PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Comparative Aspects of Studies of Amnesia

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Comparative aspects of studies of amnesia

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In recent years important advances have been made in reconciling some of the conflicting evidence regarding the contribution of the medial temporal lobe – hippocampal structures to long-term memory in man compared with laboratory animals. Despite the severe amnesic state that is seen clinically in patients, it has nevertheless emerged that both in animals and man damage to the structures leaves learning and retention of certain types of long-term memory tasks intact. The evidence from man suggests that in the amnesic syndrome the integrity is preserved of those forms of long-term memory that do not depend on the operation of a 'mediational' memory system. In particular, items stored in semantic memory can be facilitated by repetition, and simple associations can be formed if no mediating links are required, but impairments are seen in tasks in which memory depends upon the stored benefits of matching, reordering and comparing. A similar characterization seems possible for the results of animal studies. One interpretation of the differential sensitivity of memory tasks in the amnesic syndrome is in terms of a disconnection syndrome in which a semantic memory system is detached from a mediational system. The disconnection is postulated to be caused by interruption of those temporal–frontal pathways in which pathology has been found in the brains of amnesic patients, namely the mammillary bodies and the subependymal zone of the thalamus.

> '*No* [*experience of*] *memory is involved in the mere fact of recurrence. The successive editions of a feeling are so many independent events, each snug in its own skin. . . . A farther condition is required before the present image can be held to stand for a* past original. *That condition is that the fact imaged be* expressly referred to the past, *thought of as* in the past. *But how can we think of anything as in the past, except by thinking of the past together with the thing, and of the relation of the two?. . . And to 'refer' any special fact to the past epoch is to think that fact* with *the names and events which characterize its date, to think it, in short, with a lot of contiguous associates.*'
>
> (William James 1890, vol. 1, pp. 649–650.)

Introduction

In the comparative neuropsychological study of memory mechanisms, as in other areas of empirical enquiry, progress often consists of replacing one puzzlement by another. In this paper I shall focus on one of these transitions: the replacement of one apparent discontinuity by another more or less orthogonal to it. The first discontinuity separated humans from other animals; the second unites them, but introduces a new separation of distinct and dissociable memory processes.

In the early 1950s Karl Lashley's conclusion was widely accepted that memory traces (engrams) were almost uniformly distributed throughout the brain (or at least the telencephalon), in which he supposed there was a mass-action relation between the amount of neural tissue and learning. His experimental findings suggested that disorders of learning and

memory should be graded rather than all-or-none, and that they should correlate with the volume of neural tissue affected by pathology. In fact, as Lashley was well aware, there was already a wealth of clinical evidence of human patients – going back to the end of the nineteenth century – with highly specific and very severe disorders of memory that approached a discontinuous rather than a graded distribution of impairment and that could appear in some patients with tragic abruptness. There was also available a large body of neuropathological evidence derived from post-mortem examination of the brains of such amnesic patients in which there was a strongly consistent signal of pathological changes in a few small and specific sites, especially in the region of the mammillary bodies and the walls of the third ventricle, and not the diffuse pathology that one might have supposed. This evidence was rather well known to pathologists but for some reason failed to impress itself on those who were concerned with theories of brain mechanisms of memory, perhaps because they conceived of the engram as being located primarily cortically, and not in the subcortical structures in which the pathology actually turned up. Lashley's escape from such evidence was to argue that impairments did not really involve the engram directly. 'I believe,' he wrote, 'the evidence strongly favours the view that amnesia from brain injury rarely, if ever, is due to the destruction of specific memory traces. Rather the amnesias represent...a greater difficulty in activating the organised pattern of traces, or a disturbance of some broader system of organised functions' (Lashley 1950, p. 472). Lashley did not, in fact, cite the evidence to support this characteristically iconoclastic view, but the comment – vague as it is – was even more percipient than many appreciated at the time.

