

MINIREVIEW

Neural Topography and Chronology of Memory Consolidation: A Review of Functional Inactivation Findings

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Findings on the role of subcortical and cortical structures in mnemonic processes, obtained by means of the reversible functional inactivation technique, are reviewed. The main advantage of this method (subcortical or cortical administration of local anesthetics or tetrodotoxin) is that it provides information not only on “where” but also “when” and for “how long” these processes take place, thus adding to the topographical dimension the chronological one. The review covers several types of memory (e.g., passive avoidance and spatial memory) studies examining the neural substrates of memory consolidation on the basis of the functional inactivation of the nucleus of the solitary tract, parabrachial nuclei, substantia nigra, hippocampus (dorsal and ventral), nucleus basalis magnocellularis, amygdala, medial septal area, striatum, olfactory bulb, and neocortex. The data are discussed in relation to earlier research and with respect to the anatomical and functional connectivity of the examined centers. © 1999

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Learning is one of the “higher nervous functions.” It consists of acquiring information about the internal and external environment that produces transient or permanent behavioral modifications. Memory is the storage of retained information, and its existence is shown by the persistence of overt behavioral modifications, which can be observed and recorded. It is generally accepted that the mnemonic process is made up of several sequential phases. First, information is acquired (a memory trace, engram, is formed), and successively the engram is consolidated, stored, and retrieved as and when needed. Experimental evidence suggests that we must postulate a consolidation phase because, for some time after acquisition, the acquired information is vulnerable and may be altered or lost. This is illustrated by the findings on retrograde amnesia, which show that engram consolidation is a time-dependent process (McGaugh, 1966). Although the mechanisms underlying retrograde amnesia are not fully understood, it is nevertheless well established that the effects of amnesic interventions are inversely

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related to the duration of the delay between acquisition (training session in experimental psychology protocols) and the administration of amnesia eliciting interventions. On another level, much work has been devoted to the attempts to draw a brain map correlating behavioral modifications with destruction of discrete brain structures. The first results (going back to the 19th century) were obtained as functional deficits after the destruction, accidental or pathological, of portions of the encephalon (for more information, see Brazier, 1959, and Blakemore, 1977).

From these beginnings originated the practice of controlled (i.e., experimental) neural lesions in subhuman experimental subjects. The permanent lesion technique has become increasingly accurate and specific (stereotaxic method, Horsley & Clarke 1908; kainate and ibotenate lesions sparing axons, Coyle, Bird, Evans, Gulley, Nadler, Nicklas, & Olney, 1981; selective damage to mediator-specific neurons, Jonsson, Malmfors, & Sachs, 1975). Its unavoidable drawback, however, is that the effects are irreversible.

To be more precise, there are at least two kinds of drawbacks. One is the possibility that, within limits, a reorganization of the undamaged neural circuits may take place. This is obviously a time-dependent process, which may eventually compensate for the imposed loss. In this case the observable effects of a lesion will not be permanent, differing according to the time of observation. On the other hand, even in the case of a constant functional deficit, what can be observed must be interpreted cautiously because the behavior under study may be the final result of several, perhaps sequentially arranged processes. The observable behavioral deficit may result from the loss of only one of these processes, with the others being undisturbed. This complication assumes particular relevance in memory studies, in which a lesion disrupting memory formation, consolidation, storage, or retrieval is always manifested by a failure of retrieval. A lesion blocking only the retrieval circuit may leave the other stages intact but this cannot possibly be proved by irreversible lesions. On the other hand, the reversible inactivation technique has been shown to be quite adequate for investigating memory processes and mechanisms. By means of this technique, a fully reversible functional blockade may be imposed on a given cerebral site for a known duration, after which there will be no permanent residual functional impairment. This technique has been employed to provide data for a functional mnemonic topography, based on the temporary involvement of several neural sites during the subsequent phases of memory processing. In fact, it is possible to disrupt repetitively a chosen mnemonic phase without interfering with preceding or subsequent phases (Bures & Buresova, 1990). In other words, this approach makes it possible to acquire experimental information not only on the "where" of mnemonic processing, but also on the "when" and "how long." In particular, during consolidation, functional inactivations performed at different delays after acquisition may disclose the critical duration of the intact function at a given site. Evidently knowledge of the when and how long makes a considerable contribution to the understanding of memory and learning, which are essentially time-dependent functions.

The reversible inactivation of neural sites may be obtained by different methods, physical or pharmacological: focal (Brooks, 1983; Shefchyk, Jell, & Jordan, 1984) or total cooling (Handwerker, Iggo, & Zimmerman, 1975), administrations of various active compounds including neurotransmitter agonist

(muscimol, Martin, 1991), and antagonists (glutamate receptor blockers, Jerusalinsky, Ferreira, Walz, Da Silva, Bianchin, Rushel, Median, & Izquierdo, 1992), eliciting cortical spreading depression (Bures, Buresova, & Krivanek, 1974). Recently the focal injection of local anesthetics (lidocaine, tetracaine) has been employed to reversibly inactivate neural structures and/or central pathways (Albert & Madryga, 1980; Flicker & Geyer, 1982; Sandkuhler, Maisch, Gebhart, & Zimmerman, 1995). Tetrodotoxin (TTX) has been employed for the same purpose (Cahill, Coopersmith, Leon, & McGaugh, 1987; Zhuravin & Bures, 1991). It is possible to administer these compounds stereotaxically into deep subcortical neural sites. The time course and volumetric dimensions of the produced functional blockade are sufficiently well known (lidocaine: Sandkuhler, Maisch, & Zimmerman, 1987; Martin, 1991; TTX: Cahill et al., 1987, Zhuravin & Bures, 1991). Both lidocaine and TTX block the voltage-dependent sodium channels, so that they temporarily mimic the condition existing after an electrolytic lesions, but if they have a similar mode of action there is a marked difference in their efficiency. In fact, lidocaine (1 μ l of 4% lidocaine) produces a short-lasting blockade (about 20 min, Sandkuhler et al., 1987; Martin, 1991), while TTX blockade (10 ng in 1 μ l) is maximal 30–120 min after administration, decaying exponentially and completely disappearing within 24 h (Zhuravin & Bures, 1991). Consequently lidocaine and TTX are preferentially employed to induce short-lasting and long-lasting inactivations, respectively. Thus, independent of the specific characteristics of the employed blocking agent, for each compound there is a well-defined relationship between amount administered, volume of inactivated tissue, and inactivation duration (Zhuravin & Bures, 1991; Sandkuhler et al., 1987). According to Bures,

“Although the mechanisms of the TTX induced disruption remains obscure, it is conceivable that the permanent engram is supported during several days after the association by a process requiring continued impulse activity in some cerebral area. It is likely that the plastic change is maintained by a metabolic or morphogenetic process requiring continuous supply of trophic factors released at the storage site by impulse activity. Prolonged silence of the network may decrease the concentration of the putative trophic factors below the level indispensable for fixation of the plastic modification . . . It can be speculated that the prolonged impulse blockade in a network the connectivity of which has been recently changed by learning will interfere with the most recent modifications, the fixation of which may require continued input of neurotransmitters (e.g., catecholamines) as well synaptic drive maintaining the membrane potential of neuron at a level activating the intracellular plastic event.” (Bures, Buresova, & Ivanova, 1991)

Following this brief survey of the advantages of reversible inactivations in the study of learning and memory, we shall review recent experimental results obtained by this technique, particularly in research into the neural mechanisms of consolidation. The sites examined are arranged in topographical order, from medulla to neocortex.

