

## Amygdala activity at encoding correlated with long-term, free recall of emotional information

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**ABSTRACT** Positron emission tomography of cerebral glucose metabolism in adult human subjects was used to investigate amygdaloid complex (AC) activity associated with the storage of long-term memory for emotionally arousing events. Subjects viewed two videos (one in each of two separate positron emission tomography sessions, separated by 3–7 days) consisting either of 12 emotionally arousing film clips (“E” film session) or of 12 relatively emotionally neutral film clips (“N” film session), and rated their emotional reaction to each film clip immediately after viewing it. Three weeks after the second session, memory for the videos was assessed in a free recall test. As expected, the subjects’ average emotional reaction to the E films was higher than that for the N films. In addition, the subjects recalled significantly more E films than N films. Glucose metabolic rate of the right AC while viewing the E films was highly correlated with the number of E films recalled. AC activity was not significantly correlated with the number of N films recalled. The findings support the view derived from both animal and human investigations that the AC is selectively involved with the formation of enhanced long-term memory associated with emotionally arousing events.

Many studies have reported that emotional arousal is associated with enhanced long-term, conscious recall in humans. In one of the earliest examples, Stratton (1) described the unusual degree of vividness and detail of memories for emotional events, such as automobile accidents and earthquakes. Referring to hypermnnesia for events experienced during a period of emotional excitement, Stratton noted that “the person recalls in almost photographic detail the total situation at the moment of shock, the expression of face, the words uttered, the position, garments, pattern of carpet, recalls them years after as though they were the experience of yesterday.” Many other controlled laboratory investigations and “field” studies of memory clearly demonstrate that, under appropriate conditions, emotional arousal is associated with enhanced long-term, conscious recall (2–9). However, the mechanism(s) underlying the enhancement is not yet clear (10).

Considerable evidence from studies using animal subjects suggests that the amygdaloid complex (AC) plays a critical role in modulating the formation of long-term memory associated with emotionally arousing events (11–14). The findings support the view that the AC is part of an endogenous memory modulating system that functions to regulate the strength of memories in relation to their importance. The AC is proposed to interact with endogenous stress hormones (especially catecholamines) released during emotional events to modulate memory storage (11).

Further support for this view comes from recent studies of rare patients with selective AC damage. Long-term (1 week)

recall was examined in one such patient (15). Although the patient’s recall of relatively nonemotional material appeared normal, he showed no evidence of enhanced recall normally associated with emotional arousal (15). These results are consistent with other recent reports involving AC-lesioned patients that suggest a selective role for this structure in long-term, emotionally influenced conscious recall (16–18).

The present study used positron emission tomography (PET) to examine further the involvement of the AC in long-term memory for emotionally arousing experiences. Subjects in this experiment received two PET scans: one while viewing a series of relatively emotionally neutral films (“N”) and the other while viewing a series of relatively emotionally arousing (aversive) films (“E”). Retention of the films was tested 3 weeks after the second PET session. If the AC is primarily involved with the formation of long-term memory during emotionally arousing situations, then the PET analysis should reveal AC activity related to retention of the relatively emotional, but not relatively neutral, films.

### MATERIALS AND METHODS

**Subjects.** Eight right-handed male subjects were recruited through campus advertisements and were paid \$200.00 for participating in the experiment. Their average age ( $\pm$ SEM) was 21.1 ( $\pm$ 1.1) years. Exclusionary criteria included any major medical or psychiatric illness, substance abuse, or history of head injury. All gave informed consent in accordance with the University of California Irvine Institutional Human Subjects Review Committee.

**Materials.** Two videos, each composed of 12 film clips, were presented as stimuli during the PET sessions. One was composed of relatively emotionally neutral film clips (N), and the other comprised relatively emotionally arousing film clips (E). The clips were obtained from documentary-style, commercially available videos. The average length of each film clip for both videos was slightly over 2 min [average film clip length: E, 138 ( $\pm$ 18.8) sec; N, 145 ( $\pm$ 15.9) sec]. Before the experiment, independent judges viewed each of the 24 film clips and rated (*i*) how emotional they found the film to be [on a scale of 0 (“not emotional”) to 10 (“highly emotional”)] and (*ii*) how well they felt they understood the film [from 0 (“not at all”) to 10 (“completely”)]. The average rating ( $\pm$ SEM) by the judges of emotional reaction to the 12 N films was 1.98 ( $\pm$ 0.27) versus 5.25 ( $\pm$ 0.44) for the E films. This difference was highly significant ( $P < 0.001$ , two-tailed *t* test). However, the N and E films did not differ in their level of understandability; average ratings of understandability were 9.01 ( $\pm$ 0.23) for N films and 9.26 ( $\pm$ 0.12) for E films (not significant). All of the