Therefore, the impact was dramatic in the 1950s when reports appeared of patients who had been made amnesic abruptly and severely by surgery of the medial temporal lobe, as occurred in cases operated upon independently by Penfield and Scoville (Penfield & Milner 1958; Scoville & Milner 1957). Brenda Milner provided a graphic and clear account of the best-known of these patients, H.M., who is still alive and still amnesic (Milner 1959). Those interested in the neurology of memory were provided with a strong reminder that highly specific and circumscribed pathology can have a devastating and global effect on memory. Moreover, these reports emerged just when experimental psychologists were intent on discovering distinctions (also of old vintage, going back at least to William James) between various stages of memory with different encoding properties and time constants. And so there began an intense and prodigious effort, still in progress, to examine all of the properties – electrophysiological, anatomical and neurochemical – of the temporal lobe, especially the hippocampus and its neighbours, and to relate these properties to behaviour. That is the task of neuropsychology.

The first discontinuity emerged at the very outset. There was, despite strenuous efforts, a difficulty in finding the amnesic syndrome in animals. Eventually, and only relatively recently, that difficulty has probably been overcome. But in parallel with that search, and partly as a result of it, the amnesic syndrome itself came under intense scrutiny. As a result, the apparent gap between humans and other mammals has been replaced by a dissociation in both humans and animals between different types of memory processes, some of them critically dependent on the hippocampal system and others independent of it. This dissociation is one for which traditional models of memory advanced by experimental psychologists are still ill developed and indeed the lack of concepts makes the very description difficult.

The clinical properties of the amnesic syndrome are so well known that we need not spend

much time on them. The patient apparently cannot retain any new memories of day-to-day events beyond a minute or so. He will repeatedly deny (or falsely affirm), for example, having seen his doctor or nurses and will show no recognition. Much of his memory for events before the onset of the pathological condition, going back years in time, will also be apparently badly damaged, although very old memories may be available, even if with somewhat patchy content. This severely disabling state is present even though other cognitive skills can be normal (provided they are tested in a way that does not put demands on the defective long-term memory). The capacity and properties of digit span and other measures of short-term memory can also be normal. Clinically one has the impression of a slate on which some of the older jottings can still be discerned, somewhat hazily, but which resolutely fails to accept new writing for more than a minute or so, as though the writing is with rapidly disappearing chalk. From the point of view of two-stage models of memory processing, which were becoming popular when H.M. came to light (see, for example, Waugh & Norman 1965), it was almost irresistable to conclude that there was a blockade of input to long-term memory from short-term memory, or a failure of storage ('consolidation') of long-term memory. This clinical description applies not only to surgical cases such as H.M. but in its salient and primary features to amnesic patients of various aetiologies, such as Korsakoff's Psychosis and herpes simplex encephalitis, although such patients may or may not differ in various other respects, especially as neuropsychological handicaps are often multiple and compounded in group studies of patients classified together.

Animal research

Those attempting to replicate the amnesic syndrome were in search of a tempting fruit: the location and identification of the anatomical and neurochemical basis of the input to and the consolidation of long-term memory. But, as we have indicated, they early met with disappointment. Even those primate studies modelled directly on Scoville's surgery of H.M. produced results that were different from those to be expected from the human clinical picture – for example, the study by Orbach *et al.* (1960) in which it was found that monkeys with H.M.'s type of lesion could readily learn a discrimination task with trials widely spaced apart and with the intervals filled with massed trials of irrelevant discriminations, a task that one would have supposed an amnesic human subject would find impossible. Nor did these investigators find more than a mild impairment of retention of post-operatively acquired tasks. Note especially that this negative result was obtained with discrimination learning, i.e. where the subject obtains his reward by approaching one stimulus and is not rewarded for approaching the other stimulus. The immunity that discrimination learning enjoys will be a recurring and important theme.

Since those early days animal work has advanced along three fronts. First, some investigators rapidly discovered that the hippocampus was critical for various tasks that at first glance seemed to have no relevance whatever for elucidating the amnesic syndrome, but nevertheless were interesting in their own right. For example, it was commonly found that hippocampal lesions caused much slower extinction for food-rewarded tasks (Kimble & Kimble 1970) and that animals tended to perseverate with the previously positive stimulus after being required to reverse the discrimination and to approach the previously negative stimulus. Various other reports emerged, such as hyper-reactivity to novel stimuli, changes in activity levels, a

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

diminished ability to withhold responses when reward was directly contingent upon doing so, as well as changes in emotional behaviour (See *Functions of the septo-hippocampal system* (1978)).

