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Review

Involvement of the Amygdala and Its Connected Structures in Formation and Expression of Inhibitory Avoidance Memory: Issues and Implications

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Abstract

The inhibitory avoidance task contains both classical and operant conditioning components and is extensively used for studying the neural bases for formation and expression of emotion memory. While the amygdala is proposed to have a unique position for encoding, storing and retrieving memory in Pavlovian fear conditioning, extant data from manipulative studies on the inhibitory avoidance task showed that other brain regions by subserving various roles in processing different properties of the task are also involved in formation and expression memory of this task. Memory formation in this task requires the amygdala, hippocampal formation, bed nucleus of stria terminalis, nucleus accumbens, medial prefrontal cortex, as well as other cortical and subcortical regions. Expression of recent memory in this task relies on, among others, the amygdala, hippocampus and nucleus accumbens, but expression of remote memory in this task relies on cortical regions. Neural correlates for this task have been recently detected in the amygdala and hippocampus. These findings suggest that the memory operation in an inhibitory avoidance task entails a neural circuit distributing beyond the amygdala and undergoing a temporally dynamic change after acquisition.

Key Words: hippocampus, medial prefrontal cortex, nucleus accumbens, BNST, fear conditioning, memory consolidation, rats

Introduction

That memory exists in multiple forms subserved by different brain systems is well documented in human and animal literature (114). Memory of emotional experience, particularly that related to fear, differs from other forms of memory in certain characteristics and thus receives much attention. First of all, it forms rapidly as shown in many one-trial learning tasks arousing strong emotion. Further, once formed it often lasts for the rest of life and allows feeble cues to elicit recollection. As such it is highly adaptive by bestowing significance to daily events in our life and keeping us out of danger. Yet when this memory goes awe, it becomes pathogenic and underlies symptoms of some mental illness including those in the panic or post-traumatic stress disorder. Memory for emotional experience engages a specific brain system that has been extensively studied by neuroscientists in the past two decades. Abundant evidence on this topic was accrued by Pavlovian fear conditioning, in which a discrete neutral stimulus is presented in a context with an aversive stimulus, mostly electric shock; presenting the neutral stimulus or context at a later time elicits fear responses such as freezing, alterations in heart rate or blood pressure,

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defecation, urination or ultrasonic vocalization.

A prevailing view is that the amygdala is for encoding, storing and retrieving conditioned fear (28, 56, 87). Evidence conferring this role to the amygdala can be capitulated as follows: First, input conveying information of the conditioned and unconditioned stimuli converges to the amygdala, and output from the amygdala diverges to various subcortical nuclei controlling fear responses (23). Second, amygdala neurons show experience-driven plasticity—N-methyl-D-aspartate (NMDA) receptor dependent long-term potentiation (LTP) (16; 31). Third, amygdala neuronal responses to a conditioned fear stimulus could be altered by learning and could model learning in some instances (105, 106). Fourth, altering amygdala functions before or after learning impairs acquisition or expression of conditioned fear responses (86). A recent study further demonstrated that memory formation in fear conditioning preferentially recruited lateral amygdala neurons with elevated expression of CREB implicated in the neuronal plasticity cascade (34); selective ablation of these neurons with targeting toxin induced amnesia in trained rats (35), suggesting a causal role of cellular plasticity in this structure in the conditioned fear memory. While the above evidence suggests that the amygdala may mediate the stimulus-shock association in Pavlovian fear conditioning, it may not be the only brain structure responsible for such association. Our recent data showed that the dorsal hippocampus also mediates the stimulus-shock association in contextual fear conditioning (12).

As a matter of fact, an aversive event in our daily life elicits more than just being afraid in us. We may contemplate to cope with its consequence immediately or shortly afterwards, to ponder how it comes about and can be avoided, or to alter our appraisal of it in case escape is impossible (26). Such mental processes may or may not be afforded by a conditioned reflex but nonetheless are activated by an emotional incident and included in our memory. In other words, an aversive event is not only associated to the stimulus preceding it, but also incorporated into a mental network active at the moment that contains our past. This consideration poses a prospect that the neural substrate of emotional memory may go beyond what is entailed by classical fear conditioning, which models only part of our encountering a frightening event. Under this perspective, this article uses an inhibitory avoidance task as a model for emotional memory and reviews the brain circuit involved in formation and expression of such memory. It will focus mainly on findings from this and other laboratories relevant to some often concerned issues. Excellent and extensive reviews on this topic have been published elsewhere (90, 92).

The Inhibitory Avoidance Task: More than Pavlovian Fear Conditioning

This review is based on results from a one-trial inhibitory avoidance task widely used for assessing memory of aversive experience. This task was first mentioned in a now classic paper entitled “Cognitive maps in rats and men” (124), in which the thesis work of a Ph.D. student Bradford Hudson was referred. Hudson mounted a food cup on a striped-pattern visual stimulus attached to a rat cage and arranged such that as a hungry rat touched the food cup an electric shock was dispensed. It was found that one shock was enough to make the rat withdraw from the food cup for days or weeks. This was later formalized into a 1-trial avoidance learning task by Murray Javik as he visited UC Berkeley in 1955, in which a mouse entered a bird house through a hole and received a foot shock from the grid floor (42). He later invented the trough-shape alley with a slit floor to administer shock without a scrambler and the guillotine door to separate the alley into the light and dark compartments. This was further modified by McGaugh into the version now widely employed for rats (83).

A classic theory of active avoidance learning proposed that avoidance learning contains both classical and operant conditioning components (98). Miller and his colleagues once reversed the active task into a passive form in order to distinguish the amnesic effect of electroconvulsive shock between learning and performance (21). The inhibitory avoidance task has recently been viewed as a form of classical fear conditioning that the rat acquires freezing behavior in a specific context previously associated with shocks (9). However, in a typical test session, a rat well learned the task would not just stand still; it often probes with its forelimbs into the dark side or tries to get out of the alley by poking the top lid with its nose. The versatile behavior in the task was first noted by Hudson (37): “The animal withdrew from that end of the cage, or piled up saw dust and covered the pattern, or showed various other amusing responses all of which were in the nature of withdrawing from the pattern or making it disappear”. The flexibility of behavior in a test phase justifies the name of inhibitory avoidance (94) more than that of passive avoidance commonly used in the field.

Our recent finding bears on this notion. YC-1 (3-(5-hydroxymethyl-2-furyl)-1- benzyl-indazole) potentiates the sensitivity of purified soluble guanylate cyclase to NO. In accordance with a role of NO in the NMDA-dependent LTP in the amygdala (16), pre-training administration of YC-1 increased the entrance latency of treated rats in the test of an inhibitory avoidance task. An interpretation of these data is that YC-1 enhanced the synaptic efficacy in the neural