Abbreviations: AC, amygdala complex; PET, positron emission tomography; N, emotionally neutral films; E, emotionally arousing films; GMR, glucose metabolic rate; rGMR, relative GMR; CM, cannthomeatal.

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E films were described by the judges as arousing negative emotions, such as fear or disgust. The E films depicted themes such as animal mutilation or violent crime. The N film clips were taken from the same sources as the E films, and were therefore very similar to the E films in their documentary style and their depiction of a single major theme. The N films depicted themes that were much less emotionally arousing than the E films, such as a court proceeding, a stunt man performance, and a travelogue.

The order of film clips in each video was the same for all subjects. For the E video, those clips rated as most emotional by the judges were, in general, placed first in the video. Conversely, those films (of 12) rated as least emotional were placed first in the N video. The films were ordered in this way to maximize the chances of detecting glucose differences between the E and N sessions because most of the measured activity reflects the first 15–20 minutes of tracer uptake (19).

**Procedure.** Each of the eight subjects completed two PET sessions. The sessions were separated by 3–7 days (the differences were due to scheduling difficulties with the subjects). During one session, they viewed the E video; during the other session, they viewed the N video. Session order was counter-balanced across subjects: four subjects watched the N video first and the remaining four watched the E video first. Subjects were asked to watch each film clip and then rate how emotional they found the clip to be on a scale of 0 (“not emotional at all”) to 10 (“extremely emotional”). The instructions to the subjects emphasized that their rating was to reflect only their personal emotional reactions. They were told they would have  $\approx 10$  sec at the end of each film clip to write down their rating before the start of the next clip. Subjects were not told which video they were viewing nor was any mention of a memory test made. Video viewing took place in a darkened, sound-attenuated room.

Three weeks after the second session, the subjects were contacted by phone (one subject in person) and asked to recall as many film clips as possible from both film sessions. They were told to take as much time as they wished and to continue until they felt they could recall no more. The subjects took 5–15 min to complete their responses. In the vast majority of cases, the films referred to by the subject were clearly identified. In those few cases where one was not, the subjects were asked to give some more detail about the film until the film referred to was made clear to the investigator (L.C.). After the recall session, the subjects were debriefed as to the intent of the study. All subjects indicated that they were unaware that their memory would be tested.

**PET Scan Procedures.** A standard procedure was followed as described in Haier *et al.* (20). Each video began about 30 sec before the subject was injected with  $^{18}\text{F}$ -fluoro-2-deoxyglucose (FDG), a glucose analog tracer used to determine regional

brain glucose metabolic rate (GMR). Subjects then watched the video for  $\approx 32$  min while 80–90% of the FDG was taken up by the brain. Following the uptake period, the injected FDG remains metabolically fixed for several hours, with the highest concentrations occurring in the brain areas that were the most metabolically active during the 32 min. Scanning was done after the FDG uptake and labeling with a GE2048 scanner (full-width half maximum resolution about 4.5 mm in plane). Transmission scans obtained for each subject were used for attenuation correction. Thirty overlapping axial slices parallel to the canthomeatal (CM) line were obtained at 5-mm intervals (15 slices simultaneously). Each subject wore an individually molded thermoplastic mask to locate the CM line and hold the head still during the scanning. This results in head placement errors between the two scans of less than 2 mm, which is well within the spatial resolution of the scanner. GMR was calculated following Sokoloff *et al.* (19) in micromoles of glucose per 100 grams of brain tissue per minute. Relative GMR (rGMR) was calculated by dividing the GMR of each pixel by whole slice GMR. rGMR corrects for the wide individual differences typically found in whole brain GMR.

