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Neural bases of recognition memory investigated through an analysis of imprinting

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SUMMARY

Through a learning process known as imprinting, the young of some animals, including the domestic chick, come to recognize an object by being exposed to it. Visually naive chicks vigorously approach a wide range of objects. After an adequate period of exposure to one object chicks selectively approach it in a recognition test. The nervous system of dark-reared chicks is not a *tabula rasa*, as chicks have predispositions to approach some stimuli rather than others. Nevertheless, visual imprinting leads to changes in a nervous system that may not have been 'marked' by previous visual experience, and so encourages the hope of discovering the neural bases of the learning process. The intermediate and medial part of the hyperstriatum ventrale, a sheet of cells within the cerebral hemispheres, plays a crucial role in visual imprinting, particularly in the memory process of recognition. The cellular and sub-cellular changes that take place in this part of the hyperstriatum ventrale after imprinting are described. The right and left hyperstriatum ventrale regions play different roles in the imprinting process, and evidence is given for the existence of multiple memory systems in the chick brain.

1. INTRODUCTION

Animals acquire information about the world through learning and store that information as memory. It has been clear from the work of human psychologists, from studies of human patient with cerebral pathology and also from experimental studies of mammals that there are multiple memory systems in the brain, that the systems which normally interact are dissociable, and that some may involve widespread activity in the nervous system, whereas others may involve activity in particular and localized brain regions (for review see Weiskrantz (1987) and this symposium). During the past few years may colleagues and I have been studying the neural basis of imprinting in the domestic chick (*Gallus gallus domesticus*), and it has become apparent that several memory systems exist in this bird, which are strikingly similar to those found in mammals. These similarities suggest that multiple memory systems may be a fundamental part of the design of the vertebrate brain. For a variety of reasons imprinting has proved to be fruitful for analysing the neural bases of such systems.

Soon after hatching, visually naive chicks will 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 tested the chicks selectively approach the 'training' or 'imprinting' object and may not approach, or may actively avoid a novel object. This narrowing down of a chick's preference for the object to which it has been exposed implies that the chick recognizes the object. Imprinting involves a number of processes, including recognition and selective approach

to the familiar object. Whereas the motor component has a sensitive period, there is no reason to suppose that the learning and recognition processes have one: an adult fowl recognizes other birds in the flock (Candland 1969), but does not necessarily follow them (see Horn (1985), p. 273; Bateson, this symposium). Sluckin & Salzen (1961) argued that imprinting is an example of perceptual learning, although Sluckin later came to prefer the expression 'exposure learning' since it '... refers unambiguously to the perceptual registration by the organism of the environment to which it is exposed ...' (Sluckin 1972, p. 109). Such learning is not restricted to birds but occurs in a wide range of animals (see, for example, Hinde (1962); Sluckin (1972); and far from being a specialized form of learning it may be a very common form of learning (see also Suboski (1990)).

A major advantage of studying imprinting in the domestic chick is that under appropriate conditions the young bird learns the characteristics of the first conspicuous visual object that it sees. The brain of a chick is not, however, a *tabula rasa* on which experience makes its mark; although chicks will follow a wide range of visual stimuli, the range is not unlimited, and some objects are more effective than others in eliciting approach. Size, shape, contrast, the presence or absence of movement, and even particular configurations of stimuli influence the effectiveness of a stimulus in evoking approach, and this list is far from exhaustive (see Sluckin 1972; Kovach 1983; Bolhuis *et al*. 1985; Johnson & Horn 1988; Bateson, this symposium). Predispositions may serve to direct the chick's attention to certain kinds of objects, and so to learn about them, rather than to others which the

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chick may come to avoid (Bolhuis *et al.* 1985). Such learning in turn disposes the chick to act in one way rather than another, to follow the familiar object rather than an unfamiliar one. The situations to which the young animal is exposed and about which it learns will be different according to which object it follows: such choice necessarily limits the range of the young bird's subsequent experiences. Hence predispositions and dispositions, subtle though they may be, may profoundly effect the kind of information the chick acquires about the world.