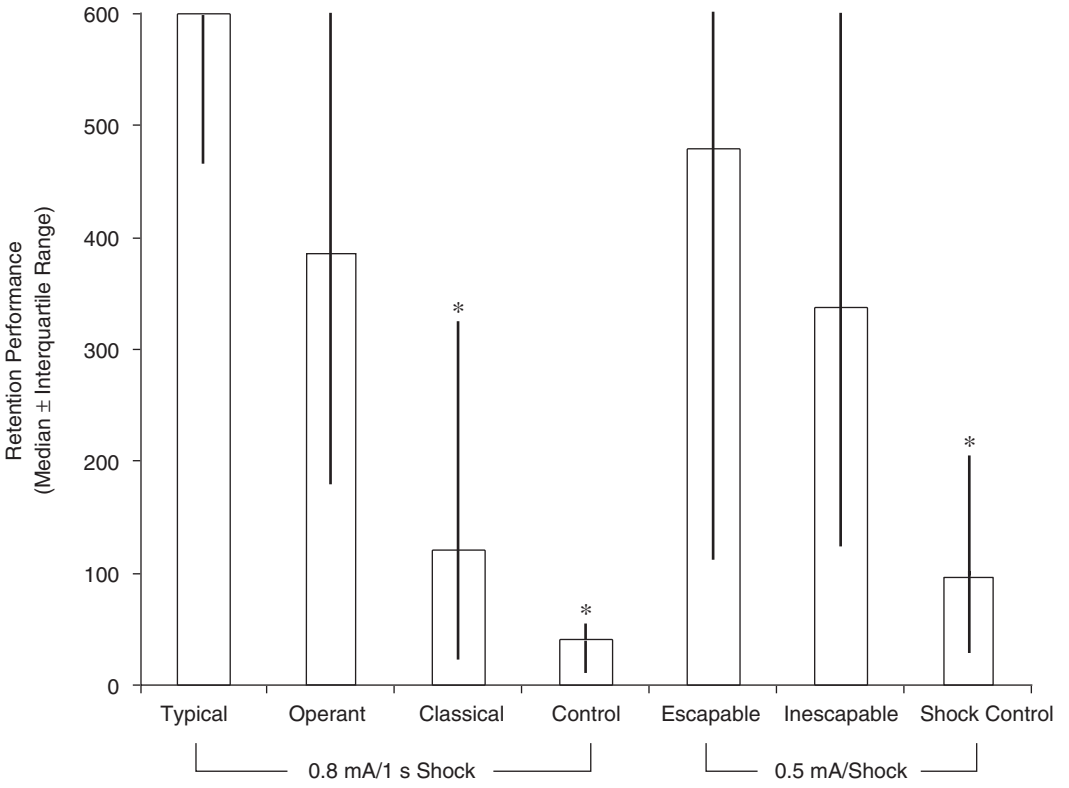

Fig. 1. Effects of various training paradigms on retention performance in the inhibitory avoidance task. Four groups of rats received the typical training, operant conditioning, classical conditioning, or contextual conditioning (control) procedure with a fixed foot shock of 0.8 mA/1 s (left side of the figure). Three groups of rats received escapable, inescapable, or shock control procedure with a shock of 0.5 mA (right side of the figure). The escapable procedure allowed the rat to run back to the safe side after receiving the foot shock. The inescapable procedure is equivalent to the typical training. Rats in the shock control group were directly placed into the dark compartment and received shock. Batches of three rats (one in each group) were trained together in three apparatuses. The shock duration varied for each training batch and was determined by when the rat in the escapable group ran back to the safe side. *Significantly different from the typical training group or the inescapable group.

pathway mediating association between the context and conditioned freezing. If this were indeed the case, the YC-1 treated rats should have frozen more if they were directly placed into the dark chamber where they had been shocked before. Contrary to this prediction, the YC-1 treated rats had the shortest latency of entering the lit side (17). A later study also showed that this drug effectively facilitated active avoidance memory (15). These data suggest that what a rat acquires in an inhibitory avoidance task is not a fixed action pattern of freezing; instead it entails an adaptive act. Flexible application of past experience to a present situation is a defining feature of human declarative memory (27).

This laboratory had another line of evidence to argue against the notion that the inhibitory avoidance task relies on conditioned freezing. Four groups of rats were subjected to various modified versions of the inhibitory avoidance task such that the presumable components involved in learning could be isolated. One group received the traditional task. A second group was subjected to an operant conditioning version in which the rat received a shock as it stepped from the lit side into the other side that was also lit, thus the shock was contingent only on the rat's act. The third group was subjected to a classical conditioning version in which the rat was directly placed into the lit side and received a shock at the offset of light, thus the shock was contingent upon a specific cue. The final group received a control training condition in which the rat was placed into the lit side and then received a shock, thus the shock is contingent upon the context rather than on rat's behavior or a discrete cue. All rats were tested two days later in a traditional way. Results are shown in the left half of Fig. 1, which indicates that avoidance performance shaped in the operant conditioning version was better than that in the classical conditioning version, which in turn better than that in the context conditioning (control) version. However, none of the modified training paradigms yielded a performance matched to that of the traditional one. Thus, a typical inhibitory avoidance task contains more than either operant or classical conditioning alone.

In contrast to classical conditioning in which a fixed contingency between the conditioned and unconditioned stimuli leaves the subject no control of the aversive event, the operant nature of inhibitory avoidance learning can be enhanced by making the shock escapable that mimics human's coping behavior in expecting to alter the consequence of a stressful event. Our laboratory made the shock escapable by leaving the separation door opened during shock administration. A serial circuit was installed to yoke three alleys together, as the rat in the escapable group leaving the shocked side, the circuit broke and the shock ended in all three alleys. Thus, each batch of three rats (one in each of the inescapable, escapable and classical conditioned groups) trained together would receive the same amount of shock. Fig. 1 (right half) shows that the escapable group did not differ significantly in retention from the inescapable group, both showed better retention that the classical conditioned group, attesting to a greater contribution from the operant component to the task.

The Inhibitory Avoidance Task as a Model for Studying Neural Basis of Emotional Memory

The nature of single-trial training and testing in the inhibitory avoidance task makes it apt for studying the neural basis of emotional memory, because each event in the memory processing timeline can be precisely pinpointed. Manipulative treatments placed before or after a training trial may influence acquisition or memory formation, respectively; while those placed before or after a test trial may influence retrieval or memory reconsolidation/extinction, respectively. Likewise, the neural correlates obtained after a training trial may reflect acquisition/memory consolidation processes, those obtained during or after a test trial may reflect retrieval, reconsolidation or extinction processes. Delineation of the neural circuit involved in memory processing in an inhibitory avoidance task requires both causal and correlative evidence. Neural activity bearing relationship with acquisition/retention in a task is necessary, but not sufficient, for assuring a structure in encoding, storing or retrieving the neural trace of memory in that task. If functional integrity of a structure is necessary for but its neural activity bears no correlation with acquisition/retention in that task, the structure may be a site for modulating rather than mediating the memory trace. Conversely, if neural activity of a structure correlates with but its functional integrity is not needed for acquisition or retention in a task, this structure may receive output from a mediating site and be involved in some other functions.

To ascertain a causal relationship, an effect of posttraining manipulation argues favorably for the interpretation of influence on memory per se because it could hardly affect sensation, motor, motivation or emotion during training; as the effect degrades by delaying the treatment from training, it further argues against any proactive action on memory retrieval (93). However, this tenet holds only under a premise that the perceptual or emotional processes terminate along with the training trial, otherwise a line could be really blurred on when pain or fear ends and memory starts. Effects on sensory preconditioning or latent learning of the task rule out a direct effect of reward or punishment for a treatment (60, 97) but fall short of proving lack of any modulating influences of a treatment on perception or emotion that may indirectly alter memory strength. For example, a previous study demonstrated that buspirone, an atypical anxiolytic drug working on 5-HT_{1A} receptors, immediately given after training caused a memory deficit and the effect was time-dependent; the results were interpreted as activation of 5-HT_{1A} receptors detrimental to memory consolidation in an inhibitory avoidance task (63). However, when training was divided into a context learning phase and a shock learning phase, buspirone had no effect given after context learning but a big effect given after shock learning, it is plausible that buspirone may reduce the fear existing after foot shock and hence indirectly reduce the aversive memory. Thus, the time-dependent effect of post-training regimen in an inhibitory avoidance task may not warrant an influence solely on memory per se; influences on pain and fear must be checked by independent assessment.

Similar argument also applies to interpreting pre-test treatment effects on retrieval. For example, this laboratory showed that buspirone injected 30 min before a retention test induced a profound deficit on memory expression in a 1-day retention test, a weak deficit in a 21-day test, and no deficit in a 90-day test (79). Influences on sensory-motor performance can not easily account for an effect varying along with the retention interval. Thus, this retention interval-dependency excludes confounding in certain performance factors in interpreting pretest treatment effects, just as the time-dependency effect in the memory formation stage. However, as buspirone affects fear or anxiety, the data may also be taken to suggest that retrieving an avoidance act of operant conditioning depends on conditioned fear or anxiety of classical conditioning in a 1-day but not in a 90-day test. Thus, the influence of a pretest treatment on emotion factors should always be checked if an effect on memory expression is noted.

Involvement of the Amygdala in Formation of Inhibitory Avoidance Memory: Evidence from Manipulative Studies

Since the demonstration that pretraining lesions

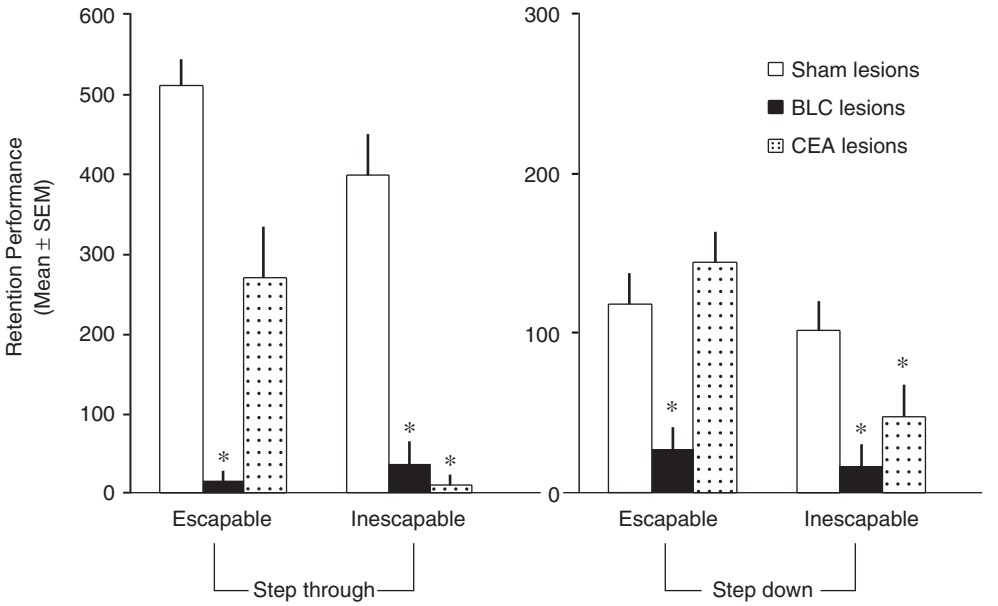

Fig. 2. Effects of pretraining electrolytic lesions of various amygdala nuclei on retention performance of rats trained on the escapable or inescapable paradigm in a step-through (left panel) or a step-down (right panel) task. The effect of the lateral nuclei lesions was not different from that of the basolateral nuclei lesions and these two groups were pooled into a single basolateral complex (BLC) lesioned group. *Significantly different from the sham lesioned group, $P < 0.05$.