The second front advanced along anatomical grounds. Doubts were raised as to whether a hippocampal lesion was either necessary or sufficient for producing mnemonic changes in behaviour. Horel (1978), for example, drew attention to the inclusion in Scoville's surgery of tissue lying in the stem of the temporal lobe and suggested on the basis of its anatomical connections that it, and not the hippocampus, was the important structure. Mishkin (1978) speculated that the stress on the hippocampus alone neglected the fact that the amygdala had also been included in the original Scoville surgery. He found dramatically enhanced impairments in a recognition task with combined hippocampal-amygdala lesions, much greater than either alone. I shall deal further with that task in a moment.

The third front for animal research was a refinement, but more especially a considerable enrichment and broadening of the animal behaviour tasks stimulated by theoretical speculation about the nature of the amnesia or the functions of the intact hippocampal system, and also by new findings with human amnesic patients. As a result, animals have been shown to possess some impressive cognitive capacities that are also sensitive in various forms to hippocampal lesions. One of these developments came from Olton *et al.* (1979), perhaps stimulated by O'Keefe & Nadel's (1978) catalytic speculations about the hippocampus's being involved in the construction of spatial maps. Olton discovered that normal laboratory rats could remember with remarkable accuracy which particular arms of a twelve-arm radial maze they had visited and which they had not. Rats with hippocampal lesions are severely impaired in such a task. Another development came from Gaffan (1974), who suggested that the amnesic syndrome was a specific impairment of recognition memory and not of memory for associations between stimuli and rewards. He exposed monkeys to 'lists' of up to ten objects in a row, and then tested their ability to respond differentially to objects they had seen before and those they had not. Monkeys with the fornix sectioned (this is the main efferent tract leaving the hippocampus) were impaired on that task, but not on a difficult reward-association task, matched in difficulty with the recognition task. It was this kind of recognition task, also, that Mishkin found was so severely disrupted by combined hippocampal-amygdala lesions. These are just some of the elaborations and enrichments that have taken place on the behavioural front with animals. Others had to do, for example, with the study of contextual cues and with interference factors in memory, based directly on comparable memory studies with human amnesic subjects. Suffice it to say that very substantial and replicable deficits could at last be found that seemed to have a direct bearing, either theoretically or by face validity, on the amnesic syndrome in humans.

Human research

I shall turn now to developments in the study of the human amnesic syndrome that were taking place simultaneously. Because it gradually emerged that human amnesic patients were surprisingly good at learning and retaining a variety of tasks, a number of studies whittled away at the syndrome to define its limits and to try to characterize it. As a result, it became apparent that a theoretical interpretation in terms of a failure of transfer from short-term to long-term memory was not so much wrong as simply irrelevant and impotent. And

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

so, paradoxically, while the animal workers were finally congratulating themselves on their success in evolving methods to reveal amnesia in animals, at the human level research was revealing that their amnesic subjects were not necessarily amnesic with certain long-term memory tasks, even when the subjects themselves appeared clinically not to appreciate their own success in learning those tasks.

Quite early it was found that H.M. was able to learn new motor skills, such as mirror drawing, and retain the skills from day to day, although he on each occasion denied having done the task (Milner 1962; Corkin 1968). Milner considered, as a result, that motor learning might not be dependent on the integrity of the hippocampal system. But later Warrington & Weiskrantz (1968, 1970) were able to demonstrate that retention even of verbal learning was possible if the amnesic subjects were given particular partial cues that matched the items to which they had previously been exposed. We showed that this was a genuine learning phenomenon, and remarkably amnesic subjects showed good retention over days. That is, they were able to *identify* a previously exposed word or picture when given a partial cue. But they still failed to recognize having seen the word or picture just recently. H.M. was similarly found to have the same capacity and indeed was found to have positive savings for pictures over 1 h and also 4 months with this type of method (Milner 1970, Milner *et al.* 1968). Sidman *et al.* (1968) showed that amnesic subjects could learn and retain visual discriminations, just as the monkeys could (cf. also Gaffan 1972). H.M. was also able to learn and retain a simple visual maze (Milner *et al.* 1968). Warrington and I also demonstrated that classical conditioning was acquired by patients and retained over at least 24 h (Weiskrantz & Warrington 1979). We also showed that they could demonstrate their having been previously exposed to 'anomalous' pictures, these being by one definition 'novel' experiences (Warrington & Weiskrantz 1973). Baddeley & Brooks (personal communication) confirmed that finding. Winocur & Weiskrantz (1976) showed that amnesic patients could readily learn verbal paired associates if they were consistently bounded by a semantic or a phonetic rule. Brooks & Baddeley showed that patients retained the specific facilitation for solving a simple maze, for solving particular jigsaw puzzles (1976), and for arranging jumbled words into sentences (personal communication). Another facilitation effect, the stereoscopic perception of random dot stereograms, was also shown by Ramachandran (personal communication) to be retained by patients, and Warrington and I found that the McCulloch colour-grating illusion was retained over a 24 h interval (unpublished observation). There are no doubt other examples, but it is now abundantly clear that a considerable variety of tasks requiring learning and memory over long time intervals are within the capabilities of amnesic subjects.

