As staying up late at night is usually associated with some degree of sleep deprivation, the effects described here are probably not solely attributable to circadian rhythms. However, the similarity between these results and those of the schoolchildren study[6] do suggest that circadian rhythms had an important role in producing them. Whatever their cause, these effects undoubtedly indicate that late-night studying is much less efficient than one's immediate impressions might imply. Much more will be forgotten later on than if the studying had taken place at a more normal time of day.

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Memory in monkeys severely impaired by combined but not by separate removal of amygdala and hippocampus

THE profound anterograde amnesia that has been attributed in the clinical literature to damage of the hippocampal system[1,2] has not been observed in animals with such damage. Hippocampal-system lesions in animals do markedly impair some forms of spatial memory[3,4], but the effects on other forms of memory have generally seemed minor[5,6] compared with the dramatic disorder described in man[7,8]. This discrepancy between the clinical and animal literature could indicate a true evolutionary shift in the functions of the hippocampus[9,10], or, at the other extreme, it could simply reflect the use of incommensurate measures across species[11,12]. (Strong support for this second interpretation has been provided by Gaffan[13].) A third possibility, however, is that the discrepancy points to inaccurate localisation of the neuropathology in man that is responsible for the profound amnesia. Support for this last alternative comes from new evidence in monkeys indicating that a striking impairment in visual memory can be produced by the combined ablation of the hippocampal formation and the amygdaloid body, but not by ablation of either of these structures alone.

Twelve monkeys (*Macaca mulatta*) weighing from 3.5 to 5 kg were trained preoperatively in a Wisconsin general testing apparatus to perform one-trial object recognition[14] for peanut rewards. The procedure involved presentation of a baited object over the central well of a three-well tray, followed 10 s later by re-presentation of that object (now negative) together with a new object (positive) over the lateral wells. Twenty such trials separated by 30 s intervals were given daily, each trial with a new pair of objects. The successive pairs were drawn randomly from a collection of several hundred unmounted junk objects of diverse sizes, colours, shapes and textures. The testing procedure exploits the monkey's natural tendency to choose the novel object in a pair even after only brief familiarisation, a few seconds earlier, with the other object of the pair[14,15]; consequently, the criterion of 90 correct choices in 100 trials is achieved extremely quickly, in this case in an average of 99 trials and 28 errors (see Table 1), or about one-third the time required to learn matching, that is, to choose the familiar object in the pair[14].

The animals were then divided into four lesion groups of three monkeys each and given either an amygdalectomy, hippocampectomy, both combined, or neither. One-stage bilateral lesions were made aseptically while the animals were under Nembutal anaesthesia (35 mg per kg body weight). To remove the amygdaloid body, the frontotemporal junction was elevated slightly and the tissue medial to the anterior tip of the rhinal sulcus was entered with a small-gauge sucker; all gray matter rostral to the pes hippocampi (which afterwards lay exposed in the ventricle) and medial to the white matter of the temporal lobe was then ablated under visual control through an operating microscope. To remove the hippocampal formation, the occipitotemporal convexity was elevated slightly and the tissue medial to the rostral half of the occipitotemporal sulcus was entered with the sucker until the ventricle was opened; the entire hippocampal formation and much of the underlying fusiform-hippocampal gyrus was then ablated, again under visual control through the microscope, the upper ventricular surface serving as a readily identifiable dorsal boundary along the entire length of the removal. For the combined ablation, both of these surgical procedures were used in a single stage. Two weeks postoperatively the monkeys were retrained to criterion, with the outcome as shown in Table 1. Neither amygdalectomy alone nor hippocampectomy alone produced appreciable impairment, but the combination of the two removals yielded a severe effect: an abrupt drop to chance levels of performance followed by an average relearning score that was ten times the average for initial learning.

When the monkeys had regained criterion, their recognition ability was tested further with procedures adapted from a study by Gaffan[12]. First, the delay between familiarisation and choice was lengthened in stages from the original 10 s delay to 30 s, then to 60 s, and finally to 120 s, each stage being tested for 100 trials. Second, the number of objects given for familiarisation before pairing each one with a novel object was increased in stages from the original single object to a series of three objects presented successively, then to a series of five objects, and finally to a series of ten objects; each of these stages was tested for 150 trials. The data in Table 1 indicate that, again, neither amygdalectomy nor hippocampectomy alone yielded more than a mild impairment. Each of these groups averaged 91% correct across the six testing conditions, as compared with an average of 97% correct for the normal controls. By contrast, the combination of the two lesions had a profound effect, yielding an average score of 60% correct, or just above chance. Since the animals had already regained the ability to perform the basic task, their sharp drop in performance with the longer delays and list lengths presumably represents a true memory loss rather than some other difficulty such as in visual perception or problem solving.