and posttraining electrical stimulation of the amygdala impaired acquisition and/or retention in an inhibitory avoidance task (32, 101, 102), this structure has been the focus of research and the extensive findings have been reviewed previously (90). Heterogeneity of this structure requests differentiation of its various subnuclei in memory functions. An early study demonstrated that the impairing effect of amygdala electrical stimulation on inhibitory avoidance memory correlated with the proximity of the electrode tip to the amygdala basomedial nucleus (33), recent findings suggest that retention in the inhibitory avoidance task was susceptible to perturbing the basolateral nuclei but less so to perturbing the central nuclei (96), even though the latter nuclei was implicated in some forms of fear conditioning (45, 128). Results from this laboratory suggest that the subnuclei involved may depend on how the avoidance response was acquired. Rats bearing electrolytic lesions of the central, lateral, or basolateral amygdala nuclei were trained with escapable and inescapable paradigms of an inhibitory avoidance task as depicted before and tested 24 h later. Fig. 2 shows the results that the avoidance memory acquired via an escapable paradigm was impaired by lesions of the lateral/basolateral nuclei, but not by lesions of the central nuclei. On the other hand, the avoidance memory acquired with an inescapable paradigm was impaired by either lateral/basolateral nuclei lesions or central nuclei lesions (80). Similar results were obtained in a step-through version motivated by shock and a step-down version motivated by painful heat on the floor (13).

Previous evidence implicates the basal or basolateral amygdala nuclei in voluntary operant responses to emotional events and the central nuclei in reflexive responses to salient stimuli due to classical conditioning (3, 47). Our results that an inescapable training paradigm engaged both classical and operant conditioning circuits but an escapable training paradigm engaged the operant conditioning one imply that during inhibitory avoidance learning a possibility of active coping makes the operant conditioning component of the task more salient. This view is in line with the findings that the basolateral amygdala nuclei processed sensory features in the emotional outcome of an instrumental act (4).

The proposal that the amygdala subserves the association in fear conditioning raises a possibility that all forms of emotional memory including that in the inhibitory avoidance task are formed and stored in the amygdala. An early study has shown that extensive amygdala lesions impaired retention of an inhibitory avoidance response if given 2 days before or within 5 days after training, but the same lesions applied 12 days after training did no more harm on the accelerated forgetting already seen in the sham lesioned rats bearing the chronically implanted electrodes (77). These data suggest that involvement of the amygdala in inhibitory avoidance memory is temporally graded and are incompatible with what would be expected

from destruction of a permanent storage site.

In addition to the electrical stimulation and lesions of the amygdala nuclei, many manipulations altering various neuorchemical systems within the amygdala also affect retention in the inhibitory avoidance task. Previous studies have shown that memory in this task was modulated bi-directionally by posttraining intra-amygdala infusion of agonists or antagonists acting on different receptors in the cholinergic, noradrenergic, dopaminergic, serotonergic, glutamatergic, GABAergic, peptidergic systems (61, 70, 71, for review see 95, 97). Treatments altering neuroendocrine systems also affect inhibitory avoidance memory when applied to the amygdala, for instance, posttraining intra-amygdala infusion of corticotrophin releasing hormone (CRH) enhanced memory in this task (66).

When appropriate doses were administered to affect a system, agonists induced memory enhancement and antagonists induced amnesia in many cases. The amnesic effects induced by blocking an intrinsic system imply that the neurotransmitter at the infusion site enables normal memory to form by exerting an action of modulation or mediation. However, our study has shown that the 5-HT_{1A} antagnoinst WAY100635 or S(-)UH-301 infused into the amygdala enhanced retention (63), indicating that serotonin may act as an endogenous memory debilitating factor. Similar results have also been shown in the amygdala for the GABAergic and opioidergic systems (38, 113), implicating a two-way control of memory formation by neurochemical systems in the amygdala. Existence of endogenous memory inhibition systems in the brain invites speculation on its adaptive value that will be discussed to at the last section.

While many neurochemical systems in the amygdala exert a modulating action on memory (97), the glutamatergic system is sometimes assumed to have a mediating role. Glutamatergic fibers convey sensory information to many brain regions causing unique spatial/temporal patterns of synaptic excitation that may contribute to learning via a putative mechanism of LTP (82, 88). Presence of NMDA-dependent LTP in the amygdala (31) is often drawn as evidence for information storage in this structure. Studies have reported effects on retention in the inhibitory avoidance task by affecting NMDA receptors, CAMKII or any biochemical cascade implicated in LTP plasticity of the amygdala (122), suggesting good parallelism between the behavioral and neural modification. These findings were sometimes taken to support a mediation role of glutamate transmission in memory formation. However, as memory enhancement was also noted by infusion of glutamate into the amygdala (40), one has to resolve the issue of how a non-discriminatory excitation induced by exogenous drugs would enhance rather than interfere with an intricate firing pattern mediating the memory code. Alternatively, glutamate may exert its influence by releasing neuromodulators. As NMDA receptors are located at noradrenergic terminals and play a role in release norepinephrine that modulates memory formation in the inhibitory avoidance task (73), the effect of NMDA antagonists on memory may be subjected to other interpretations.

This laboratory has shown that intra-amygdala infusion of β noradrenergic blockers attenuated the memory enhancing effect of glutamate and infusion of norepinephrine ameliorated the amnesic effect of APV (74). Thus, glutamate infused into the amygdala may cause norepinephrine release to modulate memory formation instead of blocking LTP induction. Previous findings that intra-amygdala infusion of glutamate attenuated the amnesic effect of propranolol (59) could be due to displacing the antagonist from receptor sites by glutamate-released norepinephrine. This account is consistent with the finding that antagonists of NMDA receptors had both memory enhancing and impairing effects on the inhibitory avoidance task depending upon the various conditions (55). Yet it should be clarified that asserting a post-training effect in a structure as modulatory does not necessarily exclude the structure from being a potential site for memory coding or storage because a modulator can still exert its effect locally at the encoding or storage site, which can only be judged by whether the amygdala neural activation bears both correlative and causal relationship with acquisition and retention performance in the inhibitory avoidance task.

Involvement of Other Brain Regions in Formation of Inhibitory Avoidance Memory: Evidence from Manipulative Studies

Various lines of evidence indicate that the amygdala is not the single structure critically involved in formation of the inhibitory avoidance memory; this function depends greatly on the integrity of its input and output. On the input side, the light information reaches the amygdala directly from the posterolateral thalamic nucleus or indirectly from the lateral geniculate nucleus *via* the visual cortices (118). Shock information from the caudal insular cortex or posterior intra-laminar thalamic nuclei activates the basolateral amygdala nuclei (117) or that from the parabrachial nuclei activates the central amygdala nuclei (6). The amygdala also receives noradrenergic inputs from the nucleus of solitary tract and locus coeruleus that are activated by somatosensory or visceral inputs induced by shock; suppressing these two regions immediately after training impaired retention and activating them improved

retention (60, 129). These inputs provide the essential influences enabling the amygdala to affect memory formation.

According to the view that the amygdala modulates memory formed elsewhere in the brain, the potential sites of formation and storage of inhibitory avoidance memory should be located at the direct or indirect targets of amygdala output. An early study showed that the amnesic effect of post-training electrical stimulation of the amygdala was blocked by lesions of the stria terminalis (ST)—an amygdala input/output pathway (68). Additionally, lesions of the ST also attenuated the memory enhancing or amnesic effect of other treatments given to the amygdala such as norepinephrine (76) or into the periphery by influencing the amygdala function (64). These data suggest that the forebrain structures innervated by the ST may play critical roles in formation of inhibitory avoidance memory.

