

## LETTERS TO NATURE

observed flow-field, resulting in reduced scatter in the perceived heading. Without static depth information, visual heading judgements are more vulnerable to noise and the confounding effects of eye and head rotation. □

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## β-Adrenergic activation and memory for emotional events

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**SUBSTANTIAL evidence from animal studies suggests that enhanced memory associated with emotional arousals results from an activation of β-adrenergic stress hormone systems during and after an emotional experience<sup>1–3</sup>. To examine this implication in human subjects, we investigated the effect of the β-adrenergic receptor antagonist propranolol hydrochloride on long-term memory for an emotionally arousing short story, or a closely matched but more emotionally neutral story. We report here that propranolol significantly impaired memory of the emotionally arousing story but did not affect memory of the emotionally neutral story. The impairing effect of propranolol on memory of the emotional story was not due either to reduced emotional responsiveness or to nonspecific sedative or attentional effects. The results support the hypothesis that enhanced memory associated with emotional experiences involves activation of the β-adrenergic system.**

Subjects received either propranolol or a placebo 1 h before viewing a series of slides accompanied by an emotional or neutral narrative, and were tested for memory of the story one week later (see Fig. 1 for methods). The stories were those used in an earlier study demonstrating an enhancing effect of emotional arousal on memory (L.C. and J.L. McG., manuscript in preparation), and were developed from earlier work by other investigators demonstrating enhancing effects of emotional arousal on memory<sup>4</sup> (Box 1). If the enhanced memory for the emotional story involved activation of β-adrenergic receptors (either centrally or peripherally), then blockade of those receptors should impair memory for the emotional story, while leaving memory for the neutral story relatively unaffected. Our results confirm this prediction.

The memory test results revealed significant and selective effects of propranolol on memory of the emotional story. Focusing first on the free recall results, we examined the mean number of slides recalled (out of 12 possible). The placebo subjects who viewed the emotional story recalled significantly more slides ( $6.0 \pm 0.6$ ) than did propranolol subjects ( $4.09 \pm 0.55$ ) ( $t(17) = 2.33$ ,  $P < 0.05$ ). In contrast, the placebo and propranolol groups

who viewed the neutral story did not differ in the number of slides recalled. Similar results were obtained in an 80-item multiple-choice recognition memory test (which assessed memory for both visual and narrative story elements). Placebo subjects who viewed the emotional story answered significantly more questions correctly ( $48.9 \pm 1.47$ ) than did the propranolol subjects ( $42.4 \pm 1.72$ ) ( $t(17) = 2.73$ ,  $P < 0.02$ ). The placebo and propranolol groups who viewed the neutral story did not differ in number of questions correctly answered.

The enhancing effects of emotional activation on recognition memory and the impairing effects of propranolol on emotionally enhanced memory were obtained primarily in story phase 2, the phase in which the emotional elements were introduced (Fig. 1). The placebo subjects displayed superior memory for those story elements associated with emotional arousal, whereas the propranolol subjects did not. A 2-factor ANOVA for the arousal story results with repeated measures on the story phase revealed significant effects of the drug treatment ( $P < 0.05$ ) and story phase ( $P < 0.01$ ). Subjects in the placebo/arousal story condition answered significantly more phase 2 questions correctly than either phase 1 ( $P < 0.01$ ) or phase 3 ( $P < 0.05$ ) questions. Furthermore, and most importantly, the retention performance of the placebo group was significantly better than that of the propranolol group for questions pertaining to phase 2 of the arousal story ( $P < 0.02$ ). In contrast, for subjects in the propranolol/arousal story condition, as well as subjects in the placebo and propranolol groups given the neutral story, the

### BOX 1 Narratives accompanying slide presentation

Slide	Neutral version	Arousal version
1.	A mother and her son are leaving home in the morning.	A mother and her son are leaving home in the morning.
2.	She is taking him to visit his father's workplace.	She is taking him to visit his father's workplace.
3.	The father is a laboratory technician at Victory Memorial Hospital.	The father is a laboratory technician at Victory Memorial Hospital.
4.	They check before crossing a busy road.	They check before crossing a busy road.
5.	While walking along, the boy sees some wrecked cars in a junk yard, which he finds interesting.	While crossing the road, the boy is caught in a terrible accident, which critically injures him.
6.	At the hospital, the staff are preparing for a practice disaster drill, which the boy will watch.	At the hospital, the staff prepare the emergency room, to which the boy is rushed.
7.	An image from a brain scan machine used in the drill attracts the boy's interest.	An image from a brain scan machine used in a trauma situation shows severe bleeding in the boy's brain.
8.	All morning long, a surgical team practised the disaster drill procedures.	All morning long, a surgical team struggled to save the boy's life.
9.	Make-up artists were able to create realistic-looking injuries on actors for the drill.	Specialized surgeons were able to re-attach the boy's severed feet.
10.	After the drill, while the father watched the boy, the mother left to phone her other child's pre-school.	After the surgery, while the father stayed with the boy, the mother left to phone her other child's pre-school.
11.	Running a little late, she phones the pre-school to tell them she will soon pick up her child.	Feeling distraught, she phones the pre-school to tell them she will soon pick up her child.
12.	Heading to pick up her child, she hails a taxi at the number nine bus stop.	Heading to pick up her child, she hails a taxi at the number nine bus stop.

recognition test scores for phase 2 did not differ from those of phases 1 or 3.