NUCLEUS OF THE SOLITARY TRACT

Memory storage can be influenced by the peripheral administration of adrenergic hormones and drugs (Martinez, Jensen, Messing, Vasquez, Soumireu-Mourat, Geddes, Liang, & McGaugh, 1980). Since these compounds do not easily pass the blood–brain barrier (Weil-Malherbe, Axelrod, & Tomchick, 1959), the effect appears to be mediated by the stimulation of peripheral receptors (Introini-Collison, Saghofi, Novack, & McGaugh, 1992). The nucleus

of the solitary tract directly receives the sensorial input from visceral afferents (Sumal, Blessing, Joh, Reis, & Pickel, 1983), the stimulation of which may affect mnemonic functioning, by some not-yet-well-understood mechanism (McGaugh & Gold, 1989). According to some authors the nucleus of the solitary tract plays an essential role in memory modulation and its functional inactivation may diminish, therefore, the memory-enhancing effects of the above-mentioned peripherally administered compounds. In fact, although in Sprague-Dawley rats systemic posttraining administration of epinephrine facilitates training in a Y-maze retention paradigm, this effect is absent after lidocaine (2% in 0.5 μ l) inactivation of the solitary tract nucleus (Williams & McGaugh, 1993). Furthermore, these results confirm previous results obtained using a one-trial inhibitory avoidance paradigm (Sprague-Dawley rats; foot-shock intensity: 0.35 mA, 0.55 s). The administration of the same lidocaine dosage in the solitary tract nucleus was followed by retention impairment. Moreover, it has been shown that lidocaine effects are time-dependent. There were amnesic effects when 0.5 ml of lidocaine (2%) was injected immediately after training, but not if it was administered 2 h later (Williams & McGaugh, 1992). These findings support the hypothesis that the neural sites receiving vagal input (like the solitary tract nucleus) mediate the memory-modulating effects of the stimulation of peripheral receptors, which appear to be especially important during the posttraining interval. Apparently both hypothalamic and amygdalar monitoring and central feedback control of the regulation of autonomic and behavioral responses are based on neural information mediated by the nucleus of the solitary tract. The regulatory influence of these structures on mnemonic storage may be altered by the absence of visceral input.

The reciprocal connections between the solitary tract nucleus and the limbic structures are well established by electrophysiological and immunochemical findings (Rogers & Fryman, 1988). For instance, neurons in the central amygdalar nuclei become active after stimulation of the vagus nerve or of the nucleus of the solitary tract, and, conversely, neurons of the nucleus of the solitary tract are activated by stimulation of the amygdala as well as by the orthodromic stimulation of the hypothalamic paraventricular nucleus (Rogers & Fryman, 1988). In addition to the projections of the nucleus of the solitary tract to limbic structures involved in memory processes, some axons from this nucleus go to the parabrachial nuclei (Kawai, Takagi, Yanai, & Tohyama, 1988; Herbert, Moga, & Saper, 1990) which play an important role in the memorization of aversively motivated behaviors (Ivanova & Bures, 1990; Tassoni, Bucherelli, & Bures, 1992). These axons project both to the amygdala (Cechetto & Calaresu, 1983) and to the solitary tract nucleus (Papas & Ferguson, 1990). Thus, peripheral physiological influences modulating the activity of brain structures involved in memory processing follow more than one route. Not only medullar structures like the nucleus of the solitary tract, but also brainstem centers, like the parabrachial nuclei, appear to cooperate with more rostral centers, through well-developed reciprocal connections.

PARABRACHIAL NUCLEI

As mentioned above, the parabrachial nuclei complex projects both to the nucleus of the solitary tract and to the amygdala. By means of bilateral TTX (10 ng in 1 μ l) inactivation in Long-Evans rats trained in a step-through

passive avoidance response (footshock intensity: 1 mA, 5 s) it has been shown that this complex must be functionally intact for no less than 24 h in order to avoid retrograde amnesia. Unilateral inactivations were without effect (Tassoni, Bucherelli, & Bures, 1992b). On the other hand, using the same experimental procedure a memory impairment followed the unilateral functional inactivation of parabrachial nuclei if the contralateral amygdala was contemporaneously inactivated by TTX. This result has been interpreted as indicating an ipsilateral linkage between these two sites (Tassoni et al., 1992b). This hypothesis is further supported by the finding that the effect of the ipsilateral inactivation of both sites is not greater than that following the isolated inactivation of either of them (Tassoni et al., 1992b). The TTX inactivation technique was also employed to investigate the mnemonic role of parabrachial nuclei in other aversive paradigms, such as the conditioned taste aversion. It was found that their integrity was necessary during the consolidation phase of the conditioned response. In fact, in Long-Evans rats, TTX (10 ng in 1 μ l) injection at this site elicited retrograde amnesia when applied 1, 2, or 4 but not 8 days after CTA acquisition (Ivanova and Bures, 1990b).

In accord with previous results, using Wistar rats trained to learn a one-trial passive avoidance response, parabrachial nuclei studies have shown that the amnesic effect is directly related to the intensity of punishment (Bucherelli & Tassoni, 1992). When weak footshocks (0.8 mA, 3 s) were delivered, functional ablation of the parabrachial nuclei was still effective when induced up to 8 days after acquisition training. On the other hand, when rats were shocked with stronger stimuli (1.2 mA, 3 s) 2 days after acquisition the functional ablation was no longer effective. Moreover, effects of TTX (10 ng in 1 μ l) blockade of parabrachial nuclei on conditioned taste aversion learning indicate that, in Long-Evans rats, amnesia was considerably attenuated when TTX was used after repeated saccharin-LiCl pairings, a result consonant with the notion that overtraining increases the strength of the memory trace, its resistance to amnesic agents, or both (Ivanova & Bures, 1990b).

SUBSTANTIA NIGRA

This structure is a constituent of two dopaminergic systems [the nigrostriatal bundle and the mesolimbic-mesocortical dopaminergic projection (Moore & Bloom, 1978)] and forms important connections with the striatum. Concerning its involvement in passive avoidance conditioning, it is believed to be subordinate to the caudate-putamen. This hierarchical arrangement was proposed on the basis of the finding that long-lasting electrical stimulation of the caudate-putamen or of the substantia nigra disrupted passive avoidance retention, while only caudate-putamen stimulation caused amnesic effects after connections with substantia nigra were cut (Fibiger & Phillips, 1976). TTX (10 ng in 1 μ l, Wistar rats) inactivation did not confirm these conclusions. In fact, it was found that an intact caudate-putamen is necessary for passive avoidance consolidation (footshock intensity: 1.2 mA, 5 s) for no less than 1.5 h after acquisition (Ambrogi Lorenzini, Baldi, Bucherelli, & Tassoni, 1995). This interval is much shorter than that reported for the substantia nigra (24 h); consequently, it seems that the latter structure plays a more important role than the former structure. The functional importance of the substantia nigra is further underscored by the fact that even its unilateral TTX inactivation

disrupts passive avoidance consolidation when applied during the first 15 min after acquisition (Ambrogi Lorenzini, Baldi, Bucherelli, & Tassoni 1994b).

HIPPOCAMPUS

It is now generally accepted that hippocampal integrity is essential for spatial learning (O'Keefe, 1983; Redish & Touretzky, 1997). The evidence was obtained not only from lesion studies but also from functional ablation experiments, like those on working memory in a modified version of the Morris water maze task, in which hippocampal inactivation was induced by lidocaine (4%, 1 μ l) (Bohbot, Othall, Liu, Nadel, & Bures, 1996).