Valuable as the chick is for investigating predispositions (see, for example, Johnson *et al.* (1985); Bolhuis *et al.* (1989*a*)), it is also valuable for investigating learning mechanisms: by rearing chicks in darkness before exposing them to an imprinting object the experimenter can be confident that no information derived from visual experience has been stored in the brain prior to training. This property of imprinting was a major attraction for investigating the neural basis of the underlying memory processes, since, by implication no prior memories had been acquired through visual experience.

In many of the studies of imprinting described below the following procedures were employed (see McCabe *et al.* 1982). 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. A chick's preference was subsequently measured by using either a sequential test or a simultaneous choice test. In the sequential test a chick is placed in a running wheel and exposed to the familiar object and to a novel object is succession and in balanced order. The ratio of approach counts (the number of rotations of the wheel) to the familiar object, to the total number of approach counts made in the test provides a measure or score of the chick's preference. In the simultaneous choice test the training and novel objects are present at the same time and the chick expresses its choice by attempting to approach one of them (Bateson & Wainwright 1972).

At the extreme ends of the spectrum of approaches to studying the neural mechanisms of memory, there is the bottom-up approach and the top-down approach, respectively. The bottom-up approach involves identifying and analysing some change observed, say at the cellular level, and searching for some correlate at the behavioural level. While this approach encounters some difficulties (see, for example, Morris (1990)) it also has had some modest success, especially for studies of habituation (Horn & Hill 1964; Bruner & Tauc 1966; Thompson & Spencer 1966; Horn 1967; Castellucci & Kandel 1974; see also Carew, this symposium); and the bottom-up approach is being hotly pursued in respect of long-term potentiation of synaptic transmission (see Morris, this symposium, for review). The top-down approach, on the other hand, involves training an animal and then attempting to relate changes in neural function to the learning

process. This is the approach we have adopted for studying imprinting; but the approach also has its difficulties. For example, it would be very surprising if the changes that take place in the brains of young chicks when they learn about the first visually conspicuous object that they see is attributable solely to information storage. Hence a major difficulty of the top-down approach 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.

2. SOME BIOCHEMICAL CORRELATES OF IMPRINTING

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. All biochemical analyses were conducted 'blind', that is without knowledge of the chicks' previous behavioural treatment or performance. One group of chicks was exposed to a conspicuous object, one group was exposed to diffuse light from an overhead lamp and one group was maintained in darkness. 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 (Bateson *et al.* 1969, 1972). This regionally localized change 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 (Horn *et al.* 1971, 1973*a*);

(ii) the magnitude of incorporation was positively correlated with a measure of how much the chicks had learned (Bateson *et al.* 1975);

(iii) the increase associated with training could not be ascribed to short-lasting effects of sensory stimulation (Bateson *et al.* 1973). These results 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 (Horn & McCabe 1977) was employed, by using [^{14}C]uracil as the probe molecule. An increased incorporation into RNA was found in a restricted part of the hyperstriatum ventrale (Horn *et al.* 1979). 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 (Horn 1981). Evidence of similar localization was obtained by Kohsaka *et al.* (1979) who used the 2-deoxyglucose technique in their studies of visual imprinting, and Maier & Scheich (1983) 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 reaches 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.

3. INTERVENTION STUDIES: NEURAL AND BEHAVIOURAL DISSOCIATIONS

If IMHV is necessary for the storage of information, then destruction of the region should prevent the acquisition of a preference through imprinting and should impair the retention of an acquired preference. Both of these predictions were confirmed in a number of lesions studies which involved the bilateral destruction of IMHV (McCabe *et al.* 1981, 1982; Takamatsu & Tsukada 1985). Similar lesions to other brain regions had no effects on acquisition (Johnson & Horn 1986) or retention (McCabe *et al.* 1982). 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 lesion 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-lesioned chicks were able to discriminate between two visual patterns when they were rewarded for making the correct choice (McCabe *et al.* 1982). Thus the lesion appeared to tease apart the memory necessary for this form of associative learning from the memory necessary for imprinting. A similar dissociation was found in a study 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. Bateson & Reese (1969) had shown that intact chicks quickly learn to press the correct pedal. After reaching criterion on this associative operant task, the chicks were given a choice test; they preferred the (familiar) reinforcing object to a novel object. These experiments showed that as the chicks learned to associate the pedal press with a view of the reinforcing object, the chicks also learned the characteristics of that object and subsequently recognized it. Thus in intact chicks, the two processes of association and recognition occur concurrently. Chicks with bilateral lesions of IMHV were not impaired in

