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A Memory System in the Monkey

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A memory system in the monkey

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A neural model is presented, based largely on evidence from studies in monkeys, postulating that coded representations of stimuli are stored in the higher-order sensory (i.e. association) areas of the cortex whenever stimulus activation of these areas also triggers a cortico-limbo-thalamo-cortical circuit. This circuit, which could act as either an imprinting or rehearsal mechanism, may actually consist of two parallel circuits, one involving the amygdala and the dorsomedial nucleus of the thalamus, and the other the hippocampus and the anterior nuclei. The stimulus representation stored in cortex by action of these circuits is seen as mediating three different memory processes: recognition, which occurs when the stored representation is reactivated via the original sensory pathway; recall, when it is reactivated via any other pathway; and association, when it activates other stored representations (sensory, affective, spatial, motor) via the outputs of the higher-order sensory areas to the relevant structures.

Introduction

How do we learn to recognize new stimuli? In particular, how do we often manage to do this after only a single, brief exposure? A reasonable guess for vision is that in the course of inspecting a new stimulus, such as a new object or face or scene, we automatically store a coded representation of it in visual association cortex; recognition occurs when this central representation is reactivated by the same stimulus on a later occasion. Evidence from studies on monkeys fits this scheme and suggests how such central representations could be formed.

In the act of perceiving a new visual stimulus, a unique constellation of prestriate outputs, representing a unique constellation of visual attributes such as size, colour, texture and shape converges on single inferior temporal neurons. This initial activation, constituting a novel perception, leaves a lasting effect after the inferior temporal neurons, in turn, trigger a cortico-limbo-thalamo-cortical circuit. Once triggered, this circuit acts as an automatic rehearsal or imprinting mechanism, strengthening the prestriate–temporal connections that participated in firing the circuit in the first place. As a result, many of the same inferior temporal neurons that were maximally activated by the stimulus initially are likely to be activated again whenever the same constellation of visual attributes (i.e. the same visual stimulus) reappears in the field; the neurons so reactivated may thus be viewed as the stored central representation for that stimulus. Once established, this central representation can enter into association with a variety of other stored central representations (sensory, affective, spatial, motor) and thereby arouse them or be aroused by them through associative recall, via the reciprocal connections of inferior temporal cortex with the relevant structures.

The neural events that have just been pictured are of course hypothetical. At the same time, they are conceived as taking place in parts of the brain that are now known to be important

for visual recognition, and in a sequence that fits our current understanding of how the parts are connected. This hypothetical scheme thus provides a convenient framework for integrating a large amount of neurobehavioural information relevant to visual memory. The purpose of my paper will be to develop that evidence.

The prestriate complex

At the outset, it is important to make clear that inferior temporal cortex, in particular area TE in Bonin & Bailey's (1947) terminology (see figure 1), stands at the end of a long line of modality-specific visual areas that begins in the striate cortex, or area OC, and continues through the prestriate and posterior temporal areas, OB, OA, and TEO (Mishkin 1972). This ventrally directed chain of cortical visual areas appears to extract stimulus-quality information

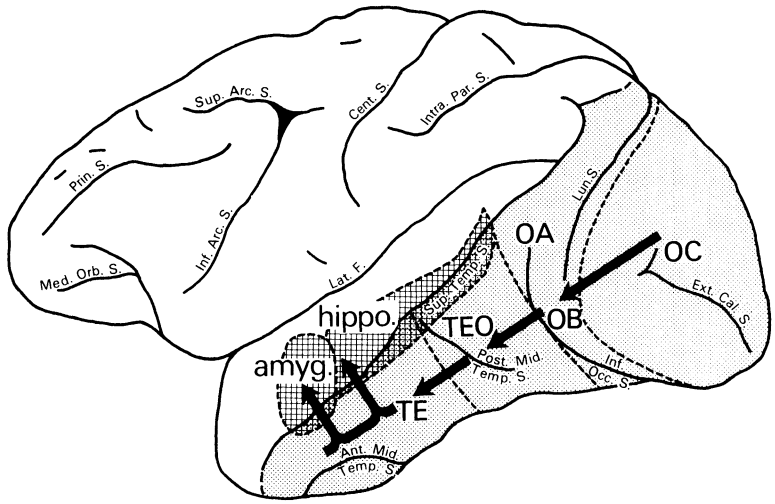

Figure 1. Flow of visual information from primary cortical area (OC) through secondary areas (OB, OA and TEO) to the highest-order visual area (TE), and from there into the medially located amygdaloid complex (amyg.) and hippocampal formation (hippo.). Cytoarchitectonic designations are those of Bonin & Bailey (1947). For clarity, the hippocampal formation is pictured slightly dorsal to its actual location.