I referred earlier to three fronts along which animal research was progressing more or less simultaneously with the human developments. How do they relate to the results of human research? Let us consider, first of all, the superficially irrelevant aspects of the hippocampal deficit. The perservation of prior learned responses, as in discrimination reversal learning with animals, can readily be demonstrated in amnesic patients by deliberately designing a task so that the same set of verbal partial cues matches the first set of items to be learned and then afterwards matches a second set of different items to be learned (Warrington & Weiskrantz 1974, 1978). The patients learned the first set just as well as controls, but when the cues were switched to match the second set they persisted in giving the first-learned items to each cue for far longer than did the controls, thereby severely impeding their learning of the second set. A special feature of this experiment was that each partial cue (the initial three

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

letters of a word) was so chosen that it matched *only* the two items in question. This meant that any error of commission in the second set had, by definition, to be a false positive intrusion from the first set, i.e. direct evidence could be adduced that the first task persisted and interfered with the learning of the second task. A closely related demonstration with rule-constrained paired associate learning was produced by Winocur & Weiskrantz (1976). In this task, the rule was kept constant from the first set of paired-associates to the second set, and the same first item of each pair was kept constant, i.e. the subjects had to switch from one paired-associate to another given the same cue. The perseverative effect is a powerful one, and so the difficulty seen in hippocampectomized animals may be far from irrelevant to human patients. Undue perseveration can interfere with new learning, and both animals and humans with hippocampal damage appear to suffer unduly from such interference. These types of results led Warrington and me to put forward an explicit interference theory of the amnesic syndrome (Warrington & Weiskrantz 1973; Weiskrantz & Warrington 1975). We have since been led to reject this view, for reasons that will become clear.

On the anatomical front, work on animals to find the minimal critical pathology will no doubt continue, but recently the brains of two of our amnesic subjects (Korsakoff cases) became available for post-mortem examination. These subjects had been studied intensively over a number of years, and we were satisfied that they had been severely amnesic without other cognitive deficits until shortly before their deaths. As I said earlier, there is already a considerable literature on the neuropathology of amnesic patients, but we believe that these are the first subjects in whom the details of the neuropathology and especially the documented quantitative neuropsychological details can be placed side by side. In all hemispheres we found two clearly defined and delimited zones of pathology: one in the medial nucleus of the mammillary body and the other along the medial wall of the thalamus, in the subependymal zone (Mair *et al.* 1979). There has long been debate as to whether the critical lesion in Korsakoff's Psychosis is in the mammillary body (which is the major target of the fornical output from the hippocampus) or in the medial thalamus (although *not* in the same medial nucleus that we found to be affected). Perhaps both lesions are necessary for the dense amnesic state. Interestingly, in connection with Mishkin's findings, the subependymal region of the thalamus appears to send a direct projection to the amygdala in the monkey (Aggleton *et al.* 1980), and may therefore also receive a reciprocal projection. There is now in progress a renewed and refined examination of mammillary body and medial thalamic lesions on memory in the monkey.