Accordingly, this laboratory has found a role of the bed nucleus of the stria terminalis (BNST) in memory. An early study showed that posttraining intra-BNST infusion of an opiate μ receptor agonist levorphanol induced a memory deficit and annihilated the protective effect of naloxone against amygdala stimulation (78). Blocking this area with lidocaine after learning induced amnesia and activating it with CRH enhanced memory (69). Later studies showed that post-training intra-BNST infusion of norepinephrine or an agonist to the α_1 or β receptor enhanced retention, while infusion of antagonists to these receptors impaired it. As the same effects were also observed in the Morris water maze (14), they are unlikely to be caused by affecting freezing behavior. In addition, intra-BNST infusion of glutamate enhanced memory in a dose- and time-dependent manner, infusion of APV attenuated this memory enhancing effect at a low dose and impaired retention at a higher dose; further, the two systems interacted to modulate memory in a way as in the amygdala (81).

Extensive data have shown the involvement of dorsal hippocampus in the inhibitory avoidance task (39, 121). A previous study has shown that training engaged a complicated sequential interaction among the hippocampal CRH, norepinephrine and glutamate systems (58). The hippocampus communicates with the amygdala by way of the ventral subicular region (10), which was implicated in conveying contextual information for contextual fear conditioning. A recent study from this laboratory has shown that in an inhibitory avoidance task post-training infusion of the muscarinic agonist oxotremorine or antagonist scopolamine into the ventral subiculum enhanced or impaired retention, respectively; and these effects involved communication with the BNST that also receives amygdala input during the memory formation phase (81). Infusion of fluoxetine or 8-OH-DPAT into the lateral septum—a hippocampal output target connected with the BNST—also affected retention in the inhibitory avoidance task (57). All these data suggest that the dorsal hippocampus accomplishes its memory function by communicating with its connected structures.

Studies also documented effects on memory of various treatments applied to the nucleus accumbens, entorhinal, parietal, insular, and medial frontal cortices shortly after training (24, 43; 54, 72, 75; for review see 92; 108). The time-dependent effects of post-training treatments suggest involvement of these regions in memory formation, but they were active in a non-synchronous manner during the consolidation period. A study has shown that retention in the task was impaired by suppression of the amygdala and dorsal hippocampus with APV or muscimol given immediately but not 30 mins after training, by suppression of the entorhinal cortex from 30 to 180 min after training, or by suppression of the parietal cortex from 60 to 120 min after training (41).

The involvement of multiple brain regions in formation of inhibitory avoidance memory invokes a question of whether these regions subserve the same or different functions. One way to answer this question is to alter the structure function in various learning tasks and infer the common factor from all affected tasks. The other way is to dissociate the various components in an inhibitory avoidance task and explore the role of each structure in different components. This laboratory has invented a two-phase training paradigm to isolate context and shock learning in the inhibitory avoidance task such that memory for each component could be manipulated independently (63). Exploiting this paradigm, Malin and McGaugh (84) differentiated the roles of several structures by infusing oxotremorine into the anterior cignulate gyrus, hippocampus or amygdala immediately after the context or shock training. They found that the drug improved memory when infused into the amygdala after either the context or shock training; memory was also improved if the drug was infused into the hippocampus after the context training or into the rostral anterior cingulate cortex after the shock training but not otherwise. The data implicates the hippocampus in context processing, the anterior cingulated cortex in shock processing and the amygdala in both of them. This is consistent with an interpretation that the amygdala cholinergic activation modulates memory processing of context in the hippocampus and memory processing of shock in the rostral anterior cingulated cortex.

We approached this issue by infusing CNQX, an AMPA receptor antagonist, into the amygdala, dorsal hippocampus and nucleus accumbens immediately

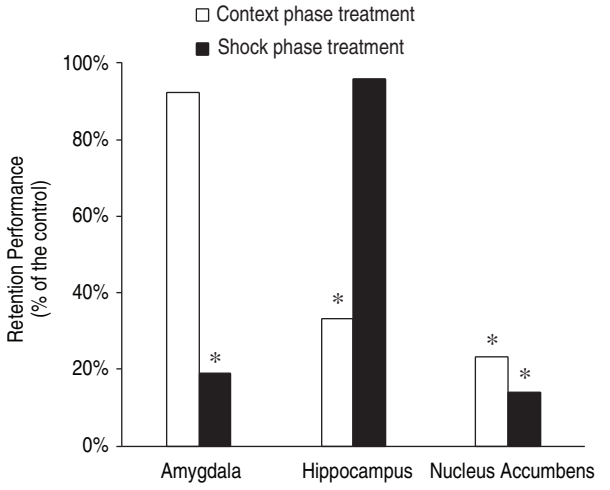

Fig. 3. Effects of CNQX infused into the amygdala, dorsal hippocampus, or nucleus accumbens immediately after the context learning phase or the shock learning phase in a two-phase training paradigm of the inhibitory avoidance task. Each bar represents the percentage of median retention score of the CNQX treated group to that of the correspondent vehicle treated groups. *Significantly different from the vehicle group, $P < 0.05$.

after the context or shock training in a two-phase training paradigm of the inhibitory avoidance task. Fig. 3 shows that CNQX infused into the dorsal hippocampus impaired memory only if it was given after the context training; infusion into the amygdala impaired memory only if it was given after shock training. Infusion of CNQX into the nucleus accumbens impaired memory no matter when it was given after the context or shock training. These findings implicate the dorsal hippocampus in context processing and the amygdala in shock processing. The nucleus accumbens by receiving inputs converged from the former two structures is critical for processing both context and shock information. Our results are corroborated by the findings that in a step-down inhibitory avoidance task APV impaired retention when it was infused into the dorsal hippocampus or basolateral amygdala immediately after a typical training trial but the amnesia induced by intra-hippocampal APV was prevented if the context memory had already been formed in a pre-exposure trial administered a day before drug infusion (109).

A caveat may be noted that probing a specific neurochemical system in a region reveals only limited facets of memory processing in that region. The amygdala AMPA receptors, while necessary for shock processing as revealed by our findings, may not be necessary for context processing that muscarinic stimulation sufficiently engaged (85). Similar discrepancy is noted in a two-phase training paradigm of contextual fear conditioning, intra-dorsal hippocampus infusion of lidocaine (12) disrupted the shock association but that of muscimol did not (89), suggesting that shock processing in the dorsal hippocampus was impervious to GABA suppression. Thus, to interpret these findings one should be cautioned that the nature of processing ascribed to a structure is constrained by the behavioral task and the treatment adopted; it is always possible that under different situations the brain uses different strategies to cope. These findings nonetheless hint that any single attribute inherent in a learning task could be processed actually by a distributed network and the nature of processing in a structure could not be fixed by findings based on the effect of a single treatment. Further, even the same property is handled by several structures the way and consequence of their processing would by no means be identical as the local circuitry may handle the same property in each structure distinctively. Thus, the amygdala may allow a warning signal to elicit emotional reflexes by associating it with the shock and send emotional significance to other brain structures. The hippocampus may integrate the shock with other information to form a unified representation of a dangerous context that affords flexible application later. The anterior cingulated cortex may allow the shock to draw attention to the warning signal and to pivot suitable behavior in a specific situation. All these may be accomplished in an inhibitory avoidance task as implicated by the flexibility of coping behavior in this task noted by Hudson (37) some sixty years ago.

Interaction between the Amygdala and Other Brain Regions in Formation of Inhibitory Avoidance Memory

As those structures involved in inhibitory avoidance memory are connected mutually, interactions among them during memory formation have been investigated. Two strategies have been used to probe information flow among structures: unilateral lesions applied to one site plus contra-lateral lesions applied to the other prevent the information transmission between the two bilaterally, thus memory formation relying on it would be impeded. However, this cross lesion strategy cannot determine the direction of information flow. A study of this sort showed that bilateral lesions of the nucleus accumbens or cross lesions of the nucleus accumbens and amygdala blocked the memory enhancing effect of dexamethasone in the inhibitory avoidance task (116). Alternatively, administration of an activating agent to one site and a suppressing agent to the other would let the effect of a downstream site to override that of an upstream site. An early study using this strategy

shows that posttraining infusion of an opiate μ antagonist naloxone into the BNST that is innervated by met-enkephalin fibers in the ST blocked the amnesic effect of electrical stimulation of the amygdala (78).

