical stimulation of the central, medial, or intercalated, but not basolateral, nuclei of the amygdala or the ventral amygdalofugal pathway markedly enhanced the startle response (Rosen and Davis, 1988). The effect of lesions of the amygdala is not specific to one sensory modality, thus affecting both visual and auditory FPS (Hitchock and Davis, 1987). Although the paradigm itself is promising and suggests involvement of the amygdala in associative learning, it seems premature to hypothesize what happens in the amygdala since most of the data pertain to uncovering the startle reflex circuit and the point in the circuit where modulation of the reflex by the CS occurs.

Concluding Remarks

Clinical studies in humans generally suggest that memory is not stored in the amygdala (Scoville and Milner, 1957). Lesions of the amygdala do not seem to drastically impair performance in formal and informal memory tests (Jurko and Andy, 1977; Narabayashi, 1980). Stimulation of the human amygdala seems to evoke "re-experiencing" phenomena mostly when afterdischarges accompany the stimulation (Halgren, 1981).

Also in animal studies, lesions of the amygdala do not always impair learning. Active avoidance learning often is not affected by amygdaloid lesions (Kemble and Tapp, 1968; Grossman *et al.* 1975). Preoperatively acquired avoidance responses may or may not be lost by lesions of the amygdala. In appetitive tasks, although amygdaloid lesions seem to make the animals less responsive to changes in the stimulus-reinforcement relationships or in the magnitudes of reinforcement, acquisition itself of appetitive tasks is not usually affected. The differential posttraining lesion effects by Liang *et al.* (1982) and Parent *et al.* (1992) show that long-term memory for the inhibitory avoidance conditioning is not stored in the amygdala. Also, overtrained active avoidance responses are not affected by amygdala lesions made shortly after learning (Thatcher and Kimble, 1966). In addition, the facilitatory effects of posttraining amygdala stimulations on memory by lesions of the stria terminalis (Liang *et al.*, 1983) strongly argue that the amygdala modulates memories stored in brain regions other than the amygdala. However, considering that the amygdala plays an important role in emotional and motivational behavior (Goddard, 1964), it remains possible that certain forms of memory can be stored in the amygdala at least for a short period of time. Thus, emotionally charged memories have not been tested in humans who underwent amygdalectomies. In animal studies, recordings of multiple and single unit activity in the amygdala during classical conditioning show that there is a correspondence between acquisition of the conditioned responses and the change in the amygdala neural activity (Ben-Ari and Le Gal La Salle, 1972; Applegate *et al.*, 1982). Non-overtrained avoidance responses are impaired by amygdala lesions made shortly after learning (Thatcher and Kimble, 1966). Together with the differential posttraining lesion effects of the amygdala (Liang *et al.*, 1982), these findings suggest that short-term memory can be stored in the amygdala. Although amygdala manipulations generally have effect on acquisition of appetitive tasks, studies by Jones and Mishkin (1972) and Mishkin (1981) suggest that the amygdala is important for acquisition of stimulus-reinforcement association. Findings from studies using changes in reinforcement magnitudes (Henke, 1972, 1973, 1979) suggest that the amygdala may be involved in linking stimuli with reinforcement eliciting strong emotional arousal. In accordance with this suggestion, posttraining electrical stimulation studies of the amygdala with reminder cues using footshock or environmental features suggest that the amygdala plays a role in encoding (and possibly storing) strong emotional attributes of memory (Baker *et al.*, 1981; Kesner and Hardy, 1983). Particularly strong evidence for neuronal changes in the amygdala is provided by studies of classical conditioning of heart rate responses by Kapp

and his colleagues (1979, 1981, 1983) and Gentile and the associates (1985, 1986, 1987) and conditional emotional responses by LeDoux and his colleagues (1986, 1988). Thus, the role of the amygdala in learning and memory remains unclear; however the experimental evidence reviewed in this paper, suggest that the amygdala is not the site for long term neural plasticity underlying stimulus-affect associations.

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