acquiring the operant task, but they failed to show a preference for the reinforcing object (Johnson & Horn 1986). This result, like that obtained by McCabe *et al.* (1982) showed that object recognition and these forms of associative learning can be dissociated in young chicks. Dissociations of a rather similar kind occur in human patients with diencephalic and/or medial temporal lobe lesions (Sidman *et al.* 1968; see also Weiskrantz (1982) and Zangwill (1983) for review) and macaque monkeys with appropriately placed brain lesions (Aggleton & Mishkin 1983; Zola-Morgan & Squire 1984). However, the question of which memories are spared and which are impaired by these lesions in human and non-human primates is far from being resolved (see Weiskrantz (1982) for review).

In the light of these uncertainties it may come as no surprise that similar problems arise in defining the residual learning abilities of chicks with lesions of IMHV. Evidence that some dissociations occur has been given above; but there is also good evidence that, in addition to playing a role in imprinting, this brain region also plays a role in passive avoidance learning (Kossut & Rose 1984; Stewart *et al.* 1984; Davies *et al.* 1988; Patterson *et al.* 1990). Chicks tend to peck spontaneously at bright beads. In a passive avoidance learning task chicks are trained by allowing them one peck of a bead coated in methylanthranylate (MeA). Within seconds after having pecked the bead the chicks show a strong aversive reaction, and are less likely than are untrained chicks, to peck a bright bead in the following hours or days (Lee Teng & Sherman 1966). Presumably the chicks have associated the bead with the aversive taste of MeA; and when the bead is presented again they are reluctant to peck it. However, after lesions have been placed in IMHV and the birds are trained with the MeA coated bead, they do not withold the peck response (Davies *et al.* 1988; Patterson *et al.* 1990): acquisition of this task by IMHV-lesioned birds is impaired.

In the passive avoidance task described above, the acquisition of which is impaired by IMHV lesions, there was only one training trial. In contrast, the associative tasks that are unaffected by IMHV lesions involve repeated trials (McCabe *et al.* 1982; Johnson & Horn 1986). It would be worth enquiring whether IMHV-lesioned chicks allowed to peck the MeA-coated bead repeatedly, gradually cease to do so. Repetition may establish a habit, a simple stimulus-response relationship (see James (1890) vol. 1, pp. 104–127), whether of approach or avoidance, in the absence of IMHV. In this regard it is of interest that Mishkin and his collaborators in their studies of brain lesions and memory in rhesus monkeys have distinguished between the memory underlying habits established through multiple-trial learning and the memory for trial-unique stimuli requiring one-trial learning (Bechevalier & Mishkin 1984; Malamut *et al.* 1984). The memory underlying the latter form of learning is considered to be mediated by limbic system structures whereas the memory underlying a habit is considered to be mediated by non-limbic structures (see Malamut *et al.* (1984) and Horn (1985), pp. 123–126, for further discussion).

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 (Bolhuis *et al.* 1989*b*). The ability of the 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.

4. CELLULAR AND MOLECULAR CONSEQUENCES OF LEARNING

It has long been supposed that memories consist of specific traces or 'engrams' left in the brain by previous, specific experiences. If a stimulus leaves its 'mark' in the brain, what is the nature of the mark? Clearly this question would be more tractable if we knew where in the brain to look for the mark. The evidence reviewed above suggests that IMHV may be a storage site for information acquired through exposure to an imprinting object. Accordingly, it made sense to enquire whether some sort of 'mark' is made in IMHV as chicks learn the characteristics of such an 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 (1949, chapter 4) suggested that learning leads to changes in synaptic connections between neurones to form a 'cell assembly', a particular cell assembly 'representing' a particular stimulus or object (see also James (1890) vol. 1, p. 655; Tanzi 1893; Cajal 1911; Kornorski 1948; McLaren & Dickinson, this symposium). Accordingly, Bradley *et al.* (1981) enquired whether imprinting leads to changes in the structure of synapses in the left and right IMHV.