from the retinal input reaching the striate cortex (Ungerleider & Mishkin 1982), processing it for the purpose of identifying the visual stimulus and ultimately assigning it some meaning through mediation of area TE's connections with the limbic system, specifically the amygdaloid complex and the hippocampal formation (Jones & Mishkin 1972; Mishkin 1979; Spiegler & Mishkin 1981). How the visual system performs its perceptual feat is still almost totally unknown. But a major aspect of its operation is the distribution of the striate output to the numerous re-representations of the visual field located within the prestriate and posterior temporal areas (Allman 1977; Merzenich & Kaas 1980), perhaps for the purpose of submodality processing (Zeki 1978; Cowey 1981). Thus such object features as size, colour, texture and shape could be analysed separately within specific subdivisions of the region. The subdivision about which we know the most from a behavioural standpoint is area TEO, and the behavioural evidence regarding it supports the foregoing conjecture. That is, area TEO appears to be critical for shape perception (Yaginuma *et al.* 1982) in that its removal impairs

the discrimination of two-dimensional patterns far more than does equivalent damage on either side of it, including even substantial damage to the striate cortex itself (Blake *et al.* 1977). At the same time, as will become clear shortly, the removal does not impair discrimination of an object's other, less complex, features, which it is therefore reasonable to assume are processed in other subdivisions of the prestriate complex and then relayed forward to area TE, bypassing TEO. According to the view being advanced here, the analysis of the several physical properties or dimensions of a visual object may proceed in parallel in the various subdivisions of the prestriate complex and perhaps even be completed within this tissue. But the synthesis of these several physical properties into a unique configuration representing the unique object may normally entail the funnelling of the outputs from the prestriate–posterior temporal region into area TE. It is this postulated convergence or integration of visual inputs in area TE that makes it particularly well suited to serve not only as the highest-order area for the perception of visual stimuli but also as the storehouse for their central representations.

Area TE

That area TE is important for some form of visual learning or memory has been known for decades (Mishkin 1954; Iwai & Mishkin 1968). But that the area is critical for visual recognition specifically was discovered only recently in a study that compared the effects of partial temporal-lobe lesions on a test of one-trial object recognition. Because the test is central to the development of the model, I shall describe it briefly. In this test (Mishkin & Delacour 1975), the monkey subject is shown a distinctive object over a central food-well, which it uncovers to obtain a concealed peanut. Ten seconds later the same object is paired with an equally distinctive novel object, each presented over a lateral well; but to find a peanut on this second occasion the monkey must avoid the familiar (previously baited) object and displace instead the unfamiliar one. The pair of objects is then discarded, not to appear again, and, 20 s later, the same procedure of single-object presentation followed by a choice trial is repeated with a new pair of objects. The procedure is repeated 20 times each day, each time with a new pair of objects, day after day, until the animal learns the principle of always selecting the novel object in the pair (i.e. delayed non-matching to sample), to a criterion of 90 correct choices in 100 trials. As it turns out, only a few days are needed to instil this principle of choosing the novel object, since it is one to which the naturally inquisitive monkey is already predisposed. Having not only learned the principle, but also, in the process, having demonstrated the ability to remember for at least 10 s something about the appearance of an object that was seen very briefly and only once before, trained animals were then given bilaterally symmetrical ablations of selected portions of the temporal lobe (Mishkin & Oubre 1977). Three animals each received complete removals of area TE, area TEO, the amygdaloid complex or the hippocampal formation, and three others were retained as unoperated controls. Two weeks after the operation the animals were retrained in the delayed non-matching principle, with the results indicated to the left of the curves in figure 2. No group required much more than about 100 trials on the average to relearn the task, except group TE, which required 1500 trials. In fact, each animal in group TE was given this amount of retraining, and yet not one fully reattained criterion within that time.