On the other hand, the hippocampus is surely associated also with aver- sively motivated behavior. Recently, the role of the dorsal and the ventral hippocampus in consolidation of passive avoidance reaction was investigated by means of reversible TTX (10 ng in 1 μ l, Wistar rats) inactivations. The two sites were studied separately because of their functional differentiation (Nadel, 1968; Moser, Moser, & Andersen, 1993). It was found that both sites are necessary for passive avoidance response (footshock intensity: 1.2 mA, 3 s) consolidation (bilateral, but not unilateral, inactivation is followed by passive avoidance response disruption). Temporal involvement of the two sites was different: dorsal hippocampus integrity was required for 90 min (Ambrogi Lorenzini, Baldi, Bucherelli, Sacchetti, & Tassoni, 1996) and the ventral for only 15 min (Ambrogi Lorenzini, Baldi, Bucherelli, Sacchetti, & Tassoni, 1997) after acquisition. The difference is thought to be due to the distinct functional characteristics of the two parts of the hippocampus. The dorsal hippocampus appears to be preferentially involved in tasks requiring the use of place strategy (Winocur & Bindra, 1976; Black, Nadel, & O'Keefe, 1977; Baker, Kesner, & Michal, 1981; Kesner & Hardy, 1983), whereas the ventral hippocampus appears to be involved in fear evaluation and elaboration. This contention is supported by the well-developed connections of the ventral hippocampus with amygdala (Ottersen, 1982; Moser et al., 1993).

From a general point of view, it is thought that posttraining mnemonic processing in the hippocampus is modulated by the amygdalae (Packard, Cahill, & McGaugh, 1994). Indeed, in that phase long-term potentiation is present both in the hippocampus and in the amygdala (Ikegaya, Saito, & Abe, 1995, 1996). The close functional relationship between the two structures is further supported by the finding that to avoid memory disruption the dorsal hippocampus and amygdala must be functionally intact for the same postacquisition duration (1.5 h) (Bucherelli, Tassoni, & Bures, 1992), although the amygdala projects mainly to the ventral hippocampus.

NUCLEUS BASALIS MAGNOCELLULARIS

This structure is a component of the cholinergic basal forebrain system (Mesulam, Mufson, Wainer, & Levey, 1983). Its role in mnemonic processing is based on both experimental and clinical evidence. Severe memory impairment in Alzheimer disease patients is accompanied by the decrease of hippocampal and cortical cholinergic acetylcholinesterase activity and by evident cell loss in the basal forebrain (Coyle, Price, & DeLong, 1983).

TTX inactivation experiments have shown that consolidation requires intact function of this structure for the longest reported duration at present: in the Wistar rat, no less than 48 h after acquisition of a passive avoidance task (footshock intensity: 1.2 mA, 3 s) in the case of bilateral TTX (10 ng in 1 μ l) administration and no less than 6 h in the case of unilateral administration (Ambrogi Lorenzini, Baldi, Bucherelli, & Tassoni, 1994a). These findings are consonant with previous assessments of the importance of the nucleus basalis magnocellularis for the integration of subcortical functions (Goldman & Coté, 1991) and for regulation of neocortical activity (Lo Conte, Casamenti, Bigi, Milaneschi, & Pepeu, 1982; Riekkinen, Riekkinen, Sirvio, Miettinen, & Riekkinen, 1992). Well-developed connections with neocortex (Saper, 1984; Dunnett, Toniolo, Fine, Ryan, Bjorklund, & Iversen, 1985; Lamour, Dutar, & Jobert, 1994), and amygdala (Todd & Kesner, 1978; Emson, Paxinos, Le Gal La Salle, Ben-Ari, & Silver, 1979; Carlsen, Zaborsky, & Heimer, 1985; Dunnett et al., 1985) support the hypothesis that this structure generates both ascending and descending influences on memory processes. Its importance for memory is further underscored by the finding that passive avoidance response loss following the lesion of nucleus basalis magnocellularis was recovered after transplantation of embryonal ventral forebrain grafts into neocortex (Dunnett et al., 1985; Fine, Dunnett, Bjorklund, & Iversen, 1985).

AMYGDALA

There is an important body of evidence showing that the amygdalar complex plays a role in emotionally loaded memory (Davis, 1992). It has been shown that posttraining manipulations of the amygdala affect retention of a number of aversively motivated tasks. Recently it was reported that lidocaine (2%, 0.5 μ l) infusion into the amygdala immediately after acquisition of an inhibitory avoidance task or of a shift in reward magnitude impairs subsequent retention. In the latter paradigm rats trained to run in a straight alley for a large food reward transiently exhibit longer latencies after reward magnitude has been reduced (the so called "Crespi effect," or "negative behavioral contrast," Crespi, 1942; Flaherty, 1982). It has been shown that Sprague-Dawley rats receiving, immediately after reduction of reward magnitude, bilateral infusion of lidocaine (2% solution, 0.5 μ l/side) into the amygdala exhibited significantly shorter latencies on the second day of reduced reward training than did rats given phosphate buffer infusions. The results suggest that lidocaine blockade of the amygdala impairs the memory of reward magnitude reduction (Salinas, Packard, & McGaugh, 1993).

According to some reports, mnemonic involvement of amygdala is lateralized (Coleman-Mesches & McGaugh, 1995a, 1995b). Unilateral infusion of lidocaine (2%, 1 μ l) attenuated the reduced reward-memory effect in Sprague-Dawley rats, but the effect was more marked following inactivation of the right amygdala than after inactivation of the left amygdala (Coleman-Mesches, Salinas, & McGaugh, 1996).

It was proposed that reduction in reward magnitude elicits aversive emotional responses similar to those induced by punishment (Amsel, 1958, 1962). Amygdalar involvement in aversively motivated learning is indicated by the necessity of this structure for the full expression of an inhibitory performance. In fact, postacquisition TTX (10 ng in 1 μ l) inactivation of both amygdalae is

followed by severe impairment of passive avoidance retention in Long–Evans rats (footshock intensity: 1 mA, 5 s) (Bucherelli et al., 1992), while unilateral inactivations are without effect (Tassoni, Bucherelli, & Bures, 1992). The amnesic effect was significant for acquisition–TTX administration delays up to 90 min. At longer delays (6 h) no amnesia was observed. These data confirm the time window of amygdalar involvement reported by authors using selective pharmacological blocking agents (Izquierdo, Medina, Bianchin, Walz, Zanatta, Da Silva, Bueno E Silva, Ruschel, & Paczko, 1993; Jerusalinsky et al., 1992). Furthermore, it has been shown by passive avoidance studies that there is a subnuclear functional specificity within the amygdala: amnesia induced by posttraining amygdalar inactivation appears to be mediated by the selective blockade of the basolateral complex. In fact, in Sprague–Dawley rats injection of 0.25 μ l of lidocaine (4% dissolved in phosphate-buffered saline) into the basolateral complex disrupts passive avoidance consolidation (footshock intensity: 0.45 mA, 1 s), while injection of the same compound into the central nucleus has no effect (Parent & McGaugh, 1994): the amnesic effects of lidocaine were present for acquisition–administration delays of up to 6 h and were absent after a 24-h delay. Moreover, immediate posttraining infusion of the same dosage of lidocaine impaired the retention performance of rats trained with stronger footshocks (0.7 mA) but not if the lidocaine was injected 6 h after training.

From these results it may be concluded that the amygdalar basolateral complex is active immediately after acquisition and is subsequently indispensable for the consolidation of inhibitory learning for durations inversely related to the intensity of punishment (more severe stimulation accelerating the consolidation process) (Gold, Hankins, Edwards, Chester, & McGaugh, 1974). Its functional integrity appears to be necessary for at least 6 h. These conclusions are consistent with other results showing that amygdalar central and basolateral nuclei mnemonic involvement varies according to the type of learning (Kesner, Walser, & Winzenried, 1989; Ambrogi Lorenzini, Bucherelli, Giachetti, Mugnai, & Tassoni, 1991; Hatfield, Graham, & Gallagher, 1992).

