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Emotional arousal regulation of memory consolidation

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Recent findings provide increased understanding of how emotional arousal creates lasting memories. The findings are consistent with those of prior studies suggesting that the enhancement assessed in human subjects results from activation of adrenergic and glucocorticoid stress hormones. Additionally, fMRI imaging findings indicate that the enhancement is influenced by activation of the amygdala and its subsequent influences on other brain systems. Findings of recent animal studies using posttraining noradrenergic or optogenetic activation of the amygdala provide extensive evidence that the basolateral amygdala modulates memory consolidation by influencing neuroplasticity in downstream brain systems involved in processing different forms of memory. Activation of these systems helps to insure that emotionally significant experiences are well remembered.

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> "Memory is assisted by anything that makes an impression on a powerful passion, inspiring fear, for example, or wonder, shame or joy," Francis Bacon, 1620. [1]

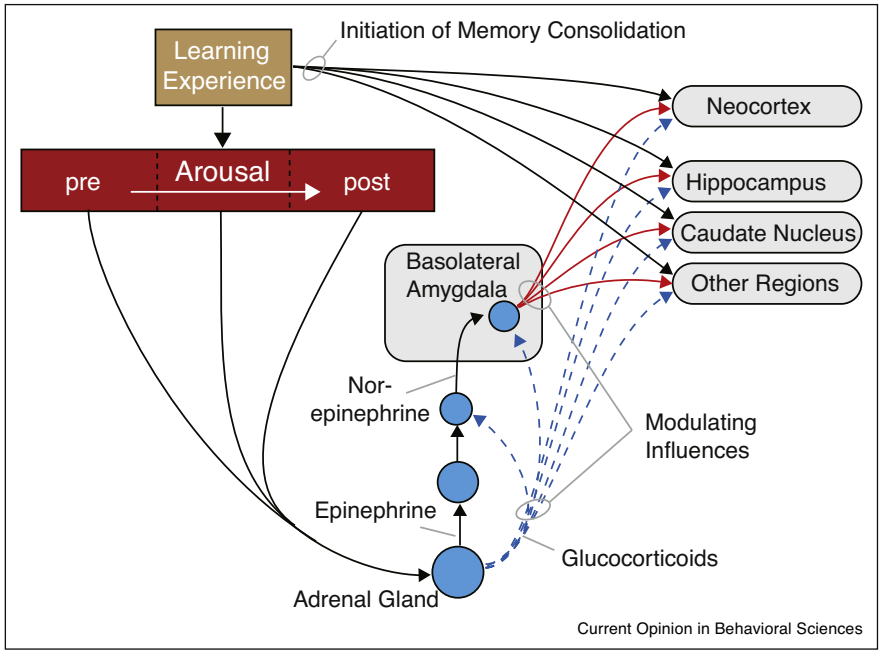
It was no doubt obvious to our ancestors, well before Francis Bacon made this observation, that emotional experiences create lasting memories. After all, strong memory of emotionally significant experiences is important for survival. Research findings of the past several decades have provided extensive evidence supporting Bacon's observation: emotionally arousing experiences, whether pleasant or unpleasant, mild or intense, tend to be remembered [2,3]. And, the findings provided significant understanding of the neurobiological processes that enable the formation of lasting memories of emotionally arousing experiences in animals as well as human subjects [4–7]. Recent findings have provided increased understanding of the conditions under which emotional arousal influences memory as well as the neurobiological bases of the influences [8–12].

Human studies of emotional enhancement of memory

Usually, in our ordinary experiences, it is the memories of the specific experiences that induced emotional arousal that are remembered. We remember achievements and praises as well as failures and insults. We remember accidents and pleasant surprises. Of course the superior memories of such experience are no doubt influenced at least in part by enhanced immediate attention to the stimulating events [13]. However, emotional arousal induced before learning can enhance the memory of information acquired even half an hour after the arousal [14]. Additionally, there is extensive evidence that emotional arousal enhances memories by modulating memory consolidation [15]. Several recent studies have reported that emotional arousal induced after learning words and pictures enhances memory consolidation. In a study by Wang and Bukuan [16•] subjects were asked either to memorize a list of words or to think about the meaning of words. Five, 30 or 45 minutes later they watched brief unpleasant and emotionally arousing or neutral films. On a 24 hour retention test all three groups that had memorized the words and viewed the emotionally arousing film had enhanced memory. The memory of subjects instructed to think about the meaning of words was also enhanced, but only with emotional arousal induced 5 or 30 minutes after viewing the words. Viewing an emotionally positive video shortly after learning of word lists also enhances memory consolidation [17] (Figure 1).