So specific and dramatic an impairment clearly indicates that the demands of the one-trial object recognition task approximate closely the functions of area TE. It was not yet clear,

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however, whether the impairment sustained by the TE group reflected a loss in recognition memory or whether it was due instead to a difficulty in relearning the delayed non-matching principle. To examine this question, once the animals had regained the principle, they were given a performance test (see Gaffan 1974) in which the delay between sample presentation and choice was increased in steps from 10 s to 2 min; after this, the number of objects to be remembered was also increased in steps from a single object to a list of ten objects. In this final condition, for example, each of the ten objects was presented in succession at 20 s intervals

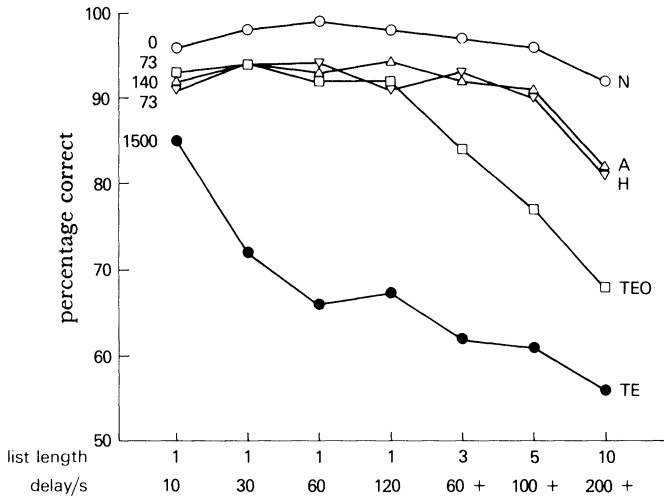

FIGURE 2. Average scores on the recognition performance test by groups with bilateral lesions of the amygdala (A), hippocampus and underlying fusiform–hippocampal gyrus (H), posterior temporal cortex (TEO), or anterior temporal cortex (TE), as well as a group of unoperated controls (N). Numerals to the left of the curves indicate the average number of trials to relearn the basic task, which entailed remembering a single object for 10 seconds, with the first point on the curve being the average final score achieved on this condition. Animals were tested on the six remaining conditions, involving gradually increasing delays and list lengths, for 1 week each.

over the central well before each one was paired for choice with a different novel object over the lateral wells. As the performance curves in figure 2 indicate, the normal animals maintained scores of better than 90% correct responses even under the last, most taxing, condition. Similarly, the animals with either amygdaloid or hippocampal lesions also maintained high levels of performance, showing only mild impairments relative to the unoperated controls. A different profile was exhibited by the animals in the TEO group, who performed as well as the best operated animals under conditions of increasing delay, but then dropped significantly below the others as the list lengths increased. This intensification of impairment on longer lists could reflect the specific disorder in shape perception that was attributed to TEO lesions. That is, an object's colour or size or texture might serve as an adequate mnemonic aid for recognition provided that this object alone had to be differentiated later from another. Consequently, a relatively intact perceptual ability along non-shape dimensions could account for the high level of performance shown by the TEO group on a list length of one, even with very long delays. When several objects in a list must be remembered and differentiated, however, then perhaps the unidimensional scales of colour, size and texture no longer serve as adequate mnemonic aids. Under these conditions, the highly variable attribute of shape may become a critical dimension, in which case a severe impairment in shape perception would account for the TEO group's sudden drop in scores during the second half of the performance test.

No such explanation, however, can account for the impairment shown by the animals with TE lesions, whose performance fell abruptly as soon as the delay between a single sample and choice was increased even slightly, and whose scores by the end of the performance test had fallen to chance. Animals with TE lesions are not markedly impaired in shape discrimination (Blake *et al.* 1977; Manning & Mishkin 1976), nor, for that matter, are they seriously impaired in discrimination along any particular dimension. Furthermore, they had already regained the non-matching principle to an average level of 85% correct responses at the end of retraining on the original condition. Their abrupt drop in performance with increasing delays, therefore, like their earlier difficulty in relearning the delayed non-matching principle with a single object and a 10 s delay, most probably reflects a severe recognition failure.