It must be stressed, however, that the amygdala does not participate in the consolidation of all forms of aversive conditioning. For instance, the amygdala does not play a role in the consolidation of the conditioned taste aversion long-term engrams. In this aversive paradigm amygdalar TTX (1 μ l of 10 ng diluted in physiological saline) inactivation was followed by amnesic effects only when induced within 1.5 h after application of the toxic US (0.15 M LiCl, 2% body weight), i.e., when there were visceral symptoms of poisoning, and was ineffective when applied at the 6-h postacquisition delay. Thus, the amygdala appears to be involved in the association of gustatory short-term memory with the visceral symptoms of poisoning, but there is no evidence indicating that it participates in the consolidation of the long-term engram of conditioned taste aversion (Roldan & Bures, 1994).

MEDIAL SEPTAL AREA

The medial septal area, consisting of the medial septum and the vertical limb of the diagonal band, is the main subcortical source of cholinergic projections to the hippocampus via the fimbria–fornix complex (McKinney, Coyle, & Hedreen, 1983). Irreversible lesion studies have shown that this neural com-

plex is an important component of the central circuits implementing passive avoidance conditioning (Wishart & Mogenson, 1970; Thomas, 1972). Functional inactivation of the medial septal area has yielded contrasting results in two studies using the same inactivating agent (TTX). In one, TTX (5 ng in 1 μ l) administered to Long-Evans rats 5 or 90 min after PAR acquisition elicited significant amnesia, but there was no amnesic effect when TTX was applied 360 min after acquisition (Rashidy-Pour, Motaghd-Larijani, & Bures, 1996). In another study, in Wistar rats postacquisition TTX (5 ng in 0.5 μ l) administration did not disrupt consolidation of passive avoidance response, but interfered with acquisition and retrieval (Ambrogi Lorenzini, Baldi, Bucherelli, & Tassoni, 1996). The contrasting results may be due to the different paradigms employed. In the first study the rats were subjected to a single, short punishment (1 mA, 1.5 s), while in the second they received two sets of unavoidable footshocks (1.2 mA, 3 s). In agreement with other results it is conceivable that the memory trace in the second study was stronger than in the first study and was, therefore, less easily disrupted.

Close connections between the medial septal area and the hippocampus are well known (Bland & Bland, 1986). Irreversible lesions either of the medial septal area or of septo-hippocampal connections were generally followed by learning deficits similar to those observed after hippocampal damage (Gray & McNaughton, 1983). On the other hand, the absence of amnesic effects caused by postacquisition inactivation were taken as evidence of the functional independence of these two structures, at least during consolidation of passive avoidance engrams (Ambrogi Lorenzini et al., 1996). In rats, the effects of 0.5 μ l of tetracaine (2%) inactivation of the medial septal area on radial maze performance were used to assess contribution of this structure to distinct aspects of spatial information processing. It was concluded that "septal activation is required for acquisition of spatial information, but septal inactivation failed to affect storage or maintenance of spatial information" (Mizumori, Perez, Alvarado, Barnes, & McNaughton, 1990).

Data on the role of the medial septum in spatial learning were provided by a study describing in Long-Evans rats the effects of TTX (10 ng in 1 μ l) or lidocaine (4%, 1 μ l) inactivations of the medial septum on reference and working memories in the Morris water maze. Posttraining administration of TTX or lidocaine failed to affect consolidation of reference and working memories, while preacquisition or preretrieval administration caused amnesic effects (Rashidy-Pour, Motamedi, & Motaghd-Larijani, 1996). It may be concluded that functional integrity of the medial septal area is necessary for acquisition and retrieval of spatial reference memory, but its involvement in postacquisition is unlikely (Rashidy-Pour et al., 1996).

STRIATUM

In addition to the hippocampus and amygdala, the dorsal striatum may also play a role in mnemonic processing. It has been suggested that although these three structures act in parallel, each of them may mediate acquisition of a distinct type of information. Three systems have been proposed: the first, including the hippocampus, acquires information on relationships among stimuli and events. The second, including the amygdala, mediates rapid acquisition of behaviors based on biologically signifi-

cant events possessing affective connotations. The third, including the striatum, mediates formation of reinforced stimulus–response associations (Izquierdo et al., 1993; McDonald & White, 1993).

All three sites can influence memory by cholinergic–dopaminergic interactions (Gasbarri, Introini-Collison, Packard, Pacitti, & McGaugh, 1993). Some findings indicate that posttraining modifications of dopaminergic activity influence retention: intracerebroventricular administration of dopamine improves retention of an inhibitory avoidance response (Haycock, Van Burskirk, Rayn, & McGaugh, 1977). These structures could constitute, alone or with other structures, a mnemonic circuit parallel to the limbic system.

To assess the role of the striatum in mnemonic processing, TTX (10 ng in 1 μ l) was employed to inactivate the caudate-putamen of Wistar rats either totally, or, on the basis of its peculiar morphology, to inactivate separately each of its three parts (anterior, intermediate, posterior). It was shown that only the intermediate part was necessary for formation of passive avoidance response memories (footshock intensity: 1.2 mA, 3s) (Ambrogi Lorenzini et al., 1995). The other two subdivisions (anterior and posterior) were not involved in passive avoidance response memorization (Ambrogi Lorenzini et al., 1995; Bermudez-Rattoni, Introini-Collison, & McGaugh, 1991 (3 ng in 0.5 μ l of citrate/phosphate buffer; footshock intensity: 0.53 mA, 0.7 s, Sprague–Dawley rats). Since PAR retention was also disrupted by the inactivation of the nucleus accumbens and globus pallidus, it was proposed that all main parts of the corpus striatum contribute to PAR consolidation (Ambrogi Lorenzini et al., 1995). Experimental evidence obtained in the above studies again indicates a negative correlation between the amnesic effect of reversible inactivation and the intensity of stimulation. Retention deficits after the lidocaine inactivation of striatum (2%, 1 μ l, Wistar rats) were observed only after very low footshock intensities (footshock intensities: 0.2, 0.3 mA). One interpretation is that stronger footshocks (0.4 mA) induce activation of several parallel elements of the consolidation circuit, which cannot be disrupted as in the case of circumscribed inactivations (Perez-Ruiz & Prado-Alcalá, 1989).

OLFACTORY BULB

Does the olfactory bulb play a role in the consolidation of newly acquired olfactory information? This question has been addressed recently by Mouly, Kindermann, Gervais, and Holley (1993). Instead of adequate chemical olfactory stimuli, multisite electrical stimuli (50 Hz) were employed, administered by means of electrodes implanted close to the output neurons of the olfactory bulb (large mitral cells). The apparent information was perceived as olfactory (Mouly, Vigouroux, & Holley, 1985; Mouly & Holley, 1986). Lidocaine (2%, 2 μ l) was injected in Wistar rats into the olfactory bulb at different delays after each training session, and the effects on acquisition and retention of a conditioned response (olfactory learning) were observed. Posttraining inactivation of olfactory neurons moderately impaired the acquisition of the associative task in a daily training schedule and severely impaired its retention after 5 days. There was mnemonic disruption when lidocaine was administered immediately after each training session, but not after a 2-h delay. It was concluded that the immediate lidocaine administration caused a retention impairment, with the

impairment exhibiting a temporal gradient: it begins after 24 h (slight alteration of final acquisition scores) and becomes more severe after 5 days.