In this study, two groups of chicks were exposed to an artificial training stimulus when they were approximately 22 h old. The chicks were placed individually in running wheels facing the stimulus. One group of chicks was exposed to the stimulus for 20 min ('undertrained') and the other group was exposed to it for 140 min ('overtrained'). These training times were chosen on the basis of an earlier experiment by Bateson (1979) in which it was shown that a training time of 20 min was inadequate to establish a preference, whereas a strong preference was formed after 80 min of training. After exposure to the training stimulus the chicks were returned to the dark. Samples of the left and right IMHV were subsequently removed, sectioned and examined with an electron microscope. Quantitative sampling techniques were used to measure various aspects of synapse morphology, including the number of synapses per unit volume of brain tissue, the volume of dendritic spines and of synaptic boutons. At chemical synapses in vertebrates part of the postsynaptic membrane is thickened into a postsynaptic density (PSD); the mean length of this structure in right and left IMHV synapses, respect-

ively, was determined for each chick. Chicks that had been trained for 140 min differed from the under-trained chicks in only one measure of synapse structure: the mean length of the PSD was increased significantly, by approximately 10%. This change occurred only in left IMHV synapses; there were no significant effects of training in the right IMHV (figure 1*a*, *b*). Synapses onto dendrites occur in two forms, axodendritic and axospinous. Axodendritic synapses are found on the shafts of dendrites; axospinous synapses are found on dendritic spines. When synapses were classified in this way, the effects of training were found to be restricted to axospinous synapses: the mean length of these postsynaptic densities in the left IMHV of overtrained chicks was approximately 17% greater than that in the undertrained group (Horn *et al.* 1985). In these studies it was also found that the mean PSD lengths of the undertrained chicks did not differ significantly from that of a group of dark-reared chicks.

There is strong evidence that at least some axo-spinous synapses in the mammalian brain are ex-citatory and possess receptors for the excitatory amino acid L-glutamate (Nafstad 1967; Errington *et al.* 1987), the receptors being associated with the postsynaptic density (Fagg & Matus 1984). Membranes with these receptors bind the radioactive isotope L-[^{3}H]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-[^{3}H]glutamate than corresponding membranes from dark-reared chicks. McCabe & Horn (1988) placed chicks individually in running wheels and exposed them to a rotating red box for 140 min. After training, all chicks were assigned codes and held individually in darkness for at least 7 h before being killed together with their dark-reared controls. The left IMHV was then removed, membranes prepared and incubated with L-[^{3}H]glutamate. Imprinting was associated with a significant increase (approximately 20%) of L-[^{3}H]glutamate binding relative to that in dark-reared controls.

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 & Horn (1988) enquired whether some at least of the increased binding of L-[^{3}H]glutamate was to receptors of this type. Chicks were trained as in the earlier experiment of this study (see above) and the effects of training on NMDA-sensitive binding to membranes prepared from IMHV determined. There was a significant increase in NMDA-sensitive binding in the left IMHV of trained chicks compared with that in dark-reared controls; there were no such differences in right IMHV binding (figure 1*c*, *d*).