A subsequent study showed that bilateral lesions of the nucleus accumbens or ST, while did not affect retention by themselves, attenuated the memory enhancing effect of a glucocorticoid receptor agonist RU 28362 infused into either the amygdala or dorsal hippocampus (111), consistent with the convergent inputs of the two structures to the nucleus accumbens. However, communication between the nucleus accumbens and amygdala is by no means one way. Dopamine infused into the basolateral amygdala nuclei or nucleus accumbens improved retention, which was blocked by infusing a general dopamine receptor antagonist cis-Flupenthixol into the other structure, suggesting a two-way communication between the two structures primed by the brain stem dopaminergic input (54). Findings from our laboratory have also shown that suppression of the nucleus accumbens blocked the effects of norepinephrine infused into the amygdala or dorsal hippocampus (62,131), suggesting possibly one way flow to the nucleus accumbens induced by noradrenergic activation of the latter two areas. The memory function of nucleus accumbens in the inhibitory avoidance is not only engaged by the amygdala and hippocampus, but also by the noradrenergic input from the nucleus of solitary tract (46). The contrast between the findings of ours and those from the McGaugh's laboratory attests to the complexity of interaction between structures involved in memory formation.

Our previous findings have shown that lidocaine infused into the basolateral amygdala or mPFC impaired retention in an inhibitory avoidance task, which could not be ameliorated by infusing an enhancing dose of glutamate into the other structure (72). Thus, once the amygdala or mPFC is suppressed, memory enhancing treatments applied to the non-suppressed structure would be no longer effective. A recent study showed that NMDA lesions of the rostral anterior cingulated cortex blocked the memory enhancing effect of oxotremorine infused into the amygdala and the same lesions placed on the basolateral amygdala nuclei blocked the memory enhancing effect of oxotremorine infused into the rostral anterior cingulated cortex, suggesting an reciprocal communication during memory formation between the two structures due to muscarinic activation (85). A similar pattern of interaction has also been demonstrated between the amygdala or dorsal hippocampus and mPFC in this laboratory (62, 131).

Interaction between the hippocampus and amygdala in the inhibitory avoidance task has also been demonstrated. Lesion or microinfusion of a β noradrenergic blocker applied to the basolateral amygdala attenuated the memory enhancement induced by infusion RU 28362 into the dorsal hippocampus, and these data was interpreted as the amygdala enabling hippocampal glucocorticoid to enhance memory (110, 112). This laboratory developed a latent learning paradigm of the inhibitory avoidance task (60). This form of learning depends upon the integrity of dorsal hippocampus but not amygdala; however, epinephrine injected to the periphery or norepinephrine infused into the amygdala immediately after the latent learning phase modulated this memory. The enhancing and impairing effects could be attenuated by suppressing different neurochemical systems in the dorsal hippocampus (62), suggesting a modulation flow from the amygdala to the hippocampus. These data are in line with that stress or amygdala activation modulated induction or maintenance of LTP in the dentate gyrus (1, 48).

An intriguing question arising from interaction among the various structures shown above is that given the intimate flow exchange among the structures processing different information during the consolidation period, why relatively clean functional segregation within the circuitry can still be observed by many studies. In other words, how functional segregation and integration can be achieved simultaneously at each site of a circuit needs to be elucidated. A possibility is that accomplishing one's own function and integrating with those of others may co-exist in a single structure but are separated by intricate temporal patterns of activity which cannot be easily resolved by the long-lasting effect of pharmacological agents. Unit activity synchronized and oscillated at the theta band frequency between the amygdala and hippocampus during fear conditioning (115) may represent an example of the potential mechanisms.

Expression of Inhibitory Avoidance Memory: Changes with Time

Pretest suppression of a site involved in memory storage would impair memory expression, although presence of such an effect for a structure does not quarantine its involvement in memory storage. Our early study has shown that pretest infusion of buspirone into the dorsal-hippocampus impaired retention in the inhibitory avoidance, active avoidance and Morris water maze tasks, but the effect was significant in the 1-day test but not in the 21-day test, hinting a temporally limited role of this area in retrieving avoidance memory (79). Whether the permanent store of affective memory involves the amygdala has been intensely debated (8, 29). This issue could be addressed by examining whether deactivation of the amygdala compromises memory expression at various

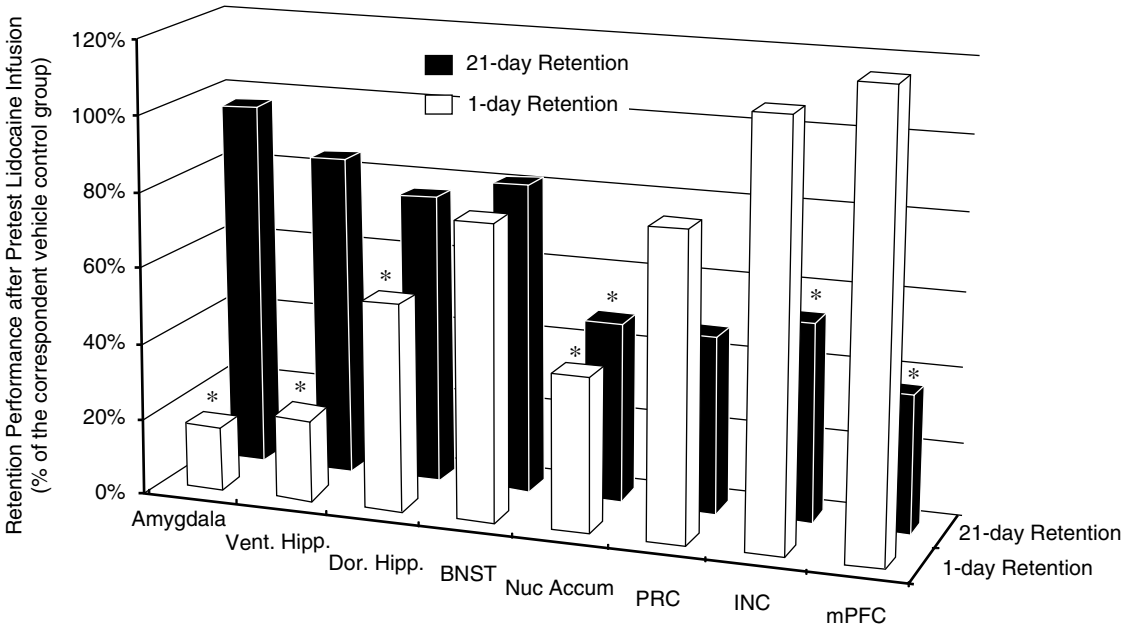

Fig. 4. Effects of pre-test suppression of various brain regions on retention in the 1-day or 21-day test. Each bar represents the percentage of median retention score of the lidocaine treated group to the correspondent vehicle treated groups. *Significantly different from the correspondent vehicle group, $P < 0.05$.

retention intervals. We addressed this issue by training various groups of rats on the inhibitory avoidance task and tested them at various times after training. Intra-cranial infusion of lidocaine was administered 5 min prior to a retention test (62). The results shown in Fig. 4 indicated that an impairing effect of pretest intra-amygdala infusion of lidocaine was observed only when retention was tested within a week after training. In the 21-day test, pretest intra-amygdala infusion of lidocaine had no effect. Pretest infusion of lidocaine into the dorsal or ventral hippocampus affected the 1-day but not 21-day retention, the nucleus accumbens was involved at both retention tests and the BNST was involved at neither test.

Thus, functional integrity of the amygdala, dorsal or ventral hippocampus is needed for expressing inhibitory avoidance memory acquired recently but not for expressing memory acquired at a remote time. Treatments applied before a test may affect retention by influencing performance factors. However, if the impaired retention were caused by compromise in sensory or motor ability, the 1-day and 21-day retention performance should have been equally impaired. As the amygdala and hippocampus are implicated in processing fear or anxiety induced by negative stimuli, the results may also suggest that retrieval of a recent memory of frightening experience relies more on the emotional state but retrieval of a remote memory of that does not.

In contrast to our findings, in conditioned-fear potentiation of startle electrolytic lesions of the amygdala 6 or 30 days after training induced the same extent of memory deficit (51) and NMDA lesions of the basolateral amygdala impaired expression of memory formed 1 day or even 16 months in contextual fear conditioning (30). It should be noted that the two studies observing retrograde amnesia without temporal gradient after posttraining amygdala lesions found that the lesions did not prevent reacquisition of the abolished response (50, 30), suggesting that the trace for fear memory underlying reacquisition must rely on structures outside the destroyed amygdala.

A follow-up question is what brain region is responsible for expressing a 21-day memory in the inhibitory avoidance task. Cortical regions have been implicated for long-term storage of information. A previous study showed that infusion of CNQX into the amygdala, dorsal hippocampus, entorhinal or parietal cortex before a 1-day test suppressed memory expression in an inhibitory avoidance task, the drug infused into the entorhinal or parietal cortex had the same effect when given before a 30-day test, but by given before a 60-day test only infusion of CNQX into the parietal cortex was effective (41). These results suggest that the regions critical for memory retrieval becomes independent of limbic structures but more upon the cortical areas as the retention interval lengthened.