NEOCORTEX

The mnemonic role of the neocortex in the consolidation phase was studied using both TTX [Bermudez-Rattoni, Intronini-Collison, & McGaugh, 1991 (3 ng in 0.5 μ l of citrate/phosphate buffer: footshock intensity: 0.35 mA, 0.7 s, Sprague-Dawley rats); Tassoni, Bucherelli, & Bures, 1992c (10 ng in 1 μ l of saline solution, footshock intensity: 1 mA, 1 s, Long-Evans rats)] and lidocaine (2%, 1 μ l, Wistar rats; footshock intensity: 0.4 mA) inactivations (Perez-Ruiz et al., 1989). The inactivating compounds were administered during the postacquisition period in several areas (insular, frontal, parietal, perirhinal). TTX inactivation of insular cortex significantly impaired conditioned performance of a one-trial inhibitory avoidance task (Bermudez-Rattoni et al., 1991). Frontal or parietal TTX inactivations did not significantly disrupt retention (Bermudez-Rattoni et al., 1991; Tassoni et al., 1992c). Administration of lidocaine (2%, 1 μ l) in the parietal cortex had no amnesic effect (Perez-Ruiz et al., 1989). Similar results were obtained when a spatial learning task was employed (Bermudez-Rattoni, Intronini-Collison, & McGaugh, 1991). Thus it may be concluded that insular cortex plays a role in aversive and spatial learning, consistent with the assessment of the insular cortex as a multimodal brain area concerned with the perception of temporal patterns of several classes of sensory stimuli (Colavita, Szeligo, & Zimmer, 1974; Colavita & Weisberg, 1979).

CONCLUDING REMARKS

As pointed out in the Introduction, the fully reversible functional inactivation of circumscribed neural sites is a useful tool for plotting the brain map of mnemonic processes. In fact, by means of this technique it is possible to superimpose on the spatial map (topography of the memory-related centers and circuits obtained by means of permanent lesions) the temporal dimension (chronology of the duration during which a given neural structure must participate in memory processing). A further advantage of this technique derives from the possibility of employing more than one inactivating agent like lidocaine and TTX, to name only two. Both compounds block the voltage-dependent sodium channels, the first for a very short period (minutes), the second for much longer period (hours). This means that there are tools appropriate for the quantitative analysis of mnemonic phenomena with quite different time courses. Amnesic affect magnitude and(or) duration are related to the administered dosage of the inactivating compound (for lidocaine sometimes a 2% concentration was ineffective, but the 4% concentration was effective). Generally speaking, this means that it may be risky to draw definitive conclusions on the function of a given neural site just from the results of a simple dosage experiment. In fact, it is well known that the possibility and degree of engram manipulation are related both to the amount of training and to the strength of posttraining treatments.

By means of this technique it has been possible not only to characterize the sequential involvement of neural sites in memory processes, but also to define

with more precision the functional relationship between neural sites, to clarify the hierarchical relationships between anatomically connected structures, and to determine the relative roles of the specific subcomponents of complex centers (hippocampus, amygdala, caudate-putamen), thus improving our understanding of mnemonic processing. It is nevertheless true that not all reported findings are completely in accord (Rashidy-Pour et al., 1996; Ambrogi Lorenzini et al., 1996). Some of these discrepancies can be explained by the different experimental protocols employed and particularly by the intensities of the aversive stimuli. It has been repeatedly confirmed by several of the reviewed papers (Gold et al., 1975; Parent and McGaugh, 1994; Bucherelli & Tassoni, 1992) that there is a positive correlation between footshock intensity and the speed and robustness of engram consolidation. It may be more useful to administer lidocaine (or its related compounds) for preacquisition investigation, because the short inactivation may disrupt only the acquisition phase, without overlap with the early consolidation period. On the same grounds, lidocaine may be quite useful for a fine assessment of consolidation time course, in order to reveal recruitment or drop-out phenomena, when neural structures are recruited only some time after the beginning of consolidation. On the other hand, a limit to lidocaine usefulness derives from the short duration of the induced inactivation compared to the longer duration of TTX. In some instances this short duration may be insufficient to cause retrograde amnesia (Bures & Buresova, 1990).

There are other studies in which the reversible inactivation technique has been used and in which the inactivating compounds were either neurotransmitter antagonists or more or less specific inhibitors of subcellular processes. We have restricted the present review to studies in which either local anesthetics (lidocaine or tetracaine) or TTX was employed, because by means of these compounds one obtains a generalized blockade of neuronal function, due to their action on voltage-dependent sodium channels. Therefore this kind of inactivation is quite distinct from those caused by selective interferences related to specific neurotransmitter action or to specific subcellular mechanisms. It must be underscored that the use of the latter compounds has contributed to the understanding of the specific mechanisms underlying mnemonic functions. By using such techniques information is obtained, not so much about the function of a neural site, but rather about the function(s) of some of its neuronal components or of some subcellular mechanism. Thus, these results lie outside the scope of the present review. A further consideration may be added. Functional inactivations induced by TTX or local anesthetics can reveal the critical spatial and chronological characteristics of a mnemonic process. It is on the basis of this information that more specific studies can be designed. For instance, how should one evaluate the finding that to learn a given conditioned response (e.g., rat's passive avoidance) during consolidation more than one subcortical site is critically active at the same time? In order to go beyond the legitimate conclusion that each site is necessary, more complex experimental designs may be employed. Combined inactivation, either uni- or bilateral, of more than one site may give useful information on the influences that single sites of an hypothetic circuit may exert on one another (Tassoni et al., 1992).

As stated in the Introduction, the reviewed findings were presented in caudo-rostral topographical sequence. This kind of presentation appeared to be the simplest one, given the ascending polarization of sensory input and of its successive elaborations. Concerning topography, it may be observed that very

caudal structures like the nucleus of the solitary tract play an important role in mnemonic processing.

Results concerning engram consolidation have been reviewed. In fact, engram consolidation is the mnemonic phase during which the reversible inactivation technique may be, and has been, employed most advantageously on the largest number of sites, as shown by the reported findings. It must be pointed out, however, that the same technique, conditions permitting, makes it possible to examine the neural processes implementing acquisition and retrieval of memories (Ivanova & Bures, 1990b; Mizumori et al., 1990; Bielavska & Bures, 1994; Coleman-Meschers et al., 1995; Ambrogio Lorenzini et al., 1996a, 1996b, 1997; Floresco, Seamans, & Phillips, 1996; Ambrogio Lorenzini, Baldi, Bucherelli, Sacchetti, & Tassoni, in press).

REFERENCES

- Albert, D. J., & Madryga, F. J. (1980). An examination of the functionally effective spread of 4 μ l of slowly infused lidocaine. *Behavioural and Neural Biology*, **29**, 378–384.
- Ambrogio Lorenzini, C., Baldi, E., Bucherelli, C., Sacchetti, B., & Tassoni, G. (1996a). Role of dorsal hippocampus in acquisition, consolidation and retrieval of rat's passive avoidance response: A tetrodotoxin functional inactivation study. *Brain Research*, **730**, 32–39.
- Ambrogio Lorenzini, C., Baldi, E., Bucherelli, C., Sacchetti, B., & Tassoni, G. (1997). Role of the ventral hippocampus in acquisition, consolidation and retrieval of rat's passive avoidance response memory trace. *Brain Research*, **768**, 242–248.
- Ambrogio Lorenzini, C., Baldi, E., Bucherelli, C., Sacchetti, B., & Tassoni, G. Temporal characterization of subcortical nuclei in mnemonic processes: Results of tetrodotoxin reversible studies in the rat. *Archives Italiennes de Biologie*, in press.
- Ambrogio Lorenzini, C., Baldi, E., Bucherelli, C., & Tassoni, G. (1994a). Post-training nucleus basalis magnocellularis functional tetrodotoxin blockade effects on passive avoidance consolidation in the rat. *Behavioural Brain Research*, **61**, 191–196.
- Ambrogio Lorenzini, C., Baldi, E., Bucherelli, C., & Tassoni, G. (1994b). Passive avoidance response disruption by post-training substantia nigra functional tetrodotoxin inactivation in the rat. *Archives Italiennes de Biologie*, **132**, 85–92.
- Ambrogio Lorenzini, C., Baldi, E., Bucherelli, C., & Tassoni, G. (1995). Time-dependent deficits of rat's memory consolidation induced by tetrodotoxin injections into the caudate-putamen, nucleus accumbens, and globus pallidus. *Neurobiology of Learning and Memory*, **63**, 87–93.
- Ambrogio Lorenzini, C., Baldi, E., Bucherelli, C., & Tassoni, G. (1996b). Amnesic effect of pre-acquisition, post-acquisition or pre-retrieval tetrodotoxin administration into the medial septal area on rat's passive avoidance memorization. *Neurobiology of Learning and Memory*, **66**, 80–84.
- Ambrogio Lorenzini, C., Bucherelli, C., Giachetti, A., Mugnai, L., & Tassoni, G. (1991). Effects of nucleus basolateralis amygdalae neurotoxic lesions on aversive conditioning in the rat. *Physiology and Behavior*, **49**, 765–770.
- Amsel, A. (1958). The role of frustrative nonreward in noncontinuous reward situations. *Psychology Bulletin*, **55**, 102–119.
- Amsel, A. (1962). Frustrative nonreward in partial reinforcement and discrimination learning. *Psychology Review*, **69**, 306–328.
- Baker, L. J., Kesner, R. P., & Michal, R. E. (1981). Differential effects of a reminder cue on amnesia induced by stimulation of amygdala and hippocampus. *Journal of Comparative Physiology and Psychology*, **95**, 312–321.
- Bermudez-Rattoni, F., Introini-Collison, I. B., & McGaugh, J. L. (1991). Reversible inactivation of the insular cortex by tetrodotoxin produces retrograde and anterograde amnesia for inhibitory avoidance and spatial learning. *Proceedings of the National Academy of Sciences of the USA*, **88**, 5379–5382.