The changes in NMDA-sensitive binding occur in a region of the brain which, as described above, plays a crucial role in the memory underlying imprinting (see also Cipolla-Neto *et al.* 1982). Accordingly, there is an *a priori* hypothesis that the changes in NMDA-sensitive binding are related to the storage process. It remained possible, however, that these changes were some indirect consequence of the learning process especially
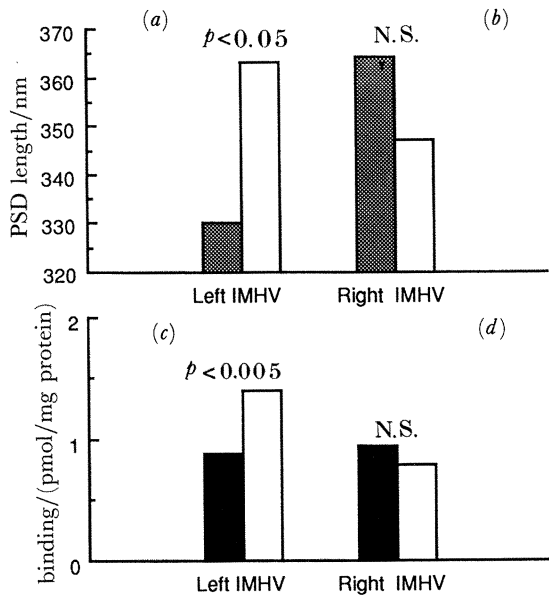
Figure 1. Effects of training on the length of postsynaptic densities (PSDs) of synapses (a, b), and on NMDA-sensitive binding (c, d) in IMHV. Mean values are shown according to hemisphere and treatment. (a, b) PSD lengths. Data for axospinous and axodendritic synapses are combined. Chicks were either exposed to the imprinting stimulus for 20 min (shaded bars, undertrained chicks) or 140 min (open bars, overtrained chicks). Further training led to a significant change (increase) in the mean length of PSDs in the left IMHV only (after Bradley *et al.* (1981). (c, d) NMDA-sensitive binding. Chicks were either dark-reared (filled bars) or trained (open bars) through exposure to the imprinting stimulus for 140 min. Training led to a significant increase in NMDA-sensitive binding in the left IMHV only (after McCabe & Horn 1988).

as, of the two groups that were compared, one was trained and hence visually experienced whereas the untrained controls were visually naive, having been reared in darkness.

In a previous study of imprinting it was found that, in a group of 106 chicks all of which were exposed to the training object for a given, fixed length of time, there was a positive correlation between the strength of preference for the training object and the amount of [^{14}C]uracil incorporated into RNA in the forebrain roof (Bateson *et al.* 1975). To determine whether a similar correlation existed between preference score and NMDA-sensitive binding, 108 chicks were trained as described above. Approximately 8 h later the chicks were given a preference test after which they were killed, IMHV removed and NMDA-sensitive binding measured. Since the IMHVs of three chicks were combined in a single sample, the three birds contributing to the sample were matched for preference scores. There was a significant positive correlation between preference score and NMDA-sensitive binding in the left IMHV samples ($r = 0.38$, $p < 0.012$, 1-tailed test). The corresponding correlation coefficient for the NMDA-sensitive binding in the right IMHV samples was not significant ($r = 0.10$). Approach during training is weakly correlated with preference score (Bateson & Jaeckel 1974). It was possible therefore that the observed correlation between NMDA-sensitive binding

and preference score reflected a relationship between binding and locomotor activity during training. Binding and preference scores were therefore corrected for training approach activity, by using the method of partial correlation. Training approach activity was measured as the number of revolutions made by the running wheel as a chick attempted to approach the red box during the training period. There was a positive partial correlation between NMDA-sensitive binding in the left IMHV and preference score ($r_{xy.z} = 0.41$; $p < 0.01$, 1-tailed test). The 36 values that contributed to this correlation were divided into three groups of equal size according to their ranked corrected preference scores. The mean corrected binding and preference scores together with the standard errors were calculated for each group of 12 values. The lowest mean corrected preference score (of the 'poor learning' group of chicks) was not significantly different from 50, the chance level of performance. The corresponding mean binding for this group (i) was not significantly different from that in the left IMHV of the dark-reared chicks of the previous study (see figure 1 c), and (ii) was significantly less than the group ('good learners') with the highest mean preference score. The partial correlation coefficient between NMDA-sensitive binding in the right IMHV samples and preference score was not significant ($r_{xy.z} = 0.09$).

The apparent K_d of the NMDA-sensitive binding of L-glutamate was 0.1 μM. Accordingly, the binding would be expected to be virtually saturated at the concentration of the radioligand used in the above studies (1 μM). The increase in binding in the left IMHV after imprinting (figure 1 c) is therefore likely to reflect an increase in the number of available binding sites, although we have not excluded the possibility that there is also a change in the affinity of these sites. These studies do not, of course, preclude the possibility of changes in L-glutamate receptors of the non-NMDA-type.