Earlier hypotheses

Finally comes the most difficult question of all: is there any formal correspondence between both the impaired and the unimpaired aspects of memory found in humans and other mammals? There is, I believe, an impressive convergence to be found. What we lack, it emerges, are the terms with which to describe them and the conceptual frame within which to place them. Let us consider the constellation of findings in terms of various hypotheses that have been advanced at either the animal or the human level in recent years, based on conventional concepts. All of the hypotheses are in difficulty. Interference effects are undoubtedly important but we ourselves provided the evidence that led us to reject the hypothesis of interference as a causal factor in the amnesic syndrome because the interference

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

effects do not appear at just the point where they should be maximal, but only later (Warrington & Weiskrantz 1978). Spatial memory (which in any event is usually more closely associated with lesions in the human brain elsewhere than the hippocampal system (De Renzi *et al.* 1977)), is not an adequate characterization because both in humans and in animals there are non-spatial deficits, as for example in Gaffan's (1974) and Mishkin's (1978) recognition studies, among others. Also, Olton (1978) has shown ingeniously that the hippocampal lesioned rats do not have any difficulty in remembering the *places* where they have never been consistently rewarded; instead, their difficulty lies in continuing return to *previously* rewarded places. Therefore, memory for place as such is not the crucial factor.

The claim that only recognition memory is impaired, leaving associative memory intact, will not suffice; Gaffan (1982) has tested his theory and it will not work. The evidence for this is that fornix-sectioned monkeys are impaired in remembering items with a Win–Shift/Lose–Stay rule, although they are normal with a Win–Stay/Lose–Shift rule: both of these rule-determined tasks are based equally on stimulus-reward association. When Spiegler & Mishkin (1979) studied combined hippocampal–amygdala lesions, they found that monkeys also had a marked deficit on learning lists of two objects in a reward-association task, and hippocampal lesions alone produced a mild effect (cf. also Mishkin *et al.* 1982). Theories based on faulty cognitive coding at input (see, for example, Butters & Cermak 1974) have been challenged by various studies showing normal cognitive processing (Warrington & Weiskrantz 1971; Meudell *et al.* 1981). One valuable suggestion by Olton *et al.* (1979) in terms of a deficit of 'working memory', leaving 'reference memory' intact, is also insufficient given the definition of working memory they have adopted, namely, 'when stimulus information is useful for one trial of an experiment, but not for subsequent trials.' For example, the comparison between recognition and Win–Stay/Lose–Shift reward association memory in animal studies involves just a single trial exposure of each stimulus, but for one task there is an impairment and for the other one, matched in difficulty, there is none. Similarly in human subjects, whether the response is relevant for just one trial or for more is not consistently correlated with the deficit. And there are deficits on multi-trial tasks, as in complex maze learning. Nor will a distinction suffice, therefore, between incremental and all-or-none one-trial learning. Nor is it clear that the distinction between episodic and semantic memory is apposite in supporting a claim (Kinsbourne & Wood 1975) that human amnesic subjects are deficient specifically in episodic (i.e. event) memory but not in semantic memory. All examples of learning of verbal paired associates would appear to qualify as episodic learning, but amnesic subjects cannot be differentiated from controls with some forms of paired associate learning. Nor can one see why the retention that amnesic patients display of the facilitation of anomalous pictures, jigsaw puzzles, or unscrambling random words into sentences are not examples of episodic memory.

In fact the great variety of tasks that amnesic subjects can learn and retain makes it extremely difficult, if not impossible, to characterize them as constituting a particular *kind* of material-specific learning, such as verbal, visual, perceptual or motor. Any claim that the amnesic syndrome is simply an exaggerated difficulty with those memory tasks that normal subjects find especially difficult cannot be sustained. Gaffan has shown unimpaired memory in his fornix-sectioned monkeys with especially trying and difficult lists of reward-association tasks in which the animals were pressed to the limits of their ability to remember (Gaffan 1982). Mishkin *et al.* (1982) have demonstrated that monkeys with the combined hippocampal-