Amygdala and hippocampus

According to the model being proposed here, the recognition failure after TE lesions is attributable to a loss of the neuronal network in which the central representations of visual stimuli are formed and stored. But the formation and storage process does not depend on the operation of the visual system alone. Despite the results from the study with partial temporal-lobe lesions described in the preceding section, there is substantial evidence now that the amygdala and hippocampus are in fact of crucial importance for the neural process underlying recognition. A clear demonstration of the role of these two structures in recognition memory, however, required removing them in combination (Mishkin 1978). This demonstration grew out of a study of object–reward association, in which an attempt to exacerbate a deficit after amygdalectomy by addition of a hippocampal ablation proved to be extremely effective (Mishkin *et al.* 1982). When the severity of the associative memory impairment after the combined amygdalo-hippocampal removal was discovered, other animals with combined amygdalo-hippocampal ablation were tested for recognition memory, with equally dramatic results. Indeed, although these animals had less difficulty than those with TE lesions in relearning the basic delayed non-matching principle, their scores on the subsequent performance test with increasing delays and list lengths were, if anything, inferior to those of the animals with TE lesions. (The average scores of the two groups across the six conditions of the recognition performance test are compared in figure 4.) Partly on the basis of these findings of severe losses in both associative and recognition memory following the limbic lesion, as well as of a finding that the recognition loss extends beyond the visual modality (Murray & Mishkin 1981), it has been proposed (Mishkin *et al.* 1982) that amygdalo-hippocampal ablation in monkeys yields an animal model of the global amnesia that follows medial temporal-lobe surgery or pathology in clinical cases.

The ancillary evidence available in the animal model implies, however, that the participation of the limbic system in memory processes depends on its interaction with the neocortex, and specifically on the input it receives from the higher-order sensory areas, which for vision is area TE (Van Hoesen & Pandya 1975; Turner *et al.* 1980). To test this notion directly, a disconnection study was undertaken according to an experimental design that had been used previously (Mishkin 1966) to study the functional dependence of area TE on input from the striate cortex. In that earlier case, an inferior temporal lesion in one hemisphere was combined with an occipital lobectomy in the other, thereby leaving only a transcallosal pathway for visual information from the intact occipital lobe to reach the intact inferior temporal tissue on the opposite side. Transection of the splenium of the corpus callosum under these conditions

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rendered the intact inferior temporal cortex functionally inactive in visual learning and memory, owing to its isolation from visual input as demonstrated subsequently both in single-unit (Rocha-Miranda *et al.* 1975) and metabolic (Jarvis *et al.* 1978) studies. The special theoretical value of such a crossed-lesion disconnection experiment is that it permits the inference that the same functional dependency of one region upon another that has been demonstrated to exist between the hemispheres also exists within the hemispheres, where such dependency cannot be studied directly because of the inaccessibility of the intrahemispheric pathways.

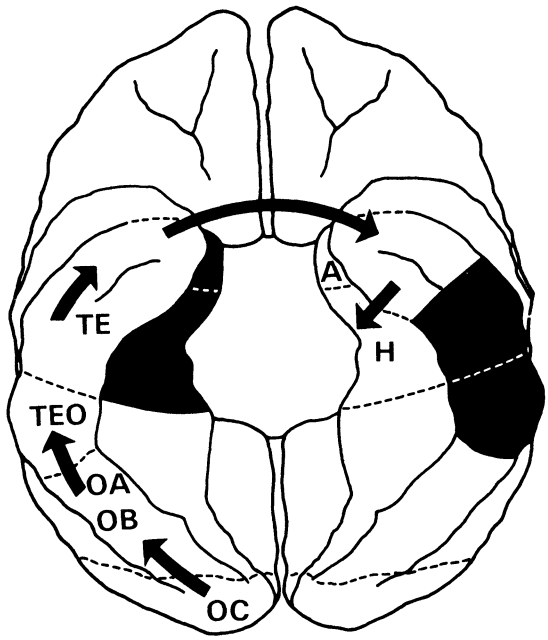

FIGURE 3. Surgical preparation for the crossed-lesion disconnection experiment, involving an amygdalo-hippocampal ablation in one hemisphere and an inferior temporal lesion in the other. Arrows on the left side of the illustration show information flow in the visually intact hemisphere, which then must cross in the anterior commissure to reach the intact amygdalo-hippocampal system on the opposite side. Animals were prepared with either these crossed lesions alone or with the crossed lesions combined with transection of the anterior commissure. Designations for cortical and limbic areas are the same as in figure 1.

Application of the crossed-lesion design to the study of cortico-limbic interaction led to the surgical preparation illustrated in figure 3. In this case, an inferior temporal lesion in one hemisphere (shown on the right) was combined with an amygdalo-hippocampal ablation in the other (shown on the left). As a result, visual information from the side with the intact visual system (areas labelled OC to TE) could reach the intact limbic system on the opposite side (areas labelled A and H) only through the anterior commissure (designated by the interhemispheric arrow). If limbic participation in visual memory requires this visual input, then transection of the anterior commissure should isolate the limbic system from vision and yield a recognition impairment equivalent to that produced by a bilateral limbic removal. To test the prediction, three animals each were given either crossed lesions alone, like those illustrated, or crossed lesions combined with anterior commissurotomy. All were trained on the recognition test in a manner identical to that described previously, with the result illustrated in figure 4. Those with crossed lesions alone obtained an average of better than 80% correct responses on the recognition performance test, a score that was about midway between the scores

of the unoperated controls and the scores of the animals with either bilateral TE or bilateral limbic lesions. Thus, this extensive amount of damage to the visual-recognition system produced significant but incomplete impairment. By contrast, when the anterior commissure was transected in addition, the scores dropped to an average of less than 65%, or about the same as those of the groups with bilaterally symmetrical lesions. In short, it appears that the participation of the limbic system in visual memory does indeed depend on its receipt of visual input from area TE.

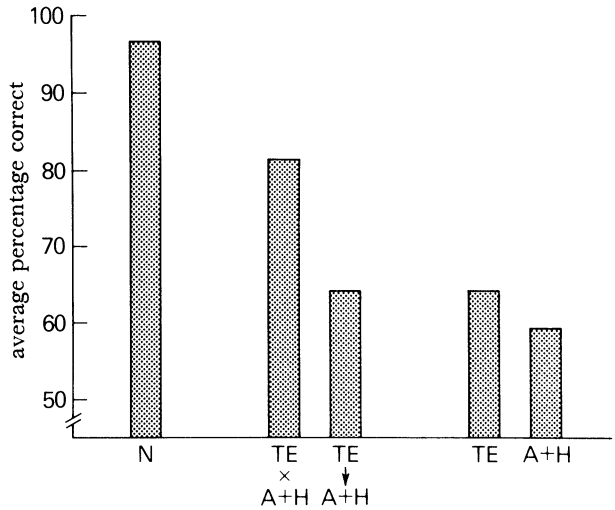

FIGURE 4. Average scores across the six conditions of the recognition performance test by the unoperated controls (N) on the left, and the animals with either bilateral inferior temporal (TE) or bilateral amygdalo-hippocampal (A+H) lesions on the right. In the middle are the scores of the two groups with crossed lesions described in figure 3, without (×) and with (↓) transection of the anterior commissure, respectively.

MEDIAL THALAMUS

Just as the visual system operating alone is insufficient to support visual recognition, so too is its interaction with the limbic system insufficient. It appears now that for stimulus recognition to occur, the limbic system must interact, in turn, with structures in the medial portion of the thalamus. The first evidence from animal work that diencephalic structures were critical for recognition memory came from studies on the effects of transections of the fornix (Gaffan 1974), the major hippocampo-diencephalic pathway. In the work in our own laboratory, by contrast, the recognition impairments that have been found to follow fornix transection alone are no more severe than those that were described above following hippocampectomy. As predicted by the effects of combined amygdalo-hippocampal ablations, however, transection of the fornix combined with amygdalectomy (see figure 5) produces a more striking impairment than either lesion by itself (Mishkin & Saunders 1979); and an equivalent combinatorial effect is produced by adding to a hippocampectomy a transection of the stria terminalis, a major amygdalo-diencephalic pathway. In both of these cases, the average scores on the recognition performance test after combined lesions were about 15% lower than those after any of the component lesions.

In considering which among the many diencephalic targets of the amygdala and hippocampus might be involved in the recognition memory process, an important clue was the clinical

evidence that, in addition to the medial temporal region, a common site for the induction of amnesia by tissue destruction or pathology was the medial thalamus (Victor *et al.* 1971; McEntee *et al.* 1976). Since both the amygdala and the hippocampus project to this region – the amygdala to the magnocellular portion of the dorsomedial nucleus, and the hippocampus to the rostrally adjacent anterior nuclei – an attempt was made in three animals to ablate the region and to evaluate the effects on visual recognition. Preliminary results (Aggleton & Mishkin 1981; Mishkin & Aggleton 1981) indicate that, once again, recognition performance was severely disrupted, pointing to the critical participation of the medial thalamus as well in the recognition process.

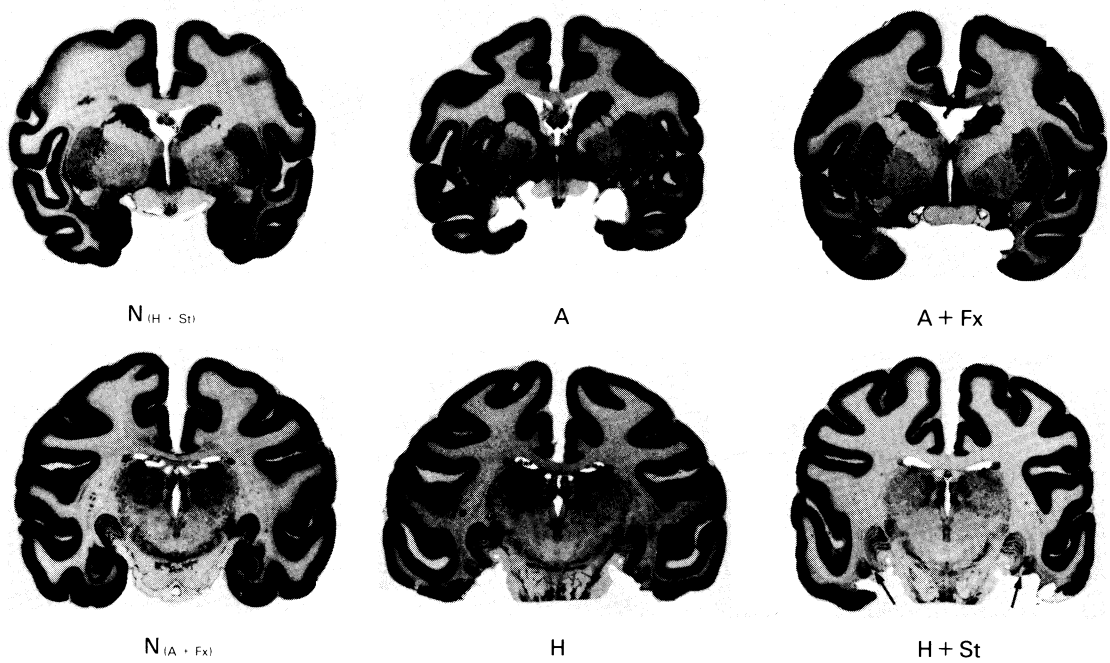

FIGURE 5. Frontal sections through the brains of animals with amygdalectomy alone (A), amygdalectomy plus fornix transection (A + Fx), hippocampectomy alone (H), or hippocampectomy plus transection of the stria terminalis (H + St). The stria terminalis transection is denoted by arrows. For comparison, a frontal section through a normal amygdala and fornix is shown from the brain of an animal with a hippocampectomy plus transection of the stria terminalis (N_{H+St}), and one through a normal hippocampus and stria terminalis is shown from the brain of an animal with an amygdalectomy plus fornix transection (N_{A+Fx}).