Results from this laboratory indicated that pre-

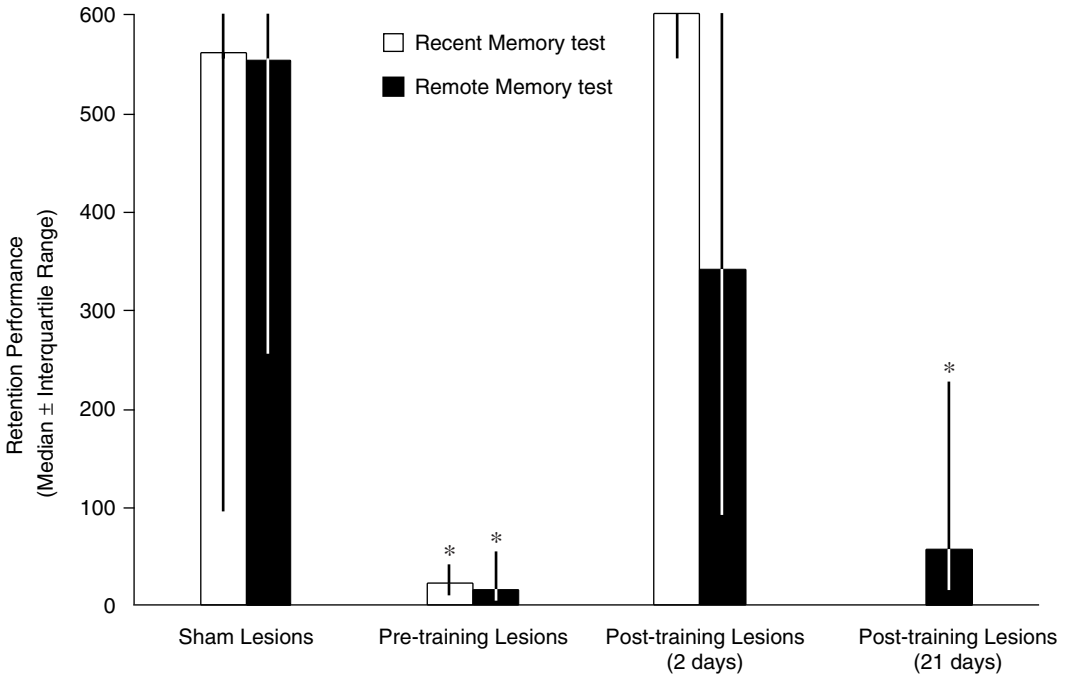

Fig. 5. Effects of NMDA lesions of the medial prefrontal cortex at various times (2 days before training, 2 days after training or 21 days after training) on recent (7 days) or remote (28 days) memory in the inhibitory avoidance task. *Significantly different from the sham lesioned group, $P < 0.05$.

test infusion of lidocaine into the insular cortex or medial aspect of the prefrontal cortex (mPFC) impaired retention performance in the 21-day test but not in the 1-day test, an effect with similar trends was also detected for the perirhinal cortex (67). We also showed that intra-amygdala infusion of CNQX before a 1-day test impaired memory expression but that before a 21-day test had no effect. In contrast, intra-mPFC infusion of CNQX prior to a 1-day test did not impair retention but that before a 21-day test did (72). These findings suggest that expression of a remote but not a recent memory requires integrity of the mPFC glutamate neurotransmission *via* AMPA receptors, yet expression of a recent but not a remote memory relies on that in the amygdala.

When results on memory formation and expression are considered together, an intriguing finding emerges: The mPFC is critical for memory formation and remote memory expression but not for recent memory expression. These results suggest that training initiated in the mPFC two processes: One involves enabling consolidation of a newly learned memory by interacting with the amygdala or other brain regions; the other involves a latent process ongoing for a period of time that eventually enables the mPFC in memory expression long after training. Effects of NMDA lesions of the mPFC at various times shown in Fig. 5 confirmed this dual processing role. Rats with the lesions given at 2 days before training, which affected acquisition and consolidation of memory, showed poor recent (7-day) and remote (28-day) memory; rats with the lesions given at 2 days after training, which did not affect acquisition and memory formation, showed no significant memory deficit in the 7-day and 28-day memory tests. However, rats with the lesions given at 21 days after training that would affect remote memory operation showed poor retention in a later (28-day) test. Thus, there is a period of time in which the mPFC appeared not to be involved in operation of the inhibitory avoidance memory.

Other data also shed lights on this discontinuity of the mPFC role in memory processing: CNQX infused into the mPFC immediately after training impaired retention in both 1- and 21-day tests, yet APV infused into the mPFC immediately after training had no effect on the 1-day retention but a marked impairing effect on the 21-day retention (72). These data are consistent with an interpretation that the mPFC interacts via normal glutamate transmission with other brain areas after training to form a memory trace elsewhere in the brain, thus blocking the AMPA receptor in it renders the animal amnesic at all times. This interaction also launches in the mPFC an NMDA-dependent process that takes a longer period to mature and is responsible for expressing a remote memory. Recent studies showed that acquisition in conditioned fear potentiation of startle altered neuronal

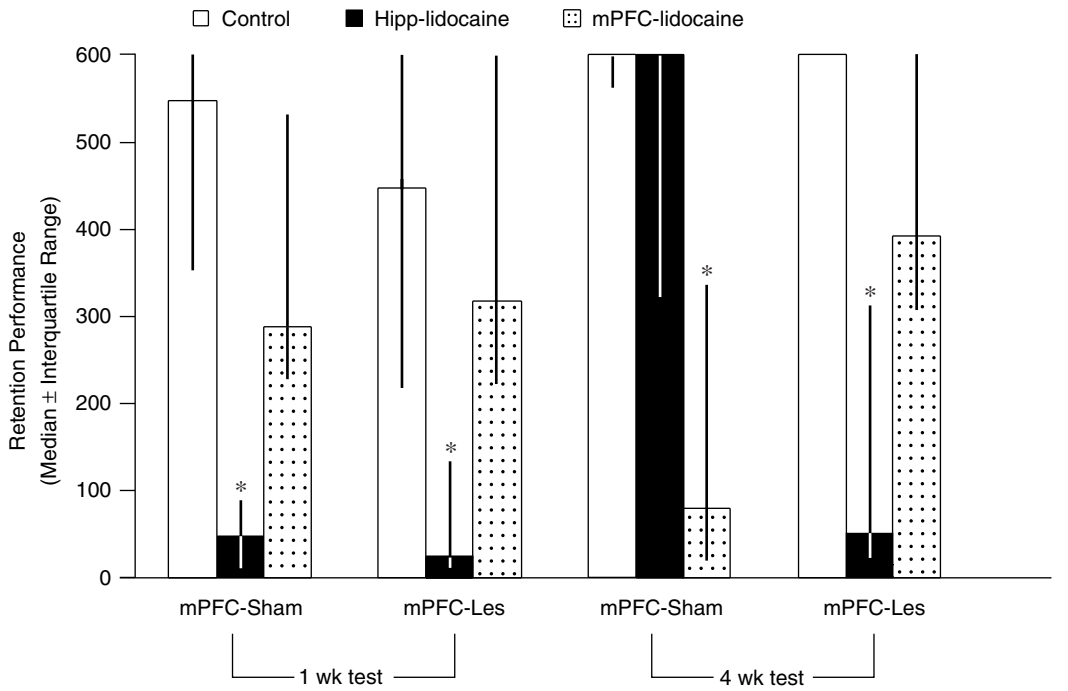

Fig. 6. Effects of pre-test infusion of lidocaine into the dorsal hippocampus or medial prefrontal cortex on retention of recent (1 week) or remote (4 weeks) memory in rats with sham lesion or NMDA lesions of the medial prefrontal cortex (mPFC) given two days after training. In the sham lesioned rats, suppressing the dorsal hippocampus impaired recent memory retrieval and suppressing the medial prefrontal cortex impaired remote memory retrieval. In the mPFC lesioned rats, suppressing the dorsal hippocampus impaired retrieval of both recent and remote memory, while lidocaine infused into the already-lesioned mPFC had no effect. *Significantly different from the correspondent control group, $P < 0.05$.

activity in the rostral anterior cingulate cortex (52) and the area was also involved in acquisition of conditioned freezing by interacting with the amygdala (7). A recent study further showed that in the mPFC neuronal correlate of memory for the eye-blink response reached its asymptotic level only one week after training on tone-shock association (120). Suppression of this region compromised remote but not recent memory expression in taste aversion conditioning (25).