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

amygdala lesions, who are so markedly impaired on relatively simple recognition tasks, can learn at a normal rate a difficult series of ten visual reward-association discriminations concurrently when exposed to just *one* trial per day on each of the ten discriminations, a most impressive achievement by these monkeys on a very demanding task, demonstrating incidentally retention for a single exposure over 24 h. Proof that difficulty is not the key comes from the fact that a double dissociation can be demonstrated in comparing these reward-association tasks with tasks that are sensitive to hippocampal damage. Visual discrimination learning has long been known to be affected by temporal neocortical lesions, which can leave performance on a recognition task untouched – the same recognition task that *is* affected by a fornix section (Gaffan & Weiskrantz 1980). And Warrington & Weiskrantz (1978) found that amnesic subjects were quite as good as normal subjects in cued recell, such that there was significant interaction between method of testing memory and subject groups. The methodological difficulties inherent in trying to simulate the amnesic state by concocting special conditions of testing, such as the use of long retention intervals for controls against short intervals for amnesic subjects, have been reviewed by Schachter & Tulving (1982). But even if simulation is technically achieved, it does not provide an unequivocal explanation or model (cf. Weiskrantz 1968). Finally, while there may still be some who cling tenaciously to an interpretation in terms of faulty consolidation, it is difficult to see how such an explanation can be usefully applied to such a variety of tasks retained normally by amnesic subjects over long intervals, or to the devastating impairment that can be seen for memory for old events, i.e. the retrograde amnesic aspects of the impairment that affect memory for events that occurred several years before the onset of the amnesic state.

Attempts at convergence

It would appear that a fresh approach is required if one is to achieve a convergence and a characterization. If we examine all the tasks that the human densely amnesic subject *can* learn, they do have one property in common. In none of them is it necessary to ask the patient 'tell me what you remember' or 'do you remember this?' to reveal his memory capacity objectively. In all cases a cue or a signal is given and the response is produced. Not only is it unnecessary to ask the patient whether or not he remembers, or what he remembers, but if you do ask him such a question he *then* convincingly reveals his amnesia in his answer to the question! But while the use of tasks that do not require 'commentary' type questions may be necessary, it is not sufficient. The amnesic subject will also fail even with certain cued-recall tasks, as was seen with reversal experiments, and of course he can learn some paired-associate tasks but not others when the only requirement is that the first item of the pair elicits the second. There is a more subtle aspect of the tasks on which the patient can succeed: the cue or signal must be unambiguously linked to the answer to be retrieved from storage so that with a degree of practice the answer is produced more or less automatically by the cue, i.e. it is produced acognitively. To be certain about some memories, it is sometimes necessary to match, to order, to reflect. These are the sorts of tasks that patients find difficult.

Remaining still at the level of the human deficit, Warrington and I have put forward a view for which time now does not permit more than a brief account but which will appear more fully elsewhere (Warrington & Weiskrantz 1982). Briefly, we suggest that the amnesic

syndrome is a disconnection syndrome in which a semantic memory system is detached from a cognitive mediational system. The semantic memory system has the capacity for long-term facilitation of stored items within it by mere repetition. Simple stimulus–response associations can also be incremented without the cognitive system. In concrete anatomical terms, we consider that the disconnection is brought about by interruption of the pathways from the temporal neocortex to the frontal lobes, via the subiculum–hippocampus–fornix–mammillary-body–anterior thalamus pathway and also via an amygdala–medial-thalamus pathway. We draw on the contrast between the memory deficit in the amnesic syndrome discussed here and the quite different and dissociable disorders of memory that are seen in the agnosias and related disorders of semantic memory, found with temporal lobe cortical lesions. We also draw on some of the similarities between the amnesic syndrome and memory disorders associated with frontal lobe pathology. When the two systems are disconnected, while semantic facilitation can still occur and automatic associations can be acquired, learning based on reordering or other cognitive manipulations of stored items in semantic memory is faulty. The amnesic subject is impaired not in his ability to engage in cognitive mediation as such, but in those memory tasks in which the stored benefits of mediation are normally important. Where such mediation is unnecessary, conversely he is unimpaired.