There are a number of reasons why the increase in NMDA-sensitive binding cannot simply be attributed to some side-effects of the training procedure. First, it is unlikely that the increase is some consequence of a general arousal response since such a response is likely to affect both the right and left IMHV. An effect of arousal, and indeed of accelerated maturation would also be expected to be expressed in behaviour. For example, the more aroused or the more developmentally mature the chicks, the more vigorously would they be expected to approach the red box during training. However, the partial correlation coefficient between NMDA-sensitive binding and preference score was significant when the effect of approach activity during training was held constant. This latter finding also shows that differences in locomotor activity during training cannot account for the correlation between binding and corrected preference score. Secondly, light exposure as such does not account for the findings, since the corrected mean binding in the left IMHV samples of chicks that had been exposed to the red box for 140 min, but had not developed a preference for it, was closely similar to that of the left IMHV samples of dark-reared chicks. Together, these considerations

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suggest that NMDA-sensitive binding in the left IMHV is not influenced by maturation, arousal, light exposure or locomotor activity *per see*. Instead, the results of this correlational study suggest either, (i) that birds with larger numbers of NMDA receptors learn better than birds with fewer NMDA receptors, or (ii) that binding increases as the chicks learn about the imprinting object and so form a preference for it. Certain considerations make it possible to distinguish between these hypotheses. The dark-reared birds were unselected for their learning abilities. Hypothesis (i) predicts that this group contained poor learners which would, if trained, achieve a low preference score, as well as good learners which would achieve a high preference score if trained. Accordingly, the variance of NMDA-sensitive binding in the left IMHV of the dark-reared chicks should be higher than that of both the poor learners and the good learners as these two groups are *ex-hypothesi* sub-groups of the unselected dark-reared chicks. The variances for the left IMHV binding from four groups of chicks, two dark-reared groups, the poor and the good learners, did not differ significantly (Bartlett's Test, $\chi^2 = 5.59$; d.f. $= 3$; $p > 0.1$). This result weakens hypothesis (i), but, like the results shown in figure 1 *c*, is consistent with the view that learning leads to an increase in the number of NMDA-type receptors in the left IMHV.

Horn & McCabe (1990) have recently completed a study of the time-course of the change in NMDA-sensitive binding up to some 8.5 h after training. Chicks were trained for 140 min, as described above (McCabe & Horn 1988) and killed approximately 0, 3, 6 or 8.5 h after the end of training. As before, there was a significant increase in binding at 8.5 h; but there were no significant changes at 0, 3 and 6 h. These findings, together with the results of our earlier studies suggest that the magnitude of increase in NMDA-sensitive binding is affected by at least two factors: the length of time that elapses between the end of training and removal of IMHV (and, presumably also the duration of training if this is particularly prolonged), and the strength of preference for the training object.

The results described by Horn & McCabe (1990) pose problems for the view that the increase in number of NMDA receptor binding sites observed in the left IMHV some 8.5 h after training (McCabe & Horn 1988) is crucial for both short-term and long-term memory. After all, if chicks are given a preference test, say 2 h after training, they prefer the training object to a novel one, just as they may do several hours after training (e.g. see control chicks in Horn *et al.* (1983)). The new findings imply that the increase in NMDA receptor numbers observed in the left IMHV after imprinting cannot support the preference when it is measured shortly after training, as there is no such increase. Hence the findings raise the possibility that at least two mechanisms are involved in recognition memory, a possibility which is not wholly surprising: different pharmacological agents have been found to disrupt retention when given at different times after training (for review, see Andrew (1980)). A clue to what might be happening comes from studies of long-term potentiation in the hippocampus (for reviews see

Collingridge & Bliss (1987); Teyler & DiScenna (1987)). The early phase of potentiation appears to depend upon an increased liberation of transmitter from the presynaptic terminal when it is invaded by a nerve impulse. The later phase of potentiation involves the postsynaptic cell, possibly an increase in number and/or affinity of L-glutamate receptors of the quisqualate type (Davies *et al.* 1989). Long-term potentiation in the rat dentate gyrus also leads to morphological changes in axospinous synapses (Desmond & Levy 1986). These changes include an increase in lengths of the postsynaptic density of certain dendritic spines.