An intriguing point shown in Fig. 5 is that mPFC lesions made 2 days after training caused no significant deficit in a 28-day test, indicating relatively normal performance at a remote memory test even without the mPFC. It is interesting to find out which brain region is responsible for operating remote memory in rats without the mPFC. We trained rats on the inhibitory avoidance task and received NMDA or sham lesions of the mPFC two days after training and tested for retention in recent (1 week) and remote (4 weeks) times. Five minutes prior to a retention test, rats received 4% lidocaine infused into the mPFC or dorsal hippocampus. Fig. 6 shows the results that in rats with sham mPFC lesions pretest intra-hippocampal infusion of lidocaine impaired retention in the 1-week test but pretest intra-mPFC infusion of lidocaine impaired retention in the 4-week test. However, in animals bearing mPFC lesions, intra-hippocampal infusion of lidocaine impaired retention in the 1-week and 4-week tests. The findings suggest that if the mPFC is damaged after initial consolidation of memory, the dorsal hippocampus would remain critical for operating the memory at all retention intervals. Whether this holds for the amygdala remains to be investigated.

The above findings indicate that the regions critical for operating memory in an inhibitory avoidance task may shift from the amygdala or hippocampus to the mPFC along with time. The process may be accomplished either in parallel or in succession: Training may set off two parallel processes in the brain with one involving the limbic structures responsible for operating a recent memory and the other involving cortical areas to operate a remote memory. Alternatively, the cortical trace is established after formation of the limbic trace and maturation of the former requires sustaining support from latter. The succession view, but not the parallel view, predicts that lesions in the limbic regions shortly after the initial consolidation period would prevent the remote memory trace from establishment and thus impair retention tested long after training. Our data have

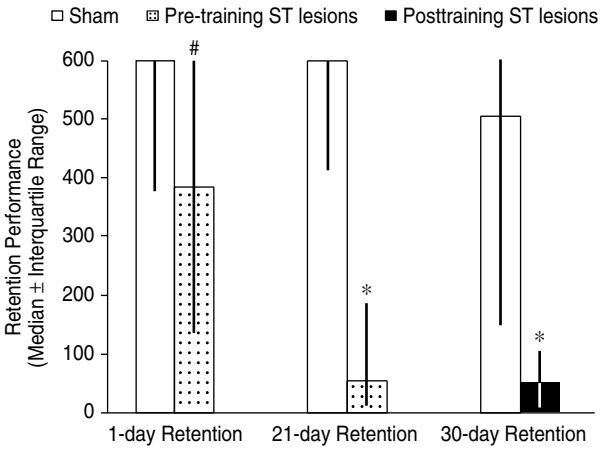

Fig. 7. Effects of pretraining (2 days before training) or posttraining (2 days after training) lesions of the stria terminalis on retention at various retention intervals. *Significantly different from the sham lesioned group, $P < 0.05$; $^{\#}P < 0.10$.

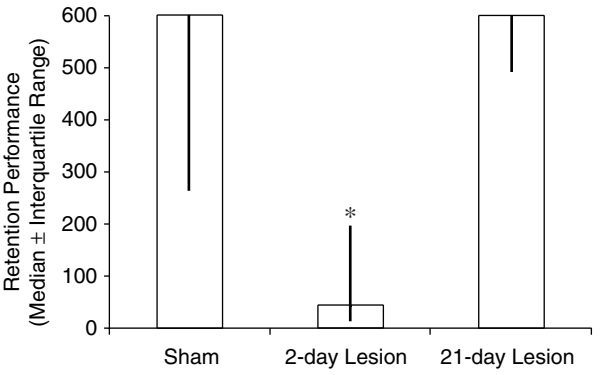

Fig. 8. Effects of posttraining ibotenic lesions of the dorsal hippocampus at 2 days or 21 days after training on retention performance in a 28-day test. *Significantly different from the sham group, $P < 0.05$.

addressed this issue.

The early results that amygdala lesions made 2 or 5 days after training impaired retention tested at 4 or 7 days after training (77) suggest necessity of the amygdala for retention in a later time. Consistently, while a previous study showed that pretraining ST lesions blocking an amygdala input-output pathway yielded an insignificant deficit unless the lesion was combined with adrenal demedullation (65), our recent results indicated that this small deficit in a 1-day retention test grew into a great deficit in a 21-day test; congruently, ST lesions administered 2 days after training did not affect retention in a recent test but impaired that in a remote test (Fig. 7). These findings attest to the necessity of an amygdala connection system for intact memory at long retention intervals. Such a role has also been shown for the dorsal hippocampus in an inhibitory avoidance task. Rats received hippocampal lesions with ibotenic acid at 2 or 21 days after training and were tested at 4 weeks after training. Results showed that rats receiving the lesions 2 days after training showed poor memory at the retention test but rats having the same lesions 21 days after training showed retention as good as the sham rats. These data suggest that maturation of remote memory depends on the integrity of dorsal hippocampus for a certain period of time after training (Fig. 8).

Neural Correlates for Formation and Expression of Inhibitory Avoidance Memory

Neurophysiological or biochemical activation measured in brain regions provides clue for their roles in acquisition and retention of the inhibitory avoidance response. A recent study showed that inhibitory avoidance training induced a form of LTP in dorsal hippocampal neurons and its expression was responsible for retention of the learned response (127). Two laboratories have recorded neuronal activity in the amygdala during training or testing of this task. Using a 1-trial conditioned emotional response paradigm, Pelletier and colleagues trained cats to press a lever for food and then at the presence of a tone lever pressing resulted in a shock (91). By continuously recording the basolateral amygdala nuclei for a long period of time around the single pairing trial, the authors detected a marked increase of unit activity induced by the shock, which on average peaked approximately at 30 min and subsided at 2 h after the shock. Further, the responsive units fired more synchronously. The elevated firing rate and the more coherent firing pattern detected in the basolateral amygdala was taken to reflect a consolidation process going on after the one-trial emotional learning and to imply the vitality of amygdala in formation of inhibitory avoidance memory (91, 103).

Our laboratory trained rats on a one-trial step-through inhibitory avoidance task, unit activity of the central, lateral, or basolateral nuclei was recorded from behaving rats before and after training to correlate with behavior change (11). Previous data have shown that within a training session of fear conditioning, some neurons in the basolateral nuclei altered their activity in an initial phase but not in a late phase and vice versa in other neurons (107). In congruence with these data, we found that some neurons were activated during training. When activity was monitored throughout all sessions and ensemble activity was collapsed from all recorded neurons, increased amygdala discharge was observed at rat's first entrance to the task chamber. Such activation habituated as the rat acclimated to the chamber. The foot shock training

re-kindled the activity increase that persisted after the task. These findings suggest that the former foot shock experience increased the amygdala firing as a rat re-entered the context.

However, when the activity change of all neurons recorded from the same rat was correlated with the retention performance, the firing score failed to predict retention performance. Neurons in an ensemble might be functionally heterogeneous with their discharge differentially linked to various behavioral aspects. As activity of individual units was examined, three types of neurons were found. Units noted as the habituation type fired vigorously only in the first acclimation session and showed no further activation thereafter. A second type of units showed learning-related activity changes with little activity change during the acclimation sessions but firing increased substantially in the test after the foot shock experience. A third kind of units was the mixed type showing in the first acclimation session vigorous activity that subsided in the third session but re-appeared in the retention test after foot shock training. This type of activity change was reported in previous findings that amygdala units showing altered activity to conditioning were those initially responsive to the conditioned stimulus (5). Responsive units distributed over the central, lateral and basolateral nuclei.

Many amygdala units showed temporal modulation of firing in a test session. As some rats shuttled back and forth between the two compartments during the test, it is feasible to check whether the unit activity had any relationship with behavior in the test chamber. When the transient ensemble activity from a bundle electrode in a rat was compared between the 5-s periods before and after a movement, it was found that the amygdala unit activity was more likely to decrease as a rat entering the dark side and to increase as the rat leaving it (11). For the single unit activity and behavior, three types of relationship were found: One type of units showed vigorous firing as a rat stayed in the lit side but decreased radically as it walked into the dark side, another type of units showed just the opposite behavior; and the last type showed a firing pattern not related to the location side. Increased firing at a preferred site pre-existed before learning in some neurons that may code the emotion significance as shown by a previous study (100), but in others the increase appeared only after training and could be related to learning processes.