Emotional arousal enhancement of memory consolidation is not restricted to the specific information learned. Twenty-four hour memory, but not immediate memory, of neutral objects such as animals or tools was enhanced when objects of the same category were presented together with emotionally arousing stimulation [18••,19]. Emotional arousal can also enhance false memories [20]. Social stress induced after learning neutral semantically related words subsequently increased false recognition of semantically related words, suggesting that stress can enhance the consolidation of gist information [21]. However, social stress can also increase resistance to misinformation effects. Stress induced before viewing a

Figure 1



Involvement of stress hormones and amygdala activation in regulating the influence of emotional arousal on memory consolidation. Learning experiences activate brain regions that process different forms of memory. The arousal induced by the learning, or arousal induced before or shortly after learning, activates the release of epinephrine and glucocorticoids that activate the release of norepinephrine within the basolateral amygdala. Projections from the basolateral amygdala modulate memory consolidation in the brain regions involved in processing different forms of memory.

slide show decreased the effects of subsequently receiving misinformation about the slideshow [22].

Stress hormone influences on human memory consolidation

As is discussed below, findings of animal experiments have provided extensive evidence that adrenergic and glucocorticoid activation after learning enhances memory consolidation and that glucocorticoid enhancement of memory requires adrenergic coactivation [23–26]. Additionally, many studies have reported that the β-adrenoreceptor antagonist propranolol impairs memory consolidation [12,27]. Findings of studies of adrenergic and glucocorticoid effects on human memory are consistent with those of animal studies. Many previous studies have reported that post-learning administration of epinephrine or treatments that induce the release of epinephrine enhance memory in human subjects and that administration of propranolol impairs memory [28–32].

Recent findings provide additional understanding of the conditions that enable adrenergic and glucocorticoid influences on memory formation. Rimmele *et al.* [33] reported that pre-learning administration of propranolol impaired subjective sense of recollection when tested 24 hour later. Propranolol administered before the retrieval test did not affect the sense of recollection. These findings are consistent with many prior studies in indicating that decreasing adrenergic arousal during or after learning impairs consolidation. As was found in many animal studies, activation of the adrenergic system of human subjects after learning enhances memory consolidation. Segal *et al.* [34] reported that in normal elderly subjects as well as mildly cognitively impaired subjects a short bout of exercise after viewing emotional pictures enhanced the subjects' subsequent memory of the pictures. As the exercise significantly elevated norepinephrine, as assessed by salivary alpha-amylase, the findings provide additional evidence that adrenergic activation enhances memory consolidation in human subjects. Post-learning exercise is also reported to enhance retention of a motor skill [35]. Other studies reported evidence that, in depressed patients, memory consolidation is enhanced by adrenergic activation induced by administration of the alpha-2 adrenoceptor antagonist yohimbine and impaired by the alpha-2 agonist clonidine. Salivary alpha-amylase measurements indicated that norepinephrine activation was increased by yohimbine and decreased by clonidine [36,37]. Thus the findings provide additional evidence that noradrenergic activation regulates memory consolidation in human subjects.

Other recent findings provide evidence indicating that adrenergic activation is essential for glucocorticoid

modulation of memory consolidation. Segal *et al.* [38•] reported that, in women subjects, administration of hydrocortisone before viewing emotional and neutral pictures selectively enhanced memory assessed one week later. Importantly, consistent with findings of animal studies, the enhanced memory was seen only in subjects who had enhanced noradrenergic activation after the learning, as assessed by measures of salivary alpha-amylase.

Emotional arousal and brain activation in human subjects

Recent studies have provided increased understanding of the neural systems involved in modulating memory consolidation. There is extensive evidence that emotional arousal activates the amygdala [39]. Recent findings have provided new evidence, consistent with those of prior studies [6,40–42], indicating the involvement of emotionally induced activation of the amygdala and its subsequent influences on other brain systems [10–12,43,44].

Several recent studies using fMRI imaging have reported evidence supporting the hypothesis that emotional arousal influences on memory consolidation involve amygdala activation of the hippocampus. Fastenrath *et al.* [45••] presented a series of positive and negative arousing pictures, as well as neutral pictures, to subjects while their brains were being scanned. On retention tests administered shortly after the scanning the memory of arousing photos was significantly better than that of neutral pictures. Additionally, and importantly, the findings indicated that the amygdala interacted with the hippocampus and that the influence was greater during the encoding of emotional pictures. Other findings [46] indicate that amygdala activity predicts memory tested 24 hour later. The memory of pictures presented together with a mild electrical shock was superior to that of neutral pictures. Further, amygdala activity during scanning predicted memory of the pictures that were paired with shock. Interestingly, and surprisingly, pupil dilation and skin conduction changes induced by the shock did not predict memory performance. The finding of enhanced memory despite lack of physiological changes associated with arousal conflicts with extensive evidence that emotional arousal predicts memory strength.