The subjects' heart rate and blood pressure were measured immediately before administration of the placebo or propranolol and again before presentation of the story. As expected (Table 1), propranolol significantly decreased heart rate and reduced blood pressure.  $\beta$ -Blockers have been reported to induce side effects, including sedation and difficulty in focusing attention in some patients<sup>5,6</sup>. If propranolol treatment impaired memory in the present study simply by increasing sedation or impairing attention, then memory for both the neutral and arousal stories should have been affected. That was clearly not the case: propranolol treatment selectively impaired memory for the more

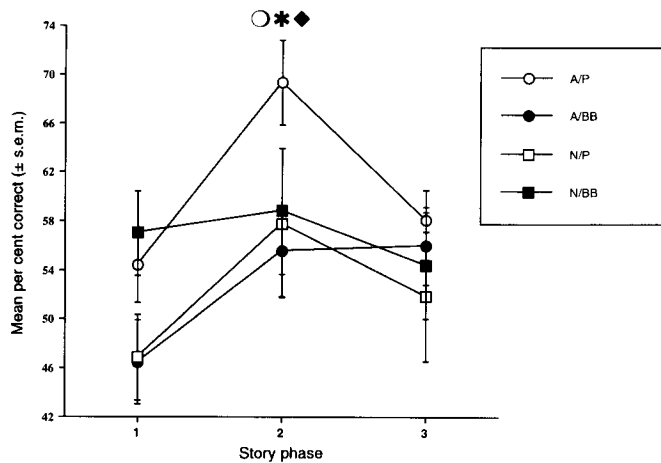


FIG. 1 Results of the recognition (multiple-choice) memory test for the three phases of the arousal and neutral stories. A/P, arousal story/placebo treatment; A/BB, arousal story/ $\beta$ -blocker treatment; N/P, neutral story/placebo treatment; N/BB, neutral story/ $\beta$ -blocker treatment. ANOVA indicated significant effects of drug treatment ( $F(1, 17)=6.62$ ,  $P<0.05$ ) and story phase ( $F(2, 34)=6.84$ ,  $P<0.01$ ). Placebo subjects given the arousal story had enhanced memory for phase 2 (arousal phase) of the story: ○,  $<0.01$  compared to phase 1 arousal story/placebo scores ( $t(14)=3.18$ ) and \*,  $<0.05$  compared to phase 3 arousal story/placebo scores ( $t(11)=2.58$ ). Propranolol blocked the enhancing effect of arousal on memory: ◆,  $P<0.02$  compared to arousal/ $\beta$ -blocker group story phase two ( $t(17)=2.58$ ). Results are expressed as per cent of questions answered correctly because of different numbers of questions given for each phase. Subjects (19 females, 17 males, mean age ( $\pm$ s.e.m.)= $27.4(\pm 4.6)$  years) received a placebo or propranolol hydrochloride tablet (Inderal, 40 mg; Wyeth-Ayerst Laboratories) 1 h before viewing either an emotionally arousing story, or a closely matched but more emotionally neutral story (Box 1). There were 8–11 subjects per group (the differences in group sizes were due primarily to failure of some subjects to appear for the memory test session). The stories were presented as a brief (about 4 min) narrated slide show. The one-sentence narrations were identical for the first 4 (of 12) slides (referred to as phase 1), nearly identical for the last three slides (phase 3), and differed primarily in the middle five slides (phase 2), during which the emotional events were introduced into the arousing story. Subjects were blind to the drug treatment received, and were tested individually. They were connected to heart rate and blood pressure monitors while viewing the story, and were told that the study concerned physiological responses to different types of stimuli. Testing was conducted between 9:00 am and 1:00 pm. One week later the subjects were given surprise memory tests. A free recall test, in which subjects were asked to recall as much as possible of the story, was followed by a 4-choice multiple-choice recognition test consisting of 5–8 questions per slide pertaining to visual and narrative elements for each story slide. For each question, one correct and three plausible (but incorrect) alternatives were provided. The free recall responses were tape-recorded for subsequent scoring. In the free recall test, subjects were credited with recall of a slide if they described some story information that could only have been known from viewing that slide. The entire study (including scoring of the recall tapes) was conducted with the experimenter blind to the drug condition.