The postsynaptic changes associated with hippocampal long-term potentiation have some rather general similarities with those described in this and in the previous section for imprinting. It is possible that there are other similarities, and that the early phase of memory in imprinting is sustained by presynaptic events as is the early phase of long-term potentiation. Although there is no direct evidence for this possibility in the case of imprinting there is some evidence that presynaptic, as well as postsynaptic elements are involved in passive avoidance learning in the domestic chick. Stewart *et al.* (1984) found that training was associated with a substantial and highly significant increase in the mean number of vesicles per synaptic bouton in the left IMHV. Stewart *et al.* also found changes in PSD length, which were similar in magnitude and direction to those found by Bradley *et al.* (1981) after imprinting neither Bradley *et al.* nor Horn *et al.* (1985) counted synaptic vesicles.) An increase in number of vesicles per synaptic bouton would be consistent with an increased mobilization of transmitter as a consequence of training. The findings raise the possibility that when such terminals are invaded by a nerve impulse more transmitter is liberated after training than before.

In the study of the effects of imprinting on synapse structure in the left IMHV, an increase in mean length of the PSDs of axospinous synapses was found approximately 3 h after the end of training (Bradley *et al.* 1981; Horn *et al.* 1985). In the study of Horn & McCabe (1990) no change in NMDA-sensitive binding was observed at this time. Taking these results on their face value they suggest that the cellular mechanisms controlling the changed length of the PSDs are different from that controlling the change in NMDA receptor numbers, even though NMDA receptors are associated with PSDs (Fagg & Matus 1984). We do not know whether changes in PSD length are present less than 3 h after training. It is, however, known that changes in PSD length can occur quickly. Thus Desmond & Levy (1986) studied the effects of long-term potentiation on the length of the PSDs of synapses in the rat dentate gyrus. The animals were killed at various times after electrical stimuli had been delivered to the afferent input to this gyrus. The length of the PSDs of certain axospinous synapses increased significantly in rats which had been killed 2 min after stimulation. Such a rapid change implies that the factors controlling the length or area of the PSD operate locally, possibly in the region of the synapse through mechanisms that are as yet unknown (see, for

example, Shashoua (1985); Siman *et al.* 1987). The long time taken for the increase in receptor number to occur after imprinting suggests that the mechanisms controlling this increase are not localized to the synapse; the timecourse is however consistent with a process which involves the modification of gene expression.

It is clear that many questions remain to be answered in addition to those implicit in the considerations set out above. 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; and are the changed synapses interconnected as in a Hebbian cell assembly (Hebb 1949)? Whereas a change in number of NMDA receptors might functionally weight the synapses to form a basis of recognition memory (cf. Horn 1962, p. 276), other possibilities exist and need to be explored. For example, the increase in NMDA receptors may play only '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. Wenk *et al.* 1989).

NMDA receptors have been implicated in the processes that control certain forms of plasticity in the developing nervous system (Cline *et al.* 1987; Rauschecker & Hahn 1987; Kleinschmidt *et al.* 1987). The implied link between developmental processes and learning is not wholly unexpected. Changes occur in the morphological and functional properties of neurones during the course of ontogeny. In some systems the direction of these changes is such that neurones largely lose their capacity for plastic change as their synaptic connections become stabilized in the course of development and maturation (Hubel & Wiesel 1971; Knudsen & Knudsen 1986; Olson & Freeman 1980). A similar direction of change may occur as a result of learning in neural circuits specialized for storage. Thus Horn *et al.* (1973*b*) suggested that neurones within the memory systems of the brain may remain plastic until they become engaged in the storage process associated with a specific learning experience. Thereafter the synaptic connections may become stabilized.