Other recent findings provide evidence suggesting that emotionally enhanced memory is induced by persistent post-learning amygdala–hippocampus activity [47]. And, importantly, the effect was greatest in subjects with stronger memory. Amygdala connectivity has also been implicated in age related memory impairment. Leal *et al.* [48] reported finding reduced amygdala-entorhinal and hippocampus functional connectivity in older adults with age-related memory impairment.

Neuromodulatory regulation of memory consolidation in animals

The findings of recent studies of animal memory have provided additional evidence, consistent with extensive previous findings [5] indicating that stress hormones activated during or shortly after emotionally arousing learning experiences enhance memory consolidation and that the enhancement involves activation of the amygdala. Additionally, the findings provide further evidence that the enhancement is induced by amygdala projections to other brain systems involved in different forms of memory [11,12,27,49–52].

In rats, as well as human subjects, as discussed above [34,35], physical exercise shortly after learning enhances memory consolidation [53]. As was found with human subjects, the enhancement involved noradrenergic activation, as posttraining intra-hippocampal infusions of a β-adrenoceptor antagonist blocked the memory enhancement. Noradrenergic activation induced after training also influences the consolidation of social recognition memory [54] as well as habit learning. Posttraining administration of a β-adrenergic antagonist into the basolateral amygdala (BLA) blocked the enhanced response learning induced by stimulation of a tone previously paired with footshock. As there is extensive evidence that response learning involves the dorsolateral striatum, these findings suggest that the BLA modulates the consolidation of response learning via projections to the dorsolateral striatum [55].

There is extensive evidence that BLA influences on memory consolidation are also mediated by projections to the hippocampus. Posttraining optogenetic activation or inhibition of BLA neurons can enhance and impair, respectively, memory consolidation [56]. Specific optogenetic activation of a BLA projection to the ventral hippocampus selectively enhanced memory of the footshock stimulation, and not the context in which the shock had been administered [57••]. These findings provide additional evidence that the modulatory influence of BLA activation on memory consolidation depends on specific information acquired in the training.

Findings of other recent experiments confirm prior findings [58] of BLA modulation of hippocampal neural processes. In replication of previous findings [59,60], posttraining β-noradrenergic activation of the BLA enhanced both inhibitory avoidance and object recognition memory. Additionally, with high arousing training conditions levels of the immediate early gene Arc protein were elevated in dorsal hippocampal synapses [61]. These findings are consistent with previous evidence that a memory enhancing dose of corticosterone increases norepinephrine in the amygdala and expression of Arc protein in the hippocampus [62] as well as the finding that post-training β-noradrenergic activation of the BLA

increases neuronal activity in the CA1 region of the hippocampus [63].

Other findings suggest that β-noradrenergic activation of the BLA produces sustained hippocampal involvement in memory following training that serves to maintain accuracy of contextual memory. Intra-BLA norepinephrine administered posttraining enhanced memory of a specific training context when tested 28 days after training. Intra-hippocampal infusions of the GABAergic agonist muscimol administered before the 28-day test impaired retention performance [64]. The findings suggest that noradrenergic activation of the BLA influences the consolidation of long-term contextual or episodic memory.

Posttraining activation of the BLA also influences other brain regions involved in memory. Considerable evidence indicates that modulation of memory emotional experiences involves chromatin remodeling [65]. Beldjoud *et al.* [66] reported evidence that posttraining noradrenergic activation that enhances object recognition memory alters chromatin remodeling, and presumably, gene transcription in the insular cortex. These findings are consistent with previous evidence that activation of glucocorticoid induced enhancement of object and object location memory requires chromatin modification in the insular cortex and hippocampus, respectively [67]. McReynolds *et al.* [68] reported that posttraining corticosterone increased Arc protein expression in the prelimbic region of the medial frontal cortex and that blockade of Arc protein expression impaired memory. Posttraining administration of corticosterone also enhances habit memory that involves the dorsolateral striatum [69•]. Consistent with prior evidence that glucocorticoid enhancement of memory requires adrenergic activation, the effect was blocked by a β-adrenergic antagonist.

Other recent experiments have investigated endocannabinoid involvement in memory [70,71]. The findings indicate that endocannabinoids interact with glucocorticoids in the basolateral amygdala in influencing memory [72] and suggest that cannabinoid activation in prefrontal limbic circuits also plays a regulatory role in the effects of emotional arousal on memory consolidation [71].

Concluding comments

The findings of recent studies have continued to provide evidence supporting Francis Bacon's observation that emotions assist memory. They have also provided additional understanding of the neurobiological systems that enable the assistance [73]. The extensive evidence from human and animal studies strongly indicates that the modulating influence is mediated by adrenergic activation of the amygdala and its projections to brain systems involved in enabling different forms of memory.

Conflict of interest statement

Nothing declared.

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- • of special interest
- •• of outstanding interest

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