Each subject's PET data were transformed to a standard brain outline where pixel-by-pixel comparisons were made following methods similar to those of Friston *et al.* (21). Results are displayed on a standard brain outline based on the Matsui and Hirano (22) stereotactic brain atlas. Modified Talairach and Tournoux (23) atlas coordinates for the major finding are also given. In a standard subtraction analysis, rGMR in each condition (E versus N) was compared by pixel-to-pixel paired *t* tests. In a second analysis, rGMR in each condition was correlated, pixel-by-pixel, with the number of films recalled from the respective session for each subject (using Pearson product-moment correlation). Although both of these computations were conducted on the whole brain, our analysis focuses only on the AC, shown best in slice 11 at 21% of head height from the CM line (22). Pixels with statistically significant *t* test differences or correlations ( $P < 0.05$ ) were displayed on the standard outline. A neuroanatomist (J.F.) confirmed the location of significant effects.

## RESULTS

**Emotional Ratings of Films and Memory.** As predicted on the basis of the prior independent ratings, the subjects in this experiment rated their emotional reaction to the E films higher than those for the N films. The average ( $\pm$ SEM) rating of emotional reaction for the E films was 5.17 ( $\pm 0.73$ ) versus 3.09 ( $\pm 0.69$ ) for the N films ( $t = 2.19$ ,  $P < 0.05$ , one-tailed paired *t* test). These results are shown in Fig. 1A. Fig. 1B shows the average number of films recalled (out of 12 possible) by the

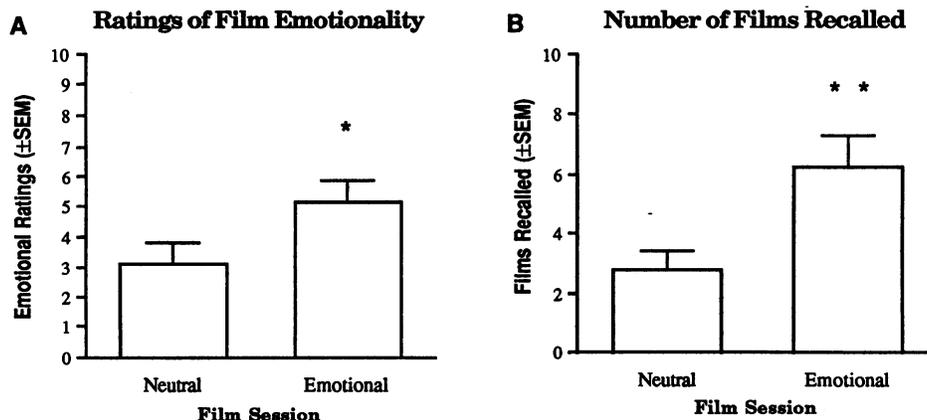


FIG. 1. (A) Average ratings of emotional reaction to films for the neutral and emotional film sessions. \*,  $P < 0.05$  from the neutral group value. (B) Average number of films recalled from both sessions (out of 12 possible for each session). \*\*,  $P < 0.05$  from neutral group value.

subjects for both film sessions. Subjects recalled significantly more E films than N films. The average ( $\pm$ SEM) number of films recalled for the E session was  $6.25 \pm 1.06$  versus  $2.75 \pm 0.67$  for the N session ( $t = 2.86$ ,  $P < 0.05$ , two-tailed paired  $t$  test).

**AC Activity.** The subtraction analysis revealed no significant differences in AC activity measured during the E and N film sessions. However, differences in AC activity between the sessions were revealed by the correlational analyses. Fig. 2 shows a horizontal brain section at the level of the AC. Fig. 2A shows brain regions from the E session in which rGMR was significantly correlated positively (orange/yellow) and negatively (blue/green) with the number of films recalled from the E session. Fig. 2B shows brain regions in which rGMR from the N session was significantly correlated with the number of films recalled from the N session. The principal finding (indicated by the arrow) was a region of the right AC [modified Talairach coordinates (23): Z,  $-16.00$  mm; X,  $+18.8$  mm; Y,  $4.8$  mm] in which activity during the E session was positively correlated with retention of E films. Activity of the same region during the N session was not correlated with the number of N films recalled. In addition, horizontal slices above and below the level represented in Fig. 2 revealed significant correlations in the center of the right AC that were also selective for the E session (data not shown). Slices below the level represented in Fig. 2 also contained pixels of significant correlation in the left and right superficial inferomedial temporal lobe, which is consistent with a localization to the periamygdaloid cortex, uncus, parahippocampal cortex, and/or Brodmann's area 38 of temporal cortex. However, these were present for both the E and N conditions. Another area related to the AC, but not in the AC proper, is the substantia innominata, which contains a portion of the extended amygdala. This region showed significant correlations bilaterally between activity and recall that were selective for the E session.