We tried to examine this approach experimentally by looking at tasks in which the degree of cognitive mediation could be varied. There is, for example, one rather direct method with the use of paired-associates (in a way, in fact, that is embedded in extreme form in Wechsler's memory battery). The 'distance' between verbal associates can be defined in terms of the prior likelihood of the first item producing the second, and likelihood tables are available. 'Distant' paired associates, which in most extreme form are random paired-associates, which all workers acknowledge are impossible for amnesic subjects to learn, require more cognitive mediation for a relatively new link to be formed. Amnesic subjects are disproportionately disabled by even a relatively slight increase in 'distance' in their learning of paired associates, so slight that control subjects are unaffected by the increase. The assumption is that the more distant the items in each pair, the more mediation any subject must bring to them to link them together in memory. One very effective method of mediating by normal subjects is to use imagery, which the experimenter can supply very explicitly for the subject's use. In an earlier study, Baddeley & Warrington (1973) found that normal subjects, as expected, were greatly helped in their learning of paired associates by this procedure. Amnesic subjects were not helped; even an explicit mediating link was ineffective (cf. also Jones 1974). Warrington & Weiskrantz (1982) have recently also examined other types of constrained paired-associate learning in human amnesic subjects and have found qualitative differences between them and controls that seem consistent with the hypothesis. Further predictions of the disconnection model also follow.

Can one vary 'cognitive distance' in animals? As it happens, Elizabeth Gaffan and E. A. Gowling have pursued such an approach in rats (reported in Gaffan 1982). They used four interchangeable maze segments that could be joined together in any order to make a T-maze. The rats were first trained to choose between two of the arms visually, as in a conventional T-maze non-spatial visual discrimination task. In this arrangement, in keeping with the literature, the hippocampal rats were no different from controls in their learning rate. Next, all animals were trained to choose between the two other arms, but these led not directly to food reward but to one or other of the original two arms, which then led to

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

reward as in the original experiment. This resulted in an impairment in the hippocampal group relative to controls. That is, when the choice led not directly to the goal but rather was presumably based on a mediation between the two sets of arms in the second part of the experiment, the experimental animals were in difficulty. Although many control experiments remain to be done, this may be a reasonable analogy to 'close' as against 'distant' paired associate learning, and seems a promising line to pursue further and to develop.

A similar contrast between disorders of semantic memory and those of the amnesic syndrome can also be drawn in animals. As we have mentioned, discrimination learning, by which an animal attaches semantic meaning of reward values to an object, is severely impaired by temporal neocortical damage and, as we have seen, not by hippocampal damage; this stands in contrast to the kinds of memory deficit that are seen with hippocampal or frontal lesions.

Not only can one see some hope of convergence between animal and human studies, but it is quite evident that a number of workers at both levels recently have been developing concepts that all have a close family resemblance to this type of approach. Thus, Baddeley (1982) refers to a deficit in 'evaluative memory' in the amnesic syndrome, Cutting (1978) to a deficit in the use of 'active cognitive strategies', and Wickelgren (1979) to the importance of 'chunking'. The characterization by Olton *et al.* (1979) of the animal deficit in terms of working memory clearly embodies a similar concept, and Mandler (1980) also discusses our cued recall results in terms that are very similar to our own appeal to facilitation in semantic memory. Jeffrey Gray (1982), approaching the behavioural analysis from quite a different starting point, in terms of behavioural inhibition and emotional behaviour, also suggests that the hippocampal system is involved critically when a comparator function is involved between new inputs and stored models. Whether or not our speculation of a disconnection and its proposed anatomical basis holds up, there appears to be a convergence of explanatory approaches from a number of workers in this field, in itself a rare historical occurrence.

Whenever one event can be predicted reliably from another, there is redundancy and hence the possibility of automaticity. It is a waste of precious cerebral processing capacity to repeat on each occasion all the mediating activity that allows, in Miller's (1956) terms, bits to be formed into chunks. Both amnesic humans and animals can learn and remember events that are reliably predictable. Inconsistency from occasion to occasion, as in a recognition situation with repeated stimuli, or reversal, or memory for arms visited today in a radial maze, in contrast to those visited yesterday, is apt to require reflection, matching, ordering and reordering. It is then that what we have termed the cognitive mediating system comes into play; without it one is left with previously acquired 'chunks' of semantic knowledge, which can be incremented through more repetition and which can be added to if new chunks are readily formed, as in discrimination learning or classical conditioning. In the absence of the benefits of mediation, previously activated or otherwise strong automatic programmes are apt to continue, i.e. to perseverate. Beyond that, without mediation the very experience phenomenally of having a memory may be lost, and with it the capacity to comment on it. We do not have the experience of 'remembering' each time we use a word, which is after all an item acquired through learning, nor when we stop at a traffic light. We stop without reflection about how the signal acquired its meaning, or if we reflect we are apt not to stop! The amnesic subject also stops as we do and even learns new signals. He too does not have an experience of remembering, and on that level in many other areas of our everyday life we are at one with him.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