This striking deficit in monkeys after amygdalo-hippocampal removals is not limited to recognition memory, where the animal must remember whether or not a test object had been seen before. An equally severe impairment has been found in associative memory (B. Spiegler and M.M., unpublished), where the animal must remember on the basis of a single trial whether or not the test object had been rewarded before[12]. On this more difficult, associative task, unlike the recognition task used here, amygdalectomy alone had a significantly greater effect than hippocampec-

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Table 1 Effects of removal of amygdala and hippocampus on memory

Groups		Preoperative Trials	Preoperative Errors	Postoperative Trials	Postoperative Errors	Delays (%correct) 30 s	60 s	120 s	Objects (% correct) 3	5	10
Normal control	1	100	26	0	0	97	98	96	96	93	91
	2	80	28	0	0	99	100	98	97	97	94
	3	40	19	0	0	98	99	98	97	96	92
Amygdalectomy	1	120	42	80	32	95	95	95	91	92	82
	2	100	27	340	85	91	89	92	88	87	77
	3	80	30	0	0	91	95	94	96	95	87
Hippocampectomy	1	60	17	80	22	98	93	94	95	92	84
	2	100	26	120	32	85	89	83	89	85	71
	3	120	31	20	4	98	99	95	95	92	88
Amygdalectomy + hippocampectomy	1	210	49	760	179	79	65	65	62	64	59
	2	100	26	1,500	429*	64	59	63	60	55	61
	3	80	22	700	203	61	47	52	53	58	44
Group means											
Normal control		73	24	0	0	98	99	98	97	96	92
Amygdalectomy		100	33	140	39	94	93	94	92	91	82
Hippocampectomy		93	25	73	19	94	94	91	93	90	81
Amygdalectomy + hippocampectomy		130	32	987	270	68	57	60	58	59	55

Scores in preoperative and postoperative columns are the numbers of trials and errors preceding criterion of 90 correct choices of the novel object in 100 trials (delay following familiarisation with the other object in the pairs was 10 s). Scores in delays columns are percentage correct in 100 trials at each of three longer delays tested in succession at the rate of 20 trials per day, except for the longest delay (120 s) which was tested for 10 trials per day. Scores in objects columns are percentage correct in 150 trials for each of three multiple-object conditions tested in succession: in the first condition, three objects were presented for familiarisation, one at a time at 20 s intervals, and then re-presented in the same order, each being paired with a novel object, again at 20 s intervals; in the next condition, five objects were presented one at a time at 20 s intervals, and so on. Thirty trials were presented daily, ten sets of 3's or six sets of 5's or three sets of 10's. The minimum delay between familiarisation and choice was 60, 100, and 200 s for the three conditions, respectively. Scores for individual animals are shown in the upper part of the table, group means in the lower part. Histological examination indicated that the lesions were as intended except in animals 'hippocampectomy 2' and 'amygdalectomy + hippocampectomy no. 2', both of which sustained, in addition to the planned removals, bilaterally asymmetrical damage to the ventral part of inferior temporal ('visual') cortex.

*Failed; final score, 85 correct in 100 trials.

tomy alone; but neither effect presaged the abrupt and permanent fall to chance levels' of performance that followed the combined ablation.

The evidence that a severe memory disorder in monkeys can be produced only by the combined removal of amygdala and hippocampus seems at first surprising; it implies that these two structures, so unlike morphologically, may nonetheless serve as functional substitutes in a still undefined memory circuit. Yet this conclusion gains plausibilty from recent anatomical studies in monkeys which show that the amygdala and hippocampus have many more inputs and outputs in common than was previously supposed. Both of these structures receive projections from many of the same frontal and temporal association areas, the amygdala receiving them directly[16,17], and the hippocampus indirectly through the entorhinal area[18–20]; and both of these structures send projections, in turn, to many of the same diencephalic and basal forebrain areas, the amygdala via both the ventral amygdalofugal pathway and the stria terminalis[21], and the hippocampus by way of the fornix[22]. Thus, while the amygdala and hippocampus undoubtedly serve different functions, they could still constitute alternative relays through which a particular group of cortical association areas could interact with a particular group of subcortical targets, such that only the combined removal of both relays would cause a complete disconnection.

Taken together, these behavioural and anatomical findings in monkeys open up a new possibility for helping to resolve the long-standing discrepancy between the animal and clinical literature on amnesia. To pursue this possibility, several kinds of additional investigations are needed. Among the most critical are: a determination of whether the severe memory impairment demonstrated here following combined amygdalo-hippocampal damage in monkeys transcends the visual modality, in keeping with the 'global amnesia' found in man; a reappraisal of the neuropathology in human amnestic cases with special attention to whether there is indeed damage to the amygdaloid system as well as the hippocampal system; and quantification of the memory impairment in clinical cases, to determine whether differences in degree of amnesia might correlate with differences in amount of pathological involvement of these two systems.

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