- Bielavska, E., & Bures, J. (1994). Universality of parabrachial mediation of conditioned taste aversion. *Behavioural Brain Research*, **60**, 35–42.
- Black, A. H., Nadel, J., & O'Keefe, J. (1977). Hippocampal function in avoidance learning and punishment. *Psychology Bulletin*, **84**, 1107–1129.
- Blakemore, C. (1977). *Mechanics of the mind*. Cambridge Univ. Press, Cambridge.
- Bland, B. H., & Bland, S. K. (1986). Medial septal modulation of hippocampal theta discharges. *Brain Research*, **375**, 102–111.
- Bohbot, V., Otahal, P., Liu, Z., Nadel, L., & Bures, J. (1996). Electroconvulsive shock and lidocaine reveal rapid consolidation of spatial working memory in the water maze. *Proceedings of the National Academy of Sciences of the USA*, **93**, 4016–4019.
- Brazier, M. A. B. (1959). The historical development of neurophysiology. In J. Field, H. W. Magoun, V. E. Hall, (Eds.), *Handbook of physiology, Section 1, Neurophysiology*. (Vol. 1, pp. 1–58). Am. Physiol. Assoc., Baltimore, MD.
- Brooks, V. B. (1983). Study of brain function by local, reversible cooling. *Reviews of Physiology, Biochemistry and Pharmacology*, **95**, 1–109.
- Bucherelli, C., & Tassoni, G. (1992). Duration of retrograde amnesia induced by tetrodotoxin inactivation of the parabrachial nuclei is inversely related to the intensity of footshock in rat's passive avoidance response. *Behavioural Brain Research*, **49**, 175–180.
- Bucherelli, C., Tassoni, G., & Bures, J. (1992). Time-dependent disruption of passive avoidance acquisition by post-training intra-amygdala injection of tetrodotoxin in rats. *Neuroscience Letters*, **140**, 231–234.
- Bures, J., & Buresova, O. (1990). Reversible lesions allow reinterpretation of system level studies of brain mechanisms of behavior. *Concepts in Neuroscience*, **1**, 69–89.
- Bures, J., Buresova, O., & Ivanova, S. F. (1991). Brain stem mechanisms of conditioned taste aversion learning in rats. *Archives Internationales de Physiologie et Biochimie*, **99**, A131–A134.
- Bures, J., Buresova, O., & Krivanek, J. (1974). *The mechanisms and applications of Leao's spreading depression of electroencephalographic activity*. New York: Academic Press.
- Cahill, L., Coopersmith, R. M., Leon, M., & McGaugh, J. L. (1987). Local injection of tetrodotoxin decreases metabolic activity in discrete brain regions: A 2-deoxyglucose autoradiography analysis. *Society of Neuroscience Abstracts*, **13**, 1414.
- Carlsen, J., Zaborsky, L., & Heimer, L. (1985). Cholinergic projections from the basal forebrain to the basolateral amygdaloid complex: A combined retrograde fluorescent and immunohistochemical study. *Journal of Comparative Neurology*, **234**, 155–167.
- Cechetto, D. F., & Calaresu, F. R. (1983). Response of single units in the amygdala to stimulation of buffer nerves in cat. *American Journal of Physiology*, **244**, R646–R651.
- Colavita, F. B., Szeligo, F. V., & Zimmer, S. D. (1974). Temporal pattern discrimination in cats with insular-temporal lesions. *Brain Research*, **79**, 153–156.
- Colavita, F. B., & Weisberg, D. H. (1979). Insular cortex and perception of temporal patterns. *Physiology and Behavior*, **22**, 827–829.
- Coleman-Meschers, K., & McGaugh, J. L. (1995a). Differential effects of pretraining inactivation of the right or left amygdala on retention of inhibitory avoidance training. *Behavioural Neuroscience*, **109**, 642–647.
- Coleman-Meschers, K., & McGaugh, J. L. (1995b). Differential involvement of the right or left amygdalae in expression of memory for aversively motivated training. *Brain Research*, **670**, 75–81.
- Coleman-Meschers, K., Salinas, J. A., & McGaugh, J. L. (1996). Unilateral amygdala inactivation after training attenuates memory for reduced reward. *Behavioural Brain Research*, **77**, 175–180.
- Coyle, J. T., Bird, S. J., Evans, R. H., Gulley, R. L., Nadler, J. V., Nicklas, W. J., & Olney, J. W. (1981). Excitatory aminoacids and neurotoxins: Selectivity, specificity and mechanism of action. *Neuroscience Research Progress Bulletin*, **19**, 335–427.
- Coyle, J. T., Price, D. L., & DeLong, M. R. (1983). Alzheimer's disease: A disorder of cortical cholinergic innervation. *Science*, **219**, 1184–1190.
- Crespi, L. P. (1942). Quantitative variation in incentive and performance in the white rat. *American Journal of Psychology*, **55**, 467–517.