TABLE 1 Propranolol effects on heart rate and blood pressure

	$\Delta$ Heart rate (beats per min, mean $\pm$ s.e.m.)	$\Delta$ Mean blood pressure (mm Hg, mean $\pm$ s.e.m.)
Placebo ( $n=15$ )	1.7 ( $\pm 2.41$ )	0.11 ( $\pm 2.4$ )
Propranolol ( $n=20$ )	-7.79 ( $\pm 1.68$ )*	-8.74 ( $\pm 0.94$ )*

The scores are based on differences between measures taken immediately before drug or placebo administration and immediately before presentation of the slides and narration. Propranolol produced the expected decreases in baseline heart rate and blood pressure (for both measures  $P<0.0005$  from placebo group ( $t$ -test)). Propranolol hydrochloride blocks both  $\beta_1$  and  $\beta_2$  adrenergic receptors and readily crosses the blood-brain barrier. It is widely used for the treatment of certain cardiac disorders such as angina pectoris and high blood pressure.<sup>15</sup> Propranolol was used in this study because it impairs  $\beta$ -adrenergic transmission both centrally and peripherally and because it attenuates memory in animal experiments using aversively motivated training tasks<sup>16–18</sup>.

emotional story. Furthermore, as propranolol did not block subjects' subjective emotional reactions to the story assessed immediately after story viewing (Fig. 2), it is clear that the effects of propranolol on memory reported here are not easily attributable to reduced subjective emotional responsiveness.

The results support the hypothesis that memory storage is modulated by  $\beta$ -adrenergic systems. In particular, they suggest that the enhanced memory for events associated with emotional arousal involves activation of  $\beta$ -adrenergic receptors and that  $\beta$ -adrenergic activation is not essential for storage of emotionally neutral information. It is well established that highly emotional experiences can activate the sympathetic nervous system as evidenced, for example, by increases in plasma adrenaline and/or noradrenaline<sup>7,8</sup>. There is also extensive evidence indicating that, in animals, administration of adrenergic and other stress-related hormones and drugs can modulate (either enhance or impair) memory in a wide variety of learning situations<sup>9</sup>. Such findings suggest that emotional experiences activate a memory-modulating system involving the release of both peripheral adrenergic hormones and brain noradrenaline<sup>3,10</sup>. Although there is extensive evidence that high doses of adrenaline can impair memory storage<sup>1,9</sup>, it is not known whether endogenous adrenaline

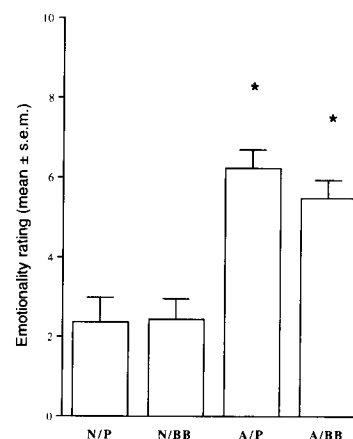


FIG. 2 Mean ( $\pm$ s.e.m.) ratings of emotional reaction to the story viewed in each experimental group. N/P, neutral story, placebo; N/BB, neutral story,  $\beta$ -blocker; A/P, arousal story, placebo; A/BB, arousal story,  $\beta$ -blocker. \*,  $P<0.01$  from both N/P and N/BB groups ( $t$ -tests). Immediately after viewing the story, subjects rated how emotional they found the story to be on a scale of 0 to 10 (with 0 as 'not emotional at all' and 10 as 'highly emotional') by marking a scale at the appropriate point.

released by high levels of emotional arousal can produce memory impairment. Findings of animal experiments indicate that memory storage is influenced by drugs affecting many neuro-modulatory systems, including  $\alpha$ -adrenergic systems<sup>1,3,9,11</sup>. Studies to date have not investigated the selective involvement of other systems in regulating emotionally influenced memory in human subject.

Although clinical reports suggest that  $\beta$ -blockers may induce memory loss in some patients<sup>12,13</sup>, controlled laboratory investigations have so far generally failed to find consistent effects of  $\beta$ -blockers on memory<sup>6,14</sup>. However, previous studies generally investigated memory for relatively unemotional events and typically studied only short-term memory. Future research using  $\beta$ -blockers with different affinities for  $\beta_1$  and  $\beta_2$  receptors and differential effectiveness in passing the blood-brain barrier should clarify the role of the  $\beta$ -adrenergic system in regulating long-term memory for emotional experiences. □

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## Changes in reliability of synaptic function as a mechanism for plasticity

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**SYNAPTIC transmission in the hippocampus is rather unreliable, with many presynaptic action potentials failing to release neurotransmitter<sup>1–4</sup>. How is this unreliability affected by the alterations in synaptic strength seen in long-term potentiation (LTP)<sup>5</sup> and long-term depression<sup>6,7</sup> (LTD)? We find that LTP increases synaptic reliability, and LTD decreases it, both without a change in the size of those postsynaptic currents that do occur. Thus LTD is a functional inverse of LTP.**

We have used 'minimal stimulation', a method for activating only one or a few synapses<sup>1</sup>: the stimulus intensity is reduced to a level that produces a postsynaptic response of uniform latency and shape in a target neuron with a probability of less than about 0.5. This method permits us to separate two components of synaptic strength: reliability, the fraction of stimuli that pro-

duce a postsynaptic current, and potency, the average peak size of the postsynaptic current when one does occur.