It is from that level, however, that apparently he has no escape. He is precluded from having those commentaries about past experience that we actually acknowledge as memories. This detachment from his own recent learning is one of the most striking aspects of the syndrome, and was commented upon even by Korsakoff who noted that one of his patients showed apprehension in front of the electrical 'faradization' apparatus after it had been used to treat his polyneuritis. He continued to say he had never seen the apparatus and did not know what it was used for (cited by Delay & Brion 1969, p. 17). This type of observation runs through the literature as a consistent thread (cf. Sidman *et al.* 1968; Milner 1970).

Weiskrantz & Warrington (1979) established eyelid conditioning in two patients, using mild puffs of air to the eyelid as the unconditioned stimulus, with sounds and lights as the conditioned stimuli. Conditioning was established relatively easily and was well retained over 24 h. In frequent rest periods the patients were questioned while they were still sitting directly in front of the apparatus. Never was there any acknowledgement of the hundreds of conditioned stimuli and air puffs, but the moment the experimental procedure resumed the conditioned responses appeared at once and reliably. One patient did comment, when pressed hard, that 'he had a weak right eye because someone had once puffed some air into it.'

Classical conditioning can occur entirely at a subcortical level in the absence of cerebral cortex in mammals, provided that the conditioned stimuli themselves are not so highly patterned as to require cortical processing. And so it may not be surprising that the capacity for classical conditioning occurred in patients. It would be untouched by the postulated disconnection between temporal and frontal lobes. But the properties of even relatively simple classical conditioning can be modified by cognitive factors, as was long ago shown by Spence (1966). He was puzzled why human subjects extinguished quite quickly, while animals (monkeys and dogs) extinguished slowly after having had eyelid conditioning. He tried to minimize cognitive influences in an experimental group of human subjects by keeping them in ignorance of the purpose of the experiment: they were told that they were to guess the position of signal lights (actually the conditioned stimuli) on each trial, in the presence of 'distracting stimuli' (air puffs and tones). These uninformed human subjects extinguished slowly, like the animal subjects, in contrast to the control subjects who extinguished quickly, as usual. If amnesic subjects similarly are detached from cognitive mediation even in simple conditioning, as is suggested by their being unable to produce an adequate commentary of their learned experiences, this would imply a disconnection not only between temporal lobe and frontal lobes, but also between those subcortical structures on which conditioning can be based and the frontal lobes. The mammillary bodies receive not only an input from the temporal lobe via the hippocampus and fornix, but also a strong mesencephalic input. A lesion in the mammillary bodies would thereby disconnect both temporal lobe and subcortical activity from frontal lobe reception and influence.

Lashley, therefore, may well have been right about memory mechanisms being diffusely distributed throughout the brain, but wrong in that they are not all the same memory mechanisms. Simple associative conditioning can occur at various levels, and linguistic and semantic processing at quite another. But for any of the outputs of any of the mechanisms to be used for comparing, ordering and reordering, by hypothesis they all require access to mediating mechanisms via those highly selective pathways in which pathology is found in amnesic patients. Because of the anatomical connections of those pathways, as well as other neuropsychological evidence, we postulate that these mediating mechanisms depend upon access

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

to the frontal lobes in the mammalian brain. When the connecting pathways are severed, the disconnected semantic and S-R systems can still allow various forms of learning to be exhibited, both by humans and other animals, but not those that depend on cognitive mediation. Whether these specific speculations are fruitful and predictions are borne out, time will tell. But if the puzzling gap between humans and animals is at last closing, the new discontinuity within humans and animals alike is even more challenging, and it both requires and suggests a new set of concepts of memory processing.

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PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES