REVIEW ARTICLE

LEARNING, MEMORY AND THE BRAIN

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Human and non-human animals acquire information about the world through the process of learning, and store that information as memory. Yet central as the storage process is to adaptive behaviour, progress in understanding its neural bases has been slow and only recently efforts have shown clear signs of being successful. The knowledge that comes from this progress strongly suggests that different kinds of learning involve different neural circuits and acordingly involve different memory systems. Indeed, it is becoming increasingly clear that multiple memory systems may be a fundamental part of the design of the vertebrate brain.

It has long been supposed that learning leads to the formation, or to the strengthening of particular pathways in the brain. Once formed, or strengthened in this way a pathway was viewed as a 'trace' or 'engram' 'representing' the particular experience or relationship which had been learned. There is substantial evidence that neural pathways, especially synaptic connectivity, can be modified by experience-as by rearing rats in an 'enriched' environment with other rats rather than rearing them in isolation (1) ; as well as by modifying the diet or by depriving young rats of their thyroid gland (2,3,4,5). This evidence demonstrates that the central nervous system is plastic, but provides no hint that such plasticity is involved in learning. The evidence that synaptic plasticity is indeed involved in learning and memory is relatively recent.

HABITUATION

During the 1960s and in the years that followed, knowledge of the neural basis of a simple form of learning, habituation, was greatly advanced. Habituation involves a reduction of a behavioural response to a repeated stimulus which is, and which may continue to be of no consequence to the animal. The animal may still respond to a novel stimulus which is, for example, threatening or rewarding. The memory that is implied by habituations is a memory not to respond. If an habituated response returns, the animal may, in some sense, be said to have forgotten the repeated stimulus. Habituation occurs throughout most, if not all of the animal kingdom; so it is likely to have great survival value.

At the neural level habituation involves a weakening of synaptic strength at some junctions in the pathways controlling the behavioural response. The evidence suggests that: (i) habituation of at least some behavioural responses can be accounted for in terms of a progressive reduction of impulse discharges in the neural circuit mediating the response (6,7,8) (ii) this depression may be brought about by activity in the circuit, and in this sense is 'self-generated' (iii) in a number of instances the depression appears to be a consequence of a reduction in the release of neurotransmitter at certain synapses in the circuit (9,10) (iv) the change in transmitter release is probably brought about through a change in the movement of calcium ions at the depressed synapses (11,12) (v) dishabituation may be effected by changing the membrane potential of the depressed presynaptic terminals (8,13) and (vi) many of the more subtle aspects of behavioural habituation can be accounted for

by a relatively simple arrangement of neural circuits possessing synapses with the above properties (8,14).

Different behavioural responses are subserved wholly or partly by different neural circuits. These may be widely distributed in the nervous system. It follows, therefore, that where a self-generated depression of synaptic transmission is a necessary and sufficient basis of the memory not to respond, this memory is embedded within these circuits and accordingly distributed, sometimes widely, in the nervous system.

For other forms of learning the main stumbling block to advance has been the difficulty of identifying brain regions in which the putative memory traces are stored. For a variety of reasons the study of imprinting the domestic chick has proved to be valuable in overcoming this difficulty, and for throwing light on the neural basis of the underlying learning process.

Imprinting is remarkable form of learning which occurs in the young of animals which show well-coordinated locomotor activity very early in life. Through this process young animals, such as the domestic chick, quickly learn the characteristics of an object to which they are exposed, and subsequently are able to recognise it.

RECOGNITION MEMORY AND IMPRINTING

General considerations : Soon after hatching, visually naive chicks approach a wide range of conspicuous objects. If the chicks continue to be exposed to a particular object they learn its characteristics. When their preferences are subsequently measured in a recognition test the chicks selectively approach the 'training' or 'imprinting' object and may not approach, or may actively avoid a novel object. A major advantage of studying imprinting in the domestic chick is that the young bird learns to recognise, and forms a social attachment to the first conspicuous visual object that it sees, if exposed to that object for a sufficient length of time. By rearing chicks in darkness before exposing them to the object, the experimenter can be confident

that no information derived from visual experience has been stored in the brain prior to training.

In many of the studies of imprinting described below the following procedures were employed (see 15). After hatching, chicks were reared in individual compartments in a dark incubator until they were between 15 and 30 h old. The chicks were then placed individually in running wheels some 50 cm from the imprinting stimulus, the whole apparatus being contained within a large black box. The chicks were exposed to the stimulus for between 1 and 4 h, depending on the experiment. During this time the chicks ran toward the stimulus. As they did so they caused the wheel to rotate. The rotations were automatically recorded as 'training approach counts'. A chick's preference was subsequently measured in a recognition test. In this test the chick is exposed to the familiar object and to a novel object in succession. During the test a record is made of the number of approach counts made towards each object. The ratio of the test approach counts to the familiar object, divided by the total test approach counts provides a measure or score of the chick's preference. In all our studies of imprinting the measures of neural function were made without knowledge of the chicks' previous behaviour or treatment.

Biochemical correlates of imprinting : A major difficulty in analysing the neural bases of memory is that of distinguishing training-related changes in neural function which are specifically related to memory from those ('side-effects' of training) which are not. In our first series of experiments, in which training-related changes were measured by using simple biochemical techniques, we attempted to overcome this difficulty. The experiments were correlative in the sense that they involved relating biochemical changes to behavioural changes without interfering with the functioning of the brain, except in one set of experiments. In the first of this series of experiments one group of chicks was exposed to diffuse light from an overhead lamp, one group was maintained in darkness and one group was exposed to the imprinting object. Training was found to be associated with an increase in the

incorporation of radioactive lysine into protein and of radioactive uracil into ribonucleic acid (RNA) in the dorsal part ('forebrain roof') of the cerebral hemispheres (16,17). This regionally localized changes is unlikely to be a simple side-effect of training because:

(i) When sensory input was restricted to one cerebral hemisphere by monocular occlusion and commisurotomy, incorporation was higher in the forebrain roof of the 'trained' hemisphere than that in the 'untrained' hemisphere (18,19); (ii) the magnitude of incorporation was positively correlated with a measure of how much the chicks had learned (20); (iii) the increase associated with training could not be ascribed to short-lasting effects of sensory stimulation (21).

These results together do not, of course, exclude all possible side-effects of training; but they do exclude or reduce the probability that several side-effects can account for the biochemical changes observed in these various studies. To this extent, therefore, we had failed to reject the hypothesis that at least some of these changes were closely related to the learning process.

To map out the distribution of the biochemical changes an autoradiographic technique (22) was employed, by using $[^{14}C]$uracil as the probe molecule. Training lead to an increased incorporation of $[^{14}C]$uracil into RNA in a restricted part of the hyperstriatum ventrale (23). The changes associated with imprinting were found in the medial part of the hyperstriatum ventrale and were restricted to the intermediate region in the antero-posterior plane. Accordingly, this part of the hyperstriatum ventrale was abbreviated to IMHV (24). Evidence of similar localization was obtained by Kohsaka et al. (25) who used the radioactive 2-deoxyglucose technique in their studies of visual imprinting; and Maier & Scheich (26), using guinea-fowl chicks, found *inter alia,* an increased incorporation of radioactive 2-deoxyglucose in the medial part of the hyperstriatum ventrale, overlapping the anterior part of IMHV, associated with acoustic imprinting.

The correlative studies described above were consistent with the view that IMHV stores information, but such studies do not provide evidence that IMHV is *necessary* for this process. If storage is indeed a function of IMHV, then behaviours that are dependent upon storage should be disturbed if this region is destroyed.

Intervention studies : If IMHV is necessary for the storage of information, then its destruction should prevent the acquisition of a preference through imprinting and impair the retention of an acquired preference. Both of these predictions were confirmed in a number of lesion studies which involved the bilateral destruction of IMHV (15,27,28). Similar lesions to other brain regions had no effects on acquisition (29) or retention (15).

The poor performance of the IMHV-lesioned chicks in preference tests need not have anything to do with memory function. The impairments could be accounted for if, for example, some sensory or motor functions were impaired by the lesions or if the chicks lacked the motivation to approach the training object. There are several reasons why such explanations are implausible. Chicks with lesions of IMHV pecked small beads or millet seeds as accurately as did sham operated controls and, when allowed to move about freely, the lesioned and control chicks could not be distinguished from each other. Furthermore, the IMHV lesion appeared to tease apart the memory necessary for one form of associative learning from the memory necessary for imprinting. This dissociation was demonstrated in an experiment in which visually naive chicks were required to press one of two pedals so as to be presented with a view of a conspicuous object which served as a reinforcer. Intact chicks quickly learn to press the correct pedal (30). After reaching criterion on this associative operant task, these chicks were given a choice test; they preferred the (familiar) reinforcing object to a novel object. Thus as the intact control chicks learned to associate the pedal press with a view of the reinforcing object, they also learned the characteristics of that object and subsequently recognized it; thus the two processes of association

and recognition occur concurrently. Chicks with bilateral lesions of IMHV were not impaired in acquiring the operant task. They failed, however to show a preference for the reinforcing object (29). These result showed that object recognition and at least one form of associative learning can be dissociated in young chicks. This dissociation implies that the brain regions involved in the two forms of learning may, in part, differ, and raises the possibility that different neural mechanisms may underlie these different forms of learning. Dissociations of a rather similar kind occur in human patients with diencephalic and/or medial temporal lobe lesions (31); see also Weiskrantz (32) and Zangwill (33 for review) and macaque monkeys with appropriately placed brain lesions (34, 35, 36).

So far as imprinting is concerned, some of the lesion studies described above served to test predictions that IMHV has a memory function, and the predictions were met. More recent studies involved placing lesions in the IMHV of day-old chicks, allowing them to grow up and then subjecting them to a number of recognition tests (37). The ability of IMHV-lesioned adults to recognize individual conspecifics was impaired. Taken together with previous findings these results suggest that IMHV is critically involved in recognition memory and may itself be a store.

Cellular and sub-cellular consequences of learning : Since IMHV may be a storage site it made sense to enquire whether some sort of 'mark' is made in IMHV as chicks learn the characteristics of an imprinting object. There has been no dearth of suggestions as to what form the putative mark might take; perhaps the most consistently popular suggestion is that a particular experience or event leads to the formation or strengthening of particular pathways in the brain. More specifically, Hebb (38, chapter 4) suggested that learning leads to changes in synaptic conncections between neurones to form a 'cell assembly', a particular cell assembly 'representing' a particular stimulus or object (see also James (39) vol. 1, p. 655; (40, 41, 42). Accordingly, Bradley et al. (43) enquired whether imprinting leads to changes in the structure of

synapses in the left and right IMHV. They found that imprinting was associated with a change in only one measure of synapse structure: the mean length of the postsynaptic density (PSD) was increased significantly. This change occurred only in the left IMHV, and (44) was restricted to dendritic spines (axospinous synapses).

There is strong evidence that at least some axospinous synapses in the mammalian brain are excitatory and possess receptors for the excitatory amino acid L-glutamate (45, 46), the receptors being associated with the postsynaptic density (47). Membranes with these receptors bind the radioactive isotope L-$[^3H]$glutamate. If imprinting leads to an increased number of receptors for this amino acid, then membranes prepared from the left IMHV of trained chicks should bind more L-$[^3H]$glutamate than corresponding membranes from dark-reared chicks. McCabe and Horn (48) found that this was indeed the case.

There are several subtypes of receptor for L-glutamate, three of which are defined by the action of selective agonists. One of these is N-methyl-D-aspartate (NMDA), and McCabe and Horn (48) found some at least of the increased binding of L-$[^3H]$ glutamate was to receptors of this type. The increase in binding probably reflects an increase in the number of NMDA receptors. This increase occurs between 6 and 9h after the end of a 140 minutes period of training (49,50). Various pieces of evidence suggested that the increased binding was not attributable to non-specific-effects such as locomotor activity, arousal or visual experience *per se*. There was however a positive correlation between a measure of how much the chicks had learned about the training object and NMDA-sensitive binding: the more the chicks had learned, the greater the binding and, by inference, the greater the number of receptors. The fact that the increase was delayed for several hours after the end of training suggests that the change in NMDA receptor number is related to memory rather to some aspect of the acquisition process.

It is clear that many question remain to be answered. For example, do the structural changes in axospinous synapses and the changes in NMDA receptors occur at the same synapses; are there changes in non-NMDA L-glutamate and other receptors; are all axospinous synapses in the left IMHV affected by training or are the changes restricted to a sub-population of them; are the changed synapses interconnected as in a Hebbian cell assembly (38)? Whereas a change in number of NMDA receptors might functionally weight the synapses to form a basis of recognition memory (cf. 51, p. 276), other possibilities exist and need to be explored. For example, the increase in NMDA receptors may play only a 'permissive role' in the cellular mechanisms of memory: the increase might allow a relatively large influx of calcium ions into the cell to initiate other changes, so far undetected, in synapse structure, after which NMDA receptor numbers may return to lower levels (cf. 52).

Answers to these questions are likely to extend our understanding of the neural basis of recognition memory. But the answers are likely to relate to relatively long-term memory. The changes in NMDA receptors occur several hours after the end of training. What is the neural basis of memory before time time? At present there are only hints. Brown and Horn (53) have provided evidence that training is associated with a increased synthesis of an≈80 kDa protein in the left IMHV; and McCabe et al. (54) have shown that exposure to an imprinting object leads to an increase in the phosphorylation of a protein of approximately similar molecular mass. This protein is a substrate of protein kinase C. Activation of this kinase has been related to

regulation of ion channels, control of growth and differentiation (for review see 55) as well as to long-term potentiation (56). Long-term potentiation (LTP) is a long-lasting, synapse specific enhancement of transmission at certain synapses that follows high frequency stimulation of presynaptic afferent fibres (for review see 57). At some synapses in the hippocampus the initiation of LTP is blocked by the drug D-aminophonovalerate (46). Preliminary studies have shown that when this drug is infused into IMHV immediately before exposing the chicks to an imprinting stimulus, they fail to acquire a preference for that stimulus; infusion of the same amount of the drug into another brain region is without effect on imprinting (58). The results of these experiments are suggestive of-or put more conservatively, are not inconsistent with a role for an LTP-like phenomenon in the early phases of the recognition memory of imprinting (59).

CONCLUSION

Although the studies of imprinting which have been described above, may have advanced knowledge of the neural basis of recognition memory, they have done so in a highly circumscribed way. Even if, to be optimistic, an understanding of information storage is within our grasp, we have yet to understand how the multiplicity of processes, predisposition, attention, approach and avoidance activity, behavioural habituation and may others, interact to produce that marvellously coordinated and seemingly simple pattern of behaviour that characterizes filial attachment in precocial birds, and which involves a form of learning which may occur in many animals, including man.

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