The correlations between right AC activity in each session and the number of films recalled from the respective session are shown in Fig. 3. The scatter plots show the relationship

between rGMR in the right AC (the colored region indicated by the arrow in Fig. 2A) in the E or N session and the number of films recalled for each subject in that session. AC rGMR during the E session was significantly correlated with the number of films recalled from that session ( $r = 0.93$ ,  $P < 0.01$ ). In contrast, rGMR in the same region during the N session was not correlated with the number of neutral films recalled ( $R = 0.33$ , not significant).

Finally, rGMR of this AC region in each session was not correlated with the average rating of emotional reaction to the films for that session (E session,  $r = -0.04$ , not significant; N session,  $r = 0.46$ , not significant).

## DISCUSSION

This experiment was designed to investigate whether the AC in human subjects is selectively involved with memory formation for emotionally arousing situations. The main finding is that the rGMR of the right AC was significantly correlated with long-term recall of film clips from a relatively emotionally arousing film session, but not with recall of clips from a relatively emotionally neutral film session. Although some investigations have questioned the role of the AC in memory (24, 25), or have emphasized its role in nonconscious conditioning processes (26), the present findings suggest a role for the AC in long-term, emotionally influenced, conscious recall. The results indicate memory-related changes in AC activity that appear selective for emotional (aversive) material and are consistent with the view that the AC modulates memory storage for emotionally arousing events (11).

Very few published reports using brain imaging techniques have specifically addressed AC function in human subjects, especially in relation to memory. In one recent report, Hugdahl *et al.* (27) used the PET technique to study brain regions involved with aversive classical conditioning (a tone paired with a shock to the wrist). They found no evidence for changes in AC activity in this paradigm, a finding that appears to

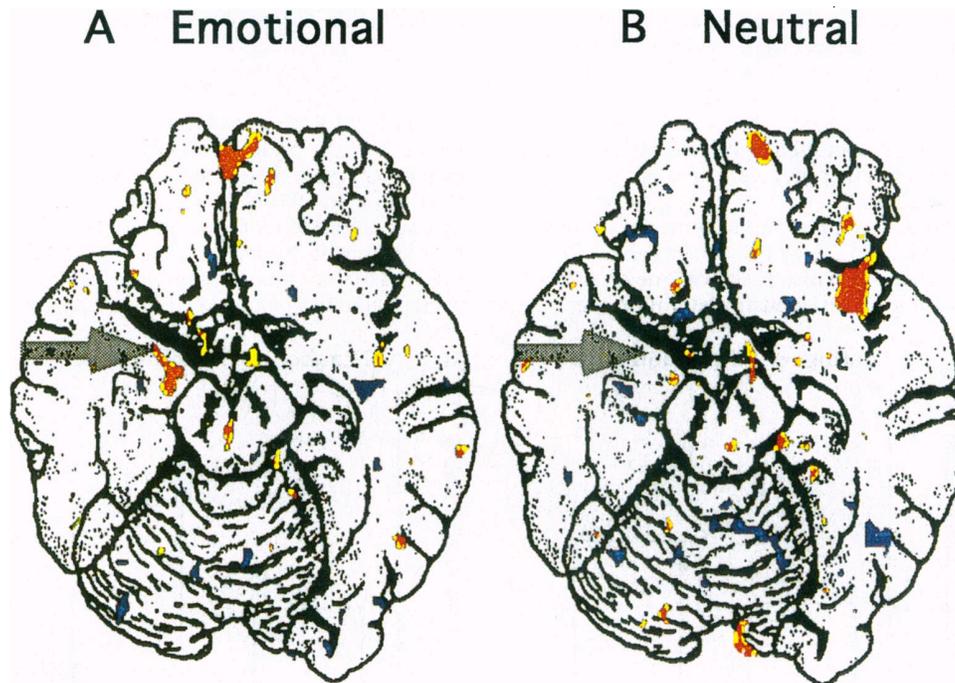


FIG. 2. (A) Axial brain section at the level of the AC [section 11 from Matsui and Hirano atlas (22), 21% of head height from CM line] showing regions whose relative GMR during the E session was significantly correlated positively (orange/yellow) or negatively (blue/green) with the number of films recalled from that session. (B) Brain regions in which relative GMR from the N session was significantly correlated with the number of films recalled from that session. The arrow points to the right AC in both cases. (Following radiologic convention, the right side of the brain is displayed on the left side of the image.) Note the area within the right AC whose activity correlated positively with recall of E, but not N, films.