THE RECOGNITION MEMORY CIRCUIT

A diagrammatic summary of the circuit that has been implicated in visual recognition memory in these experiments is shown in figure 6. Severe lesion-induced memory losses have now been demonstrated at five different loci along the postulated pathway: (1) area TE, (2) the connections between area TE and the amygdalo-hippocampal complex, (3) the amygdalo-hippocampal complex itself, (4) the limbo-diencephalic pathways, and (5) limbic targets in the medial thalamus, including at least the medial parts of the dorsomedial and anterior nuclei. Whether or not still other structures belong to this system remains to be worked out; but one other structure, the midline thalamus, has been added as a potential relay for completion of the circuit, for reasons set out below.

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As indicated at the outset, the recognition-memory model suggests that central representations of stimuli are formed and stored not within the limbic or thalamic portions of the circuit but rather within the highest levels of the cortical sensory processing areas. There are numerous arguments in favour of such a supposition, including one of parsimony – that organized percepts and perceptual memories are thereby localized in the same tissue – as well as one of capacity – that the storehouse for unique central representations within the primate sensory

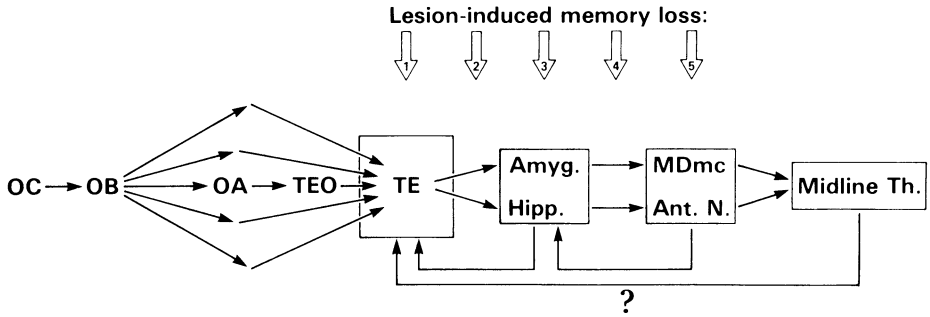

FIGURE 6. The postulated circuit for visual recognition memory. Visual information is distributed from area OC for submodality processing within the prestriate complex (areas OB, OA, and TEO) and is then reintegrated in area TE. The convergent inputs to area TE are stored as central representations of stimuli, provided that area TE activates either an amygdalo-thalamic or hippocampo-thalamic pathway, which then feeds back to strengthen the prestriate–TE synapses either through reciprocal connections or via a relay in the midline thalamus. Severe visual recognition losses have been induced by lesions at each of the five indicated loci. See text for further explanation. MDmc, magnocellular portion of the dorsomedial nucleus; Ant. N., anterior nuclei.

association cortex must be nearly limitless. But perhaps the strongest argument in favour of this localization of the store is one that derives from the clinical syndrome of global amnesia following either medial temporal or medial thalamic injury. In this syndrome, the amnesia is mainly anterograde in nature, the patient being unable to lay down new memories of people, places, and events; old memories, on the other hand, except perhaps for those formed within a year or two of the cerebral injury, are ordinarily spared (Milner 1970; Cohen & Squire 1981). The conclusion seems inescapable that the older memories were stored upstream from both the limbic system and the medial thalamus, presumably within the cortical areas on which the limbic system and medial thalamus have the greatest influence. This conclusion fits exactly the proposed scheme for the establishment of central representations, which requires some feedback action by the subcortical portions of the system on the convergent prestriate–TE projections in order to close the automatic rehearsal or imprinting circuit. In the absence of any direct functional evidence regarding such feedback, two different but mutually compatible suggestions are offered in the summary diagram. One possibility simply entails reciprocal connections along the cortico-limbo-thalamic pathway, whereas the other postulates a role for diffuse cortical projections from the midline thalamic nuclei (Herkenham 1980) with which the medial thalamic nuclei may be connected.