- Davis, M. (1992). The role of the amygdala in fear and anxiety. *Annual Review of Neuroscience*, **15**, 353–375.
- Dunnett, S. B., Toniolo, G., Fine, A., Ryan, C. N., Bjorklund, A., & Iversen, S. D. (1985). Transplantation of embryonic ventral forebrain neurons to the neocortex of rats with lesions of nucleus basalis magnocellularis. II. Sensorimotor and learning impairments. *Neuroscience*, **16**, 787–798.
- Emson, P. C., Paxinos, G., Le Gal La Salle, G., Ben-Ari, Y., & Silver, A. (1979). Cholinergic acetyltransferase and acetylcholinesterase containing projections from the basal forebrain to the amygdaloid complex of the rat. *Brain Research*, **165**, 271–282.
- Fibiger, H. C., & Phillips, A. G. (1976). Retrograde amnesia after electrical stimulation of the substantia nigra: Mediation by the dopaminergic nigro-neostriatal bundle. *Brain Research*, **116**, 23–33.
- Fine, A., Dunnett, S. B., Bjorklund, A., & Iversen, S. D. (1985). Cholinergic ventral forebrain grafts into neocortex improve passive avoidance memory in a rat model of Alzheimer disease. *Proceedings of the National Academy of Sciences of the USA*, **82**, 5227–5230.
- Flaherty, C. F. (1982). Incentive contrast: A review of behavioral changes following shifts in reward. *Animal Learning and Behavior*, **10**, 409–440.
- Flicker, C., & Geyer, M. A. (1982). Behavior during hippocampal microinfusion. III. Lidocaine versus picrotoxin. *Brain Research Review*, **4**, 129–136.
- Floresco, S. B., Seaman, J. K., & Phillips, A. G. (1996). Differential effects of lidocaine into the ventral CA1/subiculum or the nucleus accumbens on the acquisition and retention of spatial information. *Behavioural Brain Research*, **81**, 163–171.
- Gasbarri, A., Introini-Collison, I. B., Packard, M. G., Pacitti, C., & McGaugh, J. L. (1993). Interaction of cholinergic–dopaminergic systems in the regulation of memory storage in aversively motivated learning task. *Brain Research*, **627**, 72–78.
- Gold, P. E., Hankins, L., Edwards, R. M., Chester, J., & McGaugh, J. L. (1975). Memory interference and facilitation with posttrial amygdala stimulation: Effect on memory varies with footshock level. *Brain Research*, **86**, 509–513.
- Goldman, J., & Coté, L. (1991). Aging of the brain: Dementia of the Alzheimer's type. In H. Kandel, J. H. Schwartz, & T. M. Jessel (Eds.), *Principles of neural science* (3rd ed., pp. 974–983). New York: Elsevier.
- Gray, J. A., & McNaughton, N. (1983). Comparison between the behavioural effects of septal and hippocampal lesions: A review. *Neuroscience Biobehavioural Review*, **7**, 119–188.
- Handwerker, H. O., Iggo, A., & Zimmerman, M. (1975). Segmental and supraspinal actions on dorsal horn neurons responding to noxious and non-noxious skin stimuli. *Pain*, **1**, 145–165.
- Hatfield, T., Graham, P. W., & Gallagher, M. (1992). Taste-potentiated odor aversion learning: Role of the amygdaloid basolateral complex and central nucleus. *Behavioural Neuroscience*, **106**, 286–293.
- Haycock, J. W., Van Burskirt, R., Rayn, J. R., & McGaugh, J. L. (1977). Enhancement of retention with centrally administered catecholamines. *Experimental Neurology*, **54**, 199–208.
- Herbert, H., Moga, M. M., & Saper, C. B. (1990). Connections of the parabrachial nucleus with the nucleus of the solitary tract and the medullary reticular formation in the rat. *Journal of Comparative Neurology*, **293**, 540–580.
- Horsley, V., & Clarke, R. H. (1908). The structure and functions of the cerebellum examined by a new method. *Brain*, **31**, 45–124.
- Ikegaya, Y., Saito, H., & Abe, K. (1995). Requirement of basolateral amygdala neuron activity for the induction of long-term potentiation in the dentate gyrus in vivo. *Brain Research*, **671**, 351–354.
- Ikegaya, Y., Saito, H., & Abe, K. (1996). The basomedial and basolateral amygdaloid nuclei contribute to the induction of long-term potentiation in the dentate gyrus in vivo. *European Journal of Neuroscience*, **8**, 1833–1839.
- Introini-Collison, I. B., Saghafi, D., Novack, G., & McGaugh, J. L. (1992). Memory-enhancing effects of post-training dipivefrin and epinephrine: Involvement of peripheral and central adrenergic receptors. *Brain Research*, **572**, 81–86.
- Ivanova, S. F., & Bures, J. (1990a). Acquisition of conditioned taste aversion in rats is prevented

- by tetrodotoxin blockade of a small midbrain region centered around the parabrachial nuclei. *Physiology and Behavior*, **48**, 543–549.
- Ivanova, S. F., & Bures, J. (1990b). Conditioned taste aversion is disrupted by prolonged retrograde effects of intracerebral injection of tetrodotoxin in rats. *Behavioural Neuroscience*, **104**, 948–954.
- Izquierdo, I., Medina, J. H., Bianchin, M., Walz, R., Zanatta, M. S., Da Silva, R. C., Bueno e Silva, M., Ruschel, A. C., & Paczko, N. (1993). Memory processing by the limbic system: Role of specific neurotransmitter systems. *Behavioural Brain Research*, **58**, 91–98.
- Jerusalinsky, D., Ferreira, M. B. C., Walz, R., Da Silva, R. C., Bianchin, M., Ruschel, A., Median, J. H., & Izquierdo, I. (1992). Amnesia by infusion of glutamate receptor blockers into the amygdala, hippocampus and entorhinal cortex. *Behavioral and Neural Biology*, **58**, 76–80.
- Jonsson, G., Malmfors, T., & Sachs, C. H. (1975). *6-Hydroxydopamine as a denervation tool in catecholamine research*. North-Holland, Amsterdam.
- Kawai, Y., Takagi, H., Yanai, K., & Tohyama, M. (1988). Adrenergic projection from the caudal part of the nucleus of the tractus solitarius to the parabrachial nucleus in the rat: Immunocytochemical study combined with a retrograde tracing method. *Brain Research*, **459**, 369–372.
- Kesner, R. P., & Hardy, J. D. (1983). Long-term memory for contextual attributes: Dissociation of amygdala and hippocampus. *Behavioural Brain Research*, **8**, 139–149.
- Kesner, R. P., Walser, R. D., & Winzenried, G. (1989). Central but not basolateral amygdala mediates memory for positive affective experiences. *Behavioural Brain Research*, **33**, 189–195.
- Lamour, Y., Dutar, P., & Jobert, A. (1984). Cortical projections of the nucleus of the diagonal band of Broca and of the substantia innominata in the rat: An anatomical study using the anterograde transport of a conjugate of wheat germ agglutinin and horseradish peroxidase. *Neuroscience*, **12**, 395–408.
- Lo Conte, G., Casamenti, F., Bigi, V., Milaneschi, E., & Pepeu, G. (1982). Effect of magnocellular forebrain nuclei lesions on acetylcholine output from the cerebral cortex, electro-corticogram and behavior. *Archives Italiennes de Biologie*, **120**, 176–188.
- Martin, J. H. (1991). Autoradiographic estimation of the extent of reversible inactivation produced by microinjection of lidocaine and muscimol in the rat. *Neuroscience Letters*, **127**, 160–164.
- Martinez, J. L., Jensen, R. A., Messing, R. B., Vasquez, B. J., Soumireu-Mourat, B., Geddes, D., Liang, K. C., & McGaugh, J. L. (1980). Central and peripheral actions of amphetamine on memory storage. *Brain Research*, **182**, 157–166.
- McDonald, R. J., & White, N. M. (1993). A triple dissociation of memory system: Hippocampus, amygdala, and dorsal striatum. *Behavioural Neuroscience*, **107**, 3–22.
- McGaugh, J. L. (1966). Time-dependent processes in memory storage. *Science*, **153**, 1351–1358.
- McGaugh, J. L., & Gold, P. E. (1989). Hormonal modulation of memory. In R. B. Brush & S. Levine (Eds.), *Psychoendocrinology*. New York: Academic Press.
- McKinney, M., Coyle, J. T., & Hedreen, J. C. (1983). Topographic analysis of the innervation of the rat neocortex and hippocampus by the basal forebrain cholinergic system. *Journal of Comparative Neurology*, **217**, 103–121.
- Mesulam, M. M., Mufson, E. J., Wainer, B. H., & Levey, A. I. (1983). Central cholinergic pathways in the rat: An overview based on an alternative nomenclature (Ch1–Ch6). *Neuroscience*, **10**, 1185–1201.
- Mizumori, S. J. Y., Perez, G. M., Alvarado, M. C., Barnes, C. A., & McNaughton, B. L. (1990). Reversible inactivation of the medial septum differently affects two forms of learning in rats. *Brain Research*, **528**, 12–20.
- Moore, R. Y., & Bloom, F. E. (1978). Central catecholamine neuron system: Anatomy and physiology of the dopamine systems. *Annual Review of Neuroscience*, **1**, 129–169.
- Moser, E., Moser, M.-B., & Andersen, P. (1993). Spatial learning impairment parallels the magnitude of dorsal hippocampal lesions, but is hardly present following ventral lesions. *Journal of Neuroscience*, **19**, 3916–3925.
- Mouly, A. M., & Holley, A. (1986). Perceptive properties of the multisite electrical stimulation of the olfactory bulb in the rat. *Behavioural Brain Research*, **21**, 1–12.
- Mouly, A. M., Kindermann, U., Gervais, R., & Holley, A. (1993). Involvement of the olfactory bulb