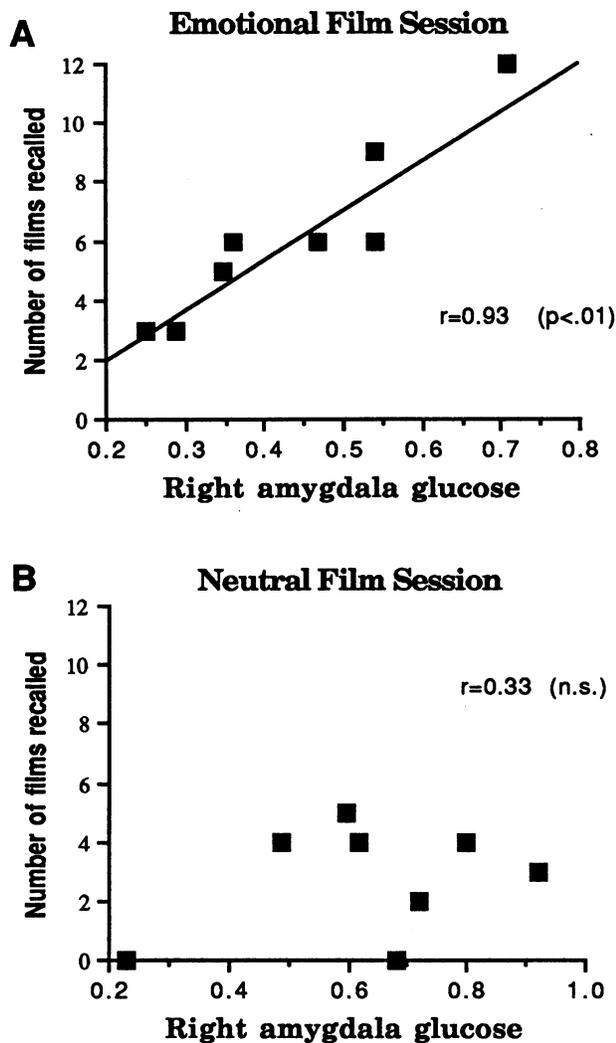


FIG. 3. Scatterplots of right AC relative GMR versus recall for both the E and N sessions. (A) Plot of relative GMR in the right AC (measured for each subject within a template defined by the large colored region in the right AC shown in Fig. 2A) during the E session and the number of E films recalled by each subject. (B) The same analysis for the N session.

contrast with a substantial animal literature on the AC role in aversive classical conditioning (26, 28). In another recent study, Rauch *et al.* (29) report that the right AC is activated during retrieval of highly emotional memories in humans, but they did not address the role of the AC in acquisition of emotional memories. Thus, the present findings appear to be the first to relate AC activity at encoding during periods of emotional arousal to subsequent retention. It is possible that the lack of correlation between AC activity and N film recall may have been due to the smaller variance in N film compared with E film recall; however, the variance in N film recall was sufficient to yield significant correlations between it and activity in other brain regions (see Fig. 2B).

AC function has been examined with brain imaging techniques in the context of various emotionally-based psychological disorders. For example, Drevets *et al.* (30) found that activity of the left AC was enhanced in depressed patients, and that the degree of activation correlated with the severity of depressive symptoms. Other studies have failed to relate AC activity to phobic fear (31–33). Finally, in a study of patients with obsessive-compulsive disorder, Horwitz *et al.* (34) found

no overall change in AC activity in the patients compared with controls. However, a correlational analysis strongly indicated that functional relationships between the AC and many other brain regions are altered in this disorder (34). It is not clear, however, how changes in AC activity during chronically altered emotional states may relate to the present finding of AC involvement in memory storage for acute emotional events.