As axons grow in the course of development or after injury there is a high level of synthesis of at least one growth-associated protein, referred to as GAP-43. The apparent molecular mass of this protein is approximately 50 kDa. As synaptic relationships become defined the synthesis of this protein declines (see Benowitz & Routtenberg (1987); Jacobson *et al.* (1986); Skene (1989)). Ali *et al.* (1988) studied protein phosphorylation at synapses in chick forebrain. They found a significant decrease in phosphorylation of a 52 kDa component of the synaptic plasma membranes after passive avoidance learning. The membranes were prepared from whole forebrains, so it would be of the greatest interest to know whether such changes are also found in samples of IMHV. Brown & Horn (1990)

studied changes in protein synthesis associated with imprinting. Slices of IMHV were removed from the left cerebral hemisphere of chicks which had been trained by exposing them to the rotating red box. The samples were incubated with [^{35}S]methione, processed for sodium dodecyl sulphate (SDS) slab gel electrophoresis and autoradiographs prepared. The optical densities of various bands were measured. There was a negative correlation between the optical density of the 50 kDa band and approach activity during training ($p < 0.01$). That is, the more chicks ran towards the red box during training, the lower was the synthesis of protein(s) with molecular mass of *ca.* 50 kDa. In addition there was a positive correlation between training approach activity and the optical density of a *ca.* 80 kDa band ($p < 0.001$). These results suggest that training is associated with both an increase and a reduction in protein synthesis. No training-related changes were observed in gels prepared from the two other samples of the left cerebral hemisphere, the posterior neostriatum and the visual Wulst. Approach activity during training is only a weak predictor of the strength of preference for the training object (Bateson & Jaeckel 1976); whether the changes in protein synthesis are related to a more direct measure of learning and whether the changes in optical density represent changes in the synthesis of only one or more than one protein of molecular mass *ca.* 50 kDa and *ca.* 80 kDa respectively, are questions that remain to be answered. However if growth associated proteins are involved in imprinting, then there may indeed be substance in the suggestion (Horn *et al.* 1973*b*) that there are continuities at the cellular and molecular levels between the development of neurones and the changes that underlie memory.

5. CEREBRAL ASYMMETRY AND MEMORY FUNCTION

In our studies of synaptic organization in IMHV in relationship to imprinting, it was found that training was associated with changes in the left IMHV, but not in the right (Bradley *et al.* 1979, 1981; Horn *et al.* 1985). The subsequent studies of NMDA-sensitive binding yielded a similar pattern of results (McCabe & Horn 1988; Horn & McCabe 1990; see also figure 1). These asymmetries were consistent with the simple hypothesis that the left IMHV has a storage function, but that the right IMHV does not. The hypothesis was examined in a series of experiments involving sequential lesions, first to one IMHV and subsequently to the other (Cipolla-Neto *et al.* 1982; Horn *et al.* 1983). On the basis of these experiments the simple hypothesis was rejected. Instead, it was proposed that when chicks are exposed to a training object, more than one long-term stores are formed. One of these is within the left IMHV, and another referred to as S' is outside IMHV. The right IMHV appears to be implicated in transferring information to S'; transfer appears to be complete within 6 h after the end of training (Davey *et al.* 1987). Beyond these bare outlines, little is known. For example, we do not know what role the right IMHV plays in this transfer function, or whether the

right IMHV serves as a temporary store or as a long-term store.

The location of S' is not known, nor do we know whether the left IMHV and S' serve different functions in the recognition memory required for imprinting. For example (see Horn 1985, pp. 143–147), if one region has the larger capacity then it may store information which is contextually rich and which, more effectively than information stored in the other region may be modified or extended through subsequent experience, and be used more flexibly, as in transferring experience gained in one situation to solving problems in another situation. Clearly, further work is needed to clarify these issues.

The idea that memories may be shifted about within the central nervous system is not new. Marr (1970, 1971), for example, suggested that information is transferred from the archicortex to the neocortex, a view that is consistent with those of Warrington & Weiskrantz (1982) and Rawlins (1985). However, IMHV is not the hippocampus; IMHV is upstream of that structure and receives afferents from it (Bradley *et al.* 1985). Nevertheless, the convergence of evidence from diverse sources for the existence of multiple memory systems is striking.

6. CONCLUSIONS

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, predispositions, attention, approach and avoidance activity, behavioural habituation and many others, interact to produce that marvellously co-ordinated 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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