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EDITORIAL

Amnesia: lesion location and functional deficit – what is the link?[1]

In its pure form organic amnesia is a condition in which intelligence and immediate memory are preserved despite the presence of two, often severe, memory disturbances. The first of these is anterograde amnesia in which recall and recognition of facts and events that are experienced post-morbidly is impaired, and the second is retrograde amnesia in which recall and recognition of facts and events that were experienced up to decades before the onset of brain damage is disrupted. Patients are not impaired at all forms of memory. In addition to preserved immediate memory they show preservation of simple classical conditioning, various forms of skill learning, other kinds of perceptual learning and adaptation, and, perhaps of most theoretical interest, certain kinds of priming (see Shimamura, 1989 for a review). Priming is a form of indirect, item-specific memory indicated by a change in the way a recently perceived item is processed. There is good evidence that amnesics show preserved priming for items like words for which they already have long-lasting memory representations (see Mayes, 1988 for a review). For example, in an unpublished study, we have recently found that amnesics perceive briefly presented words that have been previously seen as being shown for longer than other words, presented equally briefly, that have not been shown previously. This effect is as large in patients as their matched controls, although patients generally fail to recognize the words as being those that they have already seen. There is also some evidence that amnesics can show preserved priming for items that must have been novel prior to the priming experience, but this is controversial and more research will be necessary before this possibility can be firmly substantiated (Mayes, 1988).

Although amnesics are not impaired at some kinds of memory, there is evidence that they are even more impaired at certain other kinds of memory than they are at recognizing target information to which they paid attention during the learning experience. Thus, Hirst and his colleagues (1986, 1988) have found that amnesics are more impaired at free recall of targets than they are at target recognition. We have found similar results when the target material was a word list or a set of objects and have also found preliminary evidence that amnesics are disproportionately impaired at memory for context. Context may be defined as that which typically lies on the periphery of attention during learning, and which either affects the meaningful interpretation of the target (interactive context) or does not (independent context, which includes spatiotemporal information and information about mode of target presentation). Our evidence suggests that amnesics are more impaired at memory for both kinds of context than they are at target recognition memory, but we still need to exclude the possibility that subtle artefacts are operating. If confirmed, however, there would be reason to suppose that amnesics show preservation of some kinds of memory, impairment of another, and disproportionate impairment of several other kinds.

The amnesic pattern of cognitive and memory performance can be caused by independent lesions to separate brain regions – the medial temporal lobes, the midline diencephalon, and the cholinergic basal forebrain. Bachevalier & Mishkin (1986) have argued, on the basis of a monkey model of amnesia, that the syndrome can also be caused by lesions of the ventromedial frontal cortex, but evidence from human cases does not seem to support this possibility. There is still some uncertainty about where damage has to occur within the three regions that have been associated with human amnesia. It cannot be assumed, however, that because amnesia can be caused by lesions to any one of three independent brain sites that three different forms of the syndrome exist, with each one being

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caused by a distinct kind of processing deficit. This is because there are structures within the three regions that are interlinked, often reciprocally. But it remains unclear whether these structures are implicated in amnesia. Human patients with selective amnesias are rare and there are very few such patients who have been adequately described neuropsychologically on whom good post-mortem analyses have been performed. It is, of course, now possible to assess the extent and location of brain damage in life with CT and MRI and this has now been done in a number of studies although such studies cannot achieve the fine-grain analysis possible with post-mortems. If CT or MRI are used in conjunction with positron emission tomography (PET) or single positron emission tomography (SPET), however, it becomes possible, in principle, to determine which, if any, anatomically intact structures are showing abnormal activity in pure amnesics. For example, in a preliminary study, Hunter *et al.* (1989) found reduced blood flow in the frontal cortex that correlated with degree of impairment on memory tests in Korsakoff amnesics. These patients are, however, known to have frontal lobe as well as midline diencephalic lesions, and so this reduced activity may not have been secondary to damage elsewhere in the brain. In future, it will be interesting to see whether intact structures in patients fail to show normal activation during and after encoding and during retrieval.

The search for the location of the critical lesions that cause amnesia using evidence from human cases has been supplemented in recent years by the use of a monkey model in which the performance of lesioned animals is assessed particularly on an analogue of a recognition task. Two views about the structures involved in amnesia have emerged from research using the monkey model and both views have received some corroboration from the human evidence.