Asymmetries in brain function have been widely observed in both animal and human imaging studies (egs., refs. 35–40). However, there is not yet an explanation for such asymmetries. Likewise, there is no clear *a priori* explanation of the present finding of asymmetrical involvement of the AC in emotional learning. Some evidence suggests that encoding (storage) and retrieval processes differentially engage the two sides of the brain. Several studies now suggest that the left prefrontal cortex is more involved with memory storage processes, and that the right prefrontal cortex is more important for memory retrieval (37, 38). Consistent with this notion of asymmetrical function, stimulation of the left AC alone is sufficient to modulate memory storage in rats (41), whereas the right AC in rats appears more involved than the left with memory retrieval (42). Furthermore, a recent PET study implicates the right AC in retrieval of affect-laden autobiographical memories (43), a finding consistent with the report of Rauch *et al.* (29) mentioned above. Therefore, it is possible that the present findings reflect a differential involvement of the left and right AC in encoding and retrieval of emotional events.

A second possible explanation for asymmetric involvement of the AC in memory for emotionally aversive material comes from recent investigations of brain activity during experimentally induced mood states. Schneider *et al.* (44) examined regional cerebral blood flow during both happy and sad mood induction procedures. They found that cerebral blood flow in the left AC increased during sad mood induction relative to emotionally neutral conditions. Another recent report (45) demonstrated activation of the left AC in humans during intense fear (induced by intra-venous injection of procaine). These findings are consistent with those of Drevets *et al.* (30) with depressed patients. The present findings may also reflect a differential involvement of the left and right AC in positive and negative emotions.

Although AC activity in this study was correlated with retention of the emotional films, it was not correlated with the average rating of film emotionality in either the emotional or neutral sessions. This is somewhat surprising given the large literature indicating that the generation of emotion (especially negative emotions like fear) requires the AC. However, a recent report involving monkeys with ibotenic acid lesions of the AC questioned the degree to which the AC is required for emotional changes associated with Kluver–Bucy syndrome (46). Our recent study (15) of a rare patient with bilateral AC damage suggested a greater role for the AC in recall associated with emotion than in the emotional reactions of the patient. Together these studies suggest that AC activity may be more important for the translation of an emotional reaction into heightened recall than it is for the generation of an emotional reaction *per se*. However, it may be that the simple rating measure of emotional reaction used in this study was not sufficiently sensitive to detect a relationship between AC activity and emotional reaction.

In this experiment, rGMR of the right AC correlated significantly with recall from the E, but not N, film sessions. However, average AC rGMR did not differ significantly between the sessions. The findings therefore indicate that the essential difference in AC function between emotionally neutral versus arousing learning situations is in the relationship between its activity and subsequent long-term recall. AC activity during encoding appears to be related to recall of emotionally arousing experiences. We did not find a comparable relationship between AC activity at encoding and recall

of relatively nonemotional experiences. Our findings add to those of a number of brain imaging studies in which correlational analyses have revealed aspects of brain function not found with standard subtraction analyses (20, 34–36, 47). In an early example, Haier *et al.* (20) reported significant individual-difference correlations between performance on a complex visuospatial task and relative GMR in several brain regions. And in recent PET investigation of eyeblink conditioning, Logan and Grafton (35) report that activity in several brain regions (e.g., the right cerebellar deep nuclei) correlated significantly with degree of learning despite the fact that the training and control conditions did not produce different overall glucose levels in these regions.

Because this experiment tested a specific *a priori* hypothesis regarding AC function, our analyses focused only on this brain region. Of course, the AC must operate in conjunction with many other brain regions. Indeed, there is extensive evidence that the AC modulates memory through its influences on other brain regions (11, 14, 41). The correlational analyses performed in this experiment revealed brain regions other than the AC whose activity during either the E or N sessions was significantly correlated with retention (see Fig. 2). As one example, the activity of a large area of the orbitofrontal cortex was positively correlated with recall of the emotional film clips (see Fig. 2), a particularly interesting finding in that the AC has a substantial projection to this area (48, 49). The correlational analyses suggest that the storage of memory for emotional and nonemotional experiences involves activation of different brain systems.

In conclusion, the results reported here support the view, derived from both animal investigations and studies of humans with AC damage, that the AC has a selective role in learning and memory processes. AC activity during emotional experiences is related to long-term, conscious recall of those experiences, but AC activity during relatively nonemotional learning situations is not. The findings further support the view that the AC modulates memory storage during periods of emotional arousal (11).

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