Two further features of the proposed recognition memory circuit require comment. The first concerns the generalizability of the circuit to other sensory systems, through substitution of the cortical components of these other systems for those of the visual system. Since all the sensory modalities appear to be represented centrally by a hierarchical arrangement of primary, secondary and higher-order processing areas, and since the highest cortical level in each modality appears to project to both the amydala and the hippocampus (Van Hoesen & Pandya

1975; Turner *et al.* 1980), it is reasonable to suppose that the same circuit that mediates recognition memory in vision does so in the other sensory modalities as well, and perhaps according to the same basic set of principles.

Finally, at least some acknowledgement must be made of the unusual practice that has been followed here of treating the amygdala and the hippocampus as a single functional unit. In fact, from the standpoint of the recognition memory circuit, all of our experimental evidence so far does point to the nearly complete equivalence of these two structures, as well as of their projections to, and of their targets in, the medial thalamus. In short, with regard to the formation and storage of central representations of stimuli in association cortex, the parallel amygdalo-thalamic and hippocampo-thalamic systems appear to provide nearly complete substitutes for each other, such that the contribution of each to the recognition process becomes apparent only when both systems are damaged together. At the same time, reference was made earlier to other uses of stored central representations, specifically in the formation and recall of associations with the central representations of other stimuli and events, whether affective, spatial or motor. It is undoubtedly within this realm of associative as distinct from recognition memory that a clear separation between amygdaloid and hippocampal function will emerge.

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PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

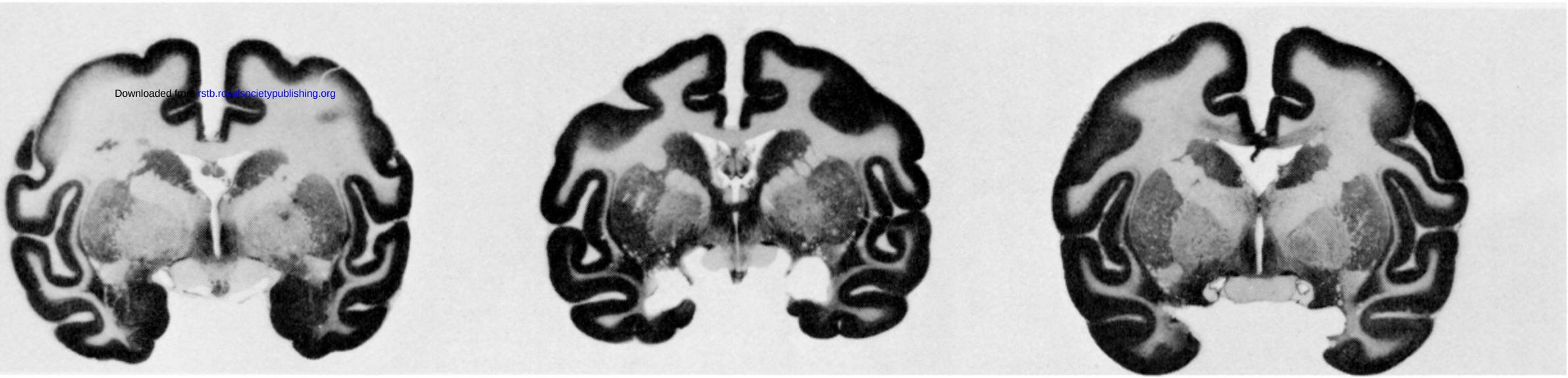

FIGURE 5. Frontal sections through the brains of animals with amygdalectomy alone (A), amygdalectomy plus fornix transection (A+Fx), hippocampectomy alone (H), or hippocampectomy plus transection of the stria terminalis (H+St). The stria terminalis transection is denoted by arrows. For comparison, a frontal section through a normal amygdala and fornix is shown from the brain of an animal with a hippocampectomy plus transection of the stria terminalis (N_{H+St}), and one through a normal hippocampus and stria terminalis is shown from the brain of an animal with an amygdalectomy plus fornix transection (N_{A+Fx}).