- in consolidation processes associated with long-term memory in rats. *Behavioural Neuroscience*, **107**, 451–457.
- Mouly, A. M., Vigouroux, M., & Holley, A. (1985). On the ability of rats to discriminate between microstimulations of the olfactory bulb in different locations. *Behavioural Brain Research*, **17**, 45–58.
- Nadel, L. (1968). Dorsal and ventral hippocampal lesions and behavior. *Physiology and Behavior*, **3**, 891–900.
- O'Keefe, J. (1983). Spatial memory within and without the hippocampal system. In N. Seifert (Ed.), *Neurobiology of the hippocampus* (pp. 375–401). London: Academic Press.
- Ottersen, O. P. (1982). Connections of the amygdala of the rat. IV. Corticoamygdaloid and intraamygdaloid connections as studied with axonal transport of horseradish peroxidase. *Journal of Comparative Neurology*, **205**, 30–38.
- Packard, M. G., Cahill, L., & McGaugh, J. L. (1994). Amygdala modulation of hippocampal-dependent and caudate nucleus-dependent memory processes. *Proceedings of the National Academy of Sciences of the USA*, **91**, 8477–8481.
- Papas, S., & Ferguson, A. V. (1990). Electrophysiological characterization of reciprocal connections between the parabrachial nuclei and the area postrema in the rat. *Brain Research Bulletin*, **24**, 577–582.
- Parent, M. B., & McGaugh, J. L. (1994). Posttraining infusion of lidocaine into the amygdala basolateral complex impairs retention of inhibitory avoidance training. *Brain Research*, **661**, 97–103.
- Perez-Ruiz, C., & Prado-Alcala, R. A. (1989). Retrograde amnesia induced by lidocaine injection into the striatum: Protective effect of the negative reinforcer. *Brain Research Bulletin*, **22**, 599–603.
- Rashidy-Pour, A., Motaghd-Larijani, Z., & Bures, J. (1996). Reversible inactivation of the medial septal area impairs consolidation but not retrieval of passive avoidance learning in rats. *Behavioural Brain Research*, **72**, 185–188.
- Rashidy-Pour, A., Motamedi, F., & Motaghd-Larijani, Z. (1996). Effects of reversible inactivations of the medial septal area on reference and working memory version of the Morris water maze. *Brain Research*, **709**, 131–140.
- Redish, A. D., & Touretzky, D. S. (1997). Cognitive maps beyond the hippocampus. *Hippocampus*, **7**, 15–35.
- Riekkinen, P., Jr., Riekkinen, M., Sirvio, J., Mettinen, R., & Riekkinen, P. (1992). Loss of cholinergic neurons in the nucleus basalis induces neocortical electroencephalographic and passive avoidance deficit. *Neuroscience*, **47**, 823–831.
- Rogers, R. C., & Fryman, D. L. (1988). Direct connections between the central nucleus of the amygdala and the nucleus of the solitary tract: An electrophysiological study in the rat. *Journal of the Autonomic Nervous System*, **22**, 83–87.
- Roldan, G., & Bures, J. (1994). Tetrodotoxin blockade of amygdala overlapping with poisoning impairs acquisition of conditioned taste aversion in rats. *Behavioural Brain Research*, **65**, 213–219.
- Salinas, J. A., Packard, M. G., & McGaugh, J. L. (1993). Amygdala modulates memory for changes in reward magnitude: Reversible post-training inactivation with lidocaine attenuates the response to a reduction in reward. *Behavioural Brain Research*, **59**, 153–159.
- Sandkuler, J., Maisch, B., Gebhart, G. F., & Zimmerman, M. (1985). Reversible microblockade in spinal cord and brainstem of cats and rats by focal lidocaine. *Pflugers Archives*, **405**, R41.
- Sandkühler, J., Maisch, B., & Zimmerman, M. (1987). The use of local anesthetic microinjections to identify central neural pathways: A quantitative evaluation of the time course and extent of the neural block. *Experimental Brain Research*, **68**, 168–178.
- Saper, C. B. (1984). Organization of cerebral cortical afferent system in rats. II. Magnocellularis basal nucleus. *Journal of Comparative Neurology*, **222**, 313–342.
- Shefchyk, S. J., Jell, R. M., & Jordan, L. M. (1984). Reversible cooling of the brainstem reveals areas required for mesencephalic locomotor region evoked treadmill locomotion. *Experimental Brain Research*, **56**, 257–262.
- Sumal, K. K., Blessing, W. W., Joh, T. H., Reis, D. J., & Pickel, V. M. (1983). Synaptic interaction

- of vagal afferents and catecholaminergic neurons in the rat nucleus tractus solitarius. *Brain Research*, **277**, 31–40.
- Tassoni, G., Bucherelli, C., & Bures, J. (1992a). Lateralized contributions of the cerebral cortex, parabrachial nucleus, and amygdala to acquisition and retrieval of passive avoidance reaction in rats: A functional ablation study. *Behavioural Neuroscience*, **106**, 933–939.
- Tassoni, G., Bucherelli, C., & Bures, J. (1992b). Postacquisition injection of tetrodotoxin into the parabrachial nuclei elicits partial disruption of passive avoidance reaction in rats. *Behavioural and Neural Biology*, **57**, 116–123.
- Tassoni, G., Bucherelli, C., & Bures, J. (1992c). Differential disruption of inhibitory conditioning by post-trial blockade of midbrain and forebrain structures of the rat brain. *Proceedings of the Fifth Conference on the Neurobiology of Learning and Memory, Irvine, CA, October 22–24, 1992*, (p. 74).
- Thomas, J. B. (1972). Non-appetitive passive avoidance in rats with septal lesions. *Physiology and Behavior*, **8**, 1087–1092.
- Todd, J. W., & Kesner, R. P. (1978). Effects of post-training injection of cholinergic agonists and antagonists into the amygdala on retention of passive avoidance training in rats. *Journal of Comparative and Physiological Psychology*, **92**, 958–968.
- Weil-Malherbe, H., Axelrod, H., & Tomchick, R. (1959). Blood–brain barrier for adrenaline. *Science*, **129**, 1226–1228.
- Williams, C. L., & McGaugh, J. L. (1992). Reversible inactivation of the nucleus of the solitary tract impairs retention performance in an inhibitory avoidance task. *Behavioral and Neural Biology*, **58**, 204–210.
- Williams, C. L., & McGaugh, J. L. (1993). Reversible lesions of the nucleus of the solitary tract attenuate the memory-modulating effects of posttraining epinephrine. *Behavioral Neuroscience*, **107**, 955–962.
- Winocur, G., & Bindra, D. (1976). Effects of additional cues on passive avoidance learning and extinction in rats with hippocampal lesions. *Physiology and Behavior*, **17**, 915–920.
- Wishart, T., & Mogenson, G. (1970). Effects of lesions of the hippocampus and septum before and after passive avoidance training. *Physiology and Behavior*, **5**, 31–34.
- Zhuravin, I. A., & Bures, J. (1991). Extent of tetrodotoxin induced blockade examined by pupillary paralysis elicited by intracerebral injection of the drug. *Experimental Brain Research*, **83**, 687–690.