An issue relevant to judge a neural correlate of learning is how well it parallels with the behavior. One way to address the issue is to determine if the activity correlate can somehow distinguish the learned information. We approached this by successively training a rat on two inhibitory avoidance tasks (80): an inescapable step-through task motivated by foot shock and an escapable step-down task motivated by floor heat. We calculated the coefficients of cross-correlation between the mean firing rates of all recorded units in the two tasks and found that the correlation was significant in the acclimation sessions but became negligible in test sessions. These findings hint that amygdala neurons appeared to react differentially to the two sets of contextual or proprioceptive cues once different aversive emotional experience is attached, thus they could be viewed as specific to the learned experience. However, scrutiny on activity of individual neurons in relation to the two tasks shows that in addition to neurons highly responsive to a selective task, some neurons responded highly to both tasks (80). Thus units with unique and general responses to two tasks are all found in the amygdala.

Whether such activation shown in a task bears any causal relationship with the learned behavior is a question kernel to the recoding studies and addressable only by a manipulative approach. As highly responsive units were found in the central, lateral and basolateral nuclei for both step-through (inescapable) and step-down (escapable) tasks (80), one would expect that lesions in any of these nuclei would impair retention of the two responses indifferently. However, as mentioned in the previous section lesions placed in any of these nuclei did impair memory in the inescapable task, but only lesions of the basolateral or lateral nuclei impaired memory in the escapable task (11). Thus the significance of activity change in the central amygdala nucleus remains obscured. In addition, the responsive neurons were found to distribute evenly in the left and right amygdala (11, 80), however, several previous studies have shown that disrupting the right amygdala is more devastating than disrupting the left one for formation or expression of an aversive memory (19, 20, 53). These results render the significance of neuronal activation in the left amygdala also obscured.

The long-lasting memory in this task provides a good opportunity for evaluating the persistence of amygdala neuronal changes in a prolonged retention period. In an experiment using a step-down task, rats were trained on and tested immediately, 1 or 10 days after training. Data on neuronal activity were available in four rats. Two of them showed good retention in an immediate test, but not in the 1- or 10-day test, the rest two showed good retention in all tests. In the two animals with long-lasting memory, the ensemble activity showed no increase in the 10 day test, indicating lack of parallelism between neuronal and behavioral changes (80). These negative results may be due to loss of the recorded neuron by the electrode in a 10-day period, or according to the previous findings that the correlated activity may shift to another set of neurons in the amygdala or even out of the amygdala. The latter possibility hints the involvement

of other brain structures in mediating the long-term storage for an inhibitory avoidance task.

In summary, abundant evidence from manipulative studies confirms a role of the amygdala in memory formation processing in the inhibitory avoidance task. Evidence on neuronal plasticity in the amygdala associated with acquiring this task begins to compile. Neuronal correlates have been detected during acquisition, consolidation, and expression of 1-day memory, but those associated with long-term retention are yet to be demonstrated. Some of the correlates appeared to involve coding for specific information in a task but others seemed to reflect the more general aspects in different tasks. Findings in the manipulative and correlative studies taken together have not yet been able to confirm a role of the amygdala in permanent storage of memory for the inhibitory avoidance task; however, they cannot refute a possibility that the amygdala may mediate some aspects of behavior changes either. Thus, the available evidence warrants at least an inferentially more conservative view that for an integrated inhibitory avoidance memory the amygdala subserves a modulatory role on formation but does not store the permanent memory trace; however, other possibilities remain viable.

Conclusion and Implication

According to the above data, how memory of an inhibitory avoidance response may operate in the brain may be speculated as follows: Training experience activates distributed structures, including the amygdala and hippocampus, which process various sorts of information contained in the experience. Neurons in the amygdala receive neural and humoral inputs signifying the emotional impact of other sensory inputs and those in the hippocampus carry out binding operation on all information from cortical and subcortical regions. They communicate with many other active forebrain regions including the BNST, nucleus accumbens, ventral subiculum, entorhinal, insular, anterior cingulate and medial prefrontal cortices during or shortly after training. To form a versatile memory trace, information processed at all brain regions has to be integrated into a unified neural trace through modulation, reverberation, suppression, or other forms of interaction in neural activity among the various sites, each of these processes may occur between specific sites at a specific time after training.

Throughout the process, the amygdala and hippocampus intimately cooperate in coordinating all kinds of interactions involved. When emotional impact of the event is optimal, the amygdala output would facilitate the hippocampus to integrate activity disseminated in the brain into a coherent neural trace. Such a process results from plasticity cascades not only at the cellular level for the target sites but also at a circuit level. That is, slight plasticity changes at an initial site in an early stage of information processing may be amplified through transmission along the multiple-synapse circuit over the processing time and eventually build up sufficient alterations to subserve the final memory trace, as previous findings have implicated (18, 126, 130). Changes at any individual site would not only alter some aspects of behavior under its control but also promote changes at its mutually connected regions. Thus, a structure in the circuit may subserve both mediating and modulatory roles during memory formation. The widespread output to various forebrain regions (104) places the amygdala in a strategic position for the latter function as a memory modulating site for the inhibitory avoidance task, yet this is not incompatible with its role in the former function such as mediating heart rate change or freezing behavior. It takes all changes in the circuitry to account for a complete memory of the inhibitory avoidance response or even any other emotional event in a normal state. Thus, rats with compromised the amygdala function froze less in a context previously paired with shock but nonetheless avoided it if other choice existed (125). We suggest that all the criteria used to scrutinize the role of the amygdala in memory should be equally applied to examine other regions also implicated in this function, such as the hippocampus or mPFC.

Results from our studies showed that the neural trace once established undergoes further dynamic changes during the retention period: Its expression relies more on the limbic structures at an early phase but eventually shifts to the cortex. Establishment of a late-matured cortical trace requires continuous support from those early operating structures for a period of time after training; this sustained support may rely on the plasticity present in the hippocampus and amygdala that are activated during training. Maturation of the cortical based operation in turn disengages the limbic areas from memory operation. This disengagement may be accomplished by the inhibitory influence sent from the mPFC to the amygdala that has been shown to be involved in extinguishing conditioned fear (99). A structure joining and leaving the memory circuitry at different times have been foretold by the learning theory of Hebb (36) as “recruitment” and “fractionation” in his concept of phase sequence that operates the complex memory in a matured brain. The above view is consistent with our previous findings that buspirone, an atypical anxiolytic drug, impaired memory expression in an inhibitory avoidance task if given before a 1-day test but had less of an effect if given before a 21-day test (79). A parallel finding is that after mastering an active avoidance response a rat showed less rather

than more fear as tested in a conditioned emotion response paradigm (44). This view fits with our subjective experience that emotion is more intensely aroused when we think of a recent aversive event than a remote one.

Our view explains the paradoxical findings reported by a brain imaging study for lack of amygdala activation in recollecting a long-past fear experience by normal human subjects (22) even though the amygdala is often activated by emotion-arousing stimuli. In contrast, during imagining the past traumatic event regional blood flow in the anterior temporal pole including the amygdala was found to be higher in the post-traumatic stress disorder (PTSD) patients than in those who experienced the same trauma but did not developed PTSD. Also in congruence with our idea of the operational shift in emotion memory is the finding that the anterior cingulated cortex was more activated in those non-PTSD subjects in response to stimuli related to the past trauma (119). These findings, taken together, suggest that disengagement of the amygdala from recalling a remote terrifying experience in the normal subjects would not occur in the PTSD patients. This disengagement may represent a fear extinction process that naturally occurs in a normal brain after encountering a frightening incident but is defective for the PTSD patients.

According to the present model, it is likely that under a traumatic event, the highly activated amygdala inhibited hippocampal LTP (2, 49) that works as a binding mechanism for integrating information processing in the cortex into a unitary memory (123). With impaired LTP in the hippocampus, cortical regions including the mPFC simply could not achieve integration and would not receive enough support to build a late trace. Without recruiting the mPFC, or other cortical regions as well, into memory operation, the amygdala could never be disengaged from the circuit since its initial engagement. Thus recalling the event would always activate this area in the PTSD patients, and hence result in hyper-vigilance and avoidance in them. Fragmental memory in re-experiencing and the impaired declarative memory in the patients may be due to suppression of the hippocampal function and failure of binding individual sensory fragments into a cohesive episodic memory. This explains why the PTSD patients showed strong emotional reactions to relevant cues but poor narrating memory for the trauma event. From this point of view, some intrinsic memory debilitating factors in the amygdala (*e.g.* serotonin) may be a natural device evolved to reduce the impact of a traumatic event on the amygdala and hence prevent the integration function of the hippocampus from being compromised. People vulnerable to traumatic experience may be due to the weakness in such memory debilitating or erasing systems. These implications on the pathogenesis of PTSD derived from this distributed and dynamic neural trace model of inhibitory avoidance memory remain to be further tested in both animals and humans.

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