Whole-cell recording<sup>8,9</sup> provides a signal-to-noise ratio that is adequate for clearly distinguishing between a release failure and a success in almost all instances. This is illustrated in Fig. 1, which reveals a clear separation between transmitter release and no release.

Data for typical LTP experiments are illustrated in Figs 1*a* and 2*a–e*. Separate averages were made (before and after the induction of LTP) for all responses, all stimulation trials for which a postsynaptic current was detected, and all records that represented failures in synaptic transmission (Fig. 2*a*). Further, non-overlapping groups of about 25 successive traces were averaged throughout the experiment, and failure probabilities were estimated for the same groups of traces; these group averages reveal stable LTP following the tetanic stimulus (Fig. 2*b*), and a sustained post-tetanic decrease in the failure rate (Fig. 2*c*). The group average potency is roughly constant throughout the experiment (Fig. 2*d*), and the histograms of excitatory postsynaptic potential (e.p.s.c.) peak amplitude for the control and LTP periods (Fig. 2*e*) are not significantly different (Kolmogorov-Smirnov test,  $P > 0.1$ ).

In this instance, stable LTP is represented as an increase in the average response, a decrease in the synaptic failure rate, and no appreciable change in the potency. As with the LTP experiment, LTD is represented by a decrease in the average response size (Fig. 3*a, b*), an increase in the failure rate (Fig. 3*c*), and no appreciable change in synaptic potency (Fig. 3*a, d, e*).

Although we find, as reported previously<sup>10</sup>, that LTP is difficult to induce after about 20 min of recording in the whole-cell mode, LTD seems not to 'wash out'. That is, we could produce LTD as late as 80 min after the start of whole-cell recording, the longest time tested. In six experiments, LTD reversed previously established LTP (data not shown).

To compare data from different experiments, we note that the average peak e.p.s.c.,  $r_j$ , is (by definition) the product of the probability  $w_j$  that a release will occur and the average size  $a_j$  of a response (when release does occur):  $r_j = w_j a_j$ ; the subscript  $j$  is 0 before the induction of LTP or LTD and 1 after. The probability of a failure  $f_j = (1 - w_j)$  is determined directly from experiment as is the average potency  $a_j$ . Synaptic plasticity  $S$  is defined as the ratio  $S = r_1 / r_0$ . If plasticity were only a change in synaptic reliability (with no change in potency), then  $a_1 / a_0$  would equal 1, and  $S$  would be just the ratio of success probabilities:  $S = w_1 / w_0$ , if  $a_1 = a_0$ . A plot of  $S$  versus the ratio  $w_1 / w_0$  would then fall on a straight line with slope 1, and a plot of the ratio  $a_1 / a_0$  would be constant (=1). Our experiments provide the data required for testing the extent to which plasticity is determined by changes in reliability and changes in potency as we estimate  $a_1 / a_0$  and  $w_1 / w_0$  directly.

The unfilled circles in Fig. 4*a* and *b* represent data from 26 experiments like the ones illustrated in Figs 1, 2 and 3. Clearly, the ratio  $w_1 / w_0$  falls along the diagonal in Fig. 4*a*, and the ratio  $a_1 / a_0$  is roughly constant in Fig. 4*b*. For these experiments, then, we conclude that the mechanism of LTP and LTD is a change in synaptic reliability with no appreciable change in potency.

The experimental situation here is a little different from previous investigations of LTP that activated a population of synapses so that all or most failures are obscured. Because we have activated fewer synapses than was usual for earlier studies, we felt that we must demonstrate that the plasticity examined here exhibits the same properties as standard LTP.

LTP is sometimes elicited by the 'pairing' stimulation model instead of by tetanic stimulation. In these 'pairing' experiments, low-frequency stimulation is paired with a postsynaptic depolarization imposed on the cell<sup>11</sup>. Data from five 'pairing' experiments, plotted in Fig. 4*c* and *d* as unfilled triangles, conform to the behaviour of synapses potentiated with tetanic stimulation.

LTP is blocked by the presence of the *N*-methyl-D-aspartate (NMDA) receptor antagonist AP-5<sup>12</sup>, and by hyperpolarization