The first view is that of Mishkin and his colleagues (see Mishkin, 1982) and states that severe, permanent amnesia only results when there is damage to both a hippocampal and an amygdalar circuit or the parts of the cholinergic basal forebrain that modulate both the hippocampal and amygdalar circuits. The hippocampus receives an input of processed sensory information mainly indirectly via the entorhinal cortex from polysensory association cortices (most notably the perirhinal and parahippocampal cortex) and, in turn, not only projects back to the cortical regions from which it receives an input, but also projects directly via the fornix to the anterior thalamus and indirectly to the same structure via the forniceal projection to the mammillary bodies. The anterior thalamus projects to the cingulate cortex, which projects via the entorhinal cortex back to the hippocampus. Like the hippocampus, the amygdala receives projections from several cortical regions that include the orbitofrontal, insular and anterior temporal cortices and itself projects both directly and indirectly to the dorsomedial nucleus of the thalamus and other midline thalamic nuclei. The dorsomedial thalamus projects to the orbitofrontal cortex, which completes the circuit back to the amygdala. Finally, hippocampal activity is modulated by input from the septum and diagonal band of Broca whereas the amygdala as well as the cortex receives modulation from the basal nucleus of Meynert (see Amaral, 1987 for a review of the anatomy of amnesia). On Mishkin's view, damage to any part of the hippocampal or amygdalar circuit, or to the selective modulating system in the basal forebrain, will cause a mild amnesia whereas a severe amnesia will result if both circuits are damaged or made dysfunctional.

The second view has been less fully articulated and derives from recent work by Zola-Morgan and his colleagues, which is critical of Mishkin's hypothesis (Zola-Morgan *et al.* 1989*a*, *b*). These workers have found that lesions confined to the amygdala without damage to the underlying polysensory association cortex neither cause mild amnesia nor exacerbate the amnesia caused by hippocampal lesions. In contrast, they found that lesions of the perirhinal and parahippocampal cortices cause a more severe amnesia than lesions of the hippocampus alone. One interpretation of these findings is that selective hippocampal lesions cause a mild amnesia partly because they disrupt a hippocampal–entorhinal cortex-polysensory association cortex loop. As two-thirds of the cortical input to the hippocampus comes from the perirhinal and parahippocampal cortices a lesion to these structures would be expected to cause an amnesia because it would largely disconnect the hippocampus from its cortical input. Damage to other polysensory association cortices would make the disconnection greater and so lesions to them should worsen the amnesia although this remains

to be shown. Lesions to perirhinal and parahippocampal cortices cause a more severe amnesia than hippocampal lesions alone because these cortices may also project to midline diencephalic structures that operate relatively independently of the hippocampus. Damage to these diencephalic structures may cause a mild amnesia which will become severe if there is also damage to diencephalic structures in the hippocampal circuit. Damage to the basal forebrain can cause a relatively severe amnesia because this structure projects to both the hippocampus and the midline diencephalic region involved in amnesia which operates relatively independently of the hippocampus.

The second view is better supported by the human evidence about medial temporal lobe amnesia. It is known that a selective bilateral lesion of the CA1 field of the hippocampus is sufficient to cause a mild amnesia. The mildly amnesic patient R.B. (see Zola-Morgan *et al.* 1986), who suffered an ischaemic episode, was shown at post-mortem to have suffered a lesion of this kind. In contrast, there is little evidence that selective bilateral amygdalar lesions cause even mild global amnesia in humans (see Markowitsch & Pritzel, 1985) whereas lesions that extend into temporal lobe polysensory cortex as occurs with patient H.M. (see Shimamura, 1989) and many patients with post-encephalitic amnesia suffer from a much more severe memory disruption. Tranel & Hyman (1990) have, however, described a patient who apparently had selective bilateral amygdalar damage. This patient had preserved verbal memory and impaired non-verbal memory, so amygdalar lesions may contribute to amnesia that is selective for non-verbal information. The evidence relating to amnesia caused by basal forebrain lesions is scantier, but Phillips *et al.* (1987) have reported a patient with severe amnesia in whom post-mortem analysis revealed damage to the septum and diagonal band of Broca which modulate the hippocampus, but not to the basal nucleus of Meynert which modulates the amygdala.

There are, nevertheless, problems with the position. Thus, Bachevalier *et al.* (1985) have reported that monkeys with combined fornix and amygdalofugal lesions show a severe recognition deficit, whereas, lesions to either pathway alone have minimal effects, which would mean that damage to the amygdalar circuit contributes to amnesia. It remains to be shown whether these lesions may also have disrupted pathways between perirhinal and parahippocampal cortices and midline diencephalon. Also consistent with the importance for amnesia of amygdalar circuit lesions, Aggleton & Mishkin (1983*a*, *b*) found that monkeys only showed severe amnesia if they were given dorsomedial thalamic as well as anterior thalamic lesions. Furthermore, Graf-Radford *et al.* (1990), in a study of four patients with bilateral diencephalic lesions, who were studied neuropsychologically for over a year and for whom lesion locations were identified using MRI, argued that patients develop amnesia following thalamic lesions only when there is conjoint damage to the mammillothalamic tract and the amygdalofugal pathway (or presumably to the nuclei to which these tracts project). Some conflicting evidence exists. Thus, in a CT study, Gentilini *et al.* (1987) have argued that amnesia results from mammillothalamic damage alone although Von Cramon *et al.*'s (1985) CT-based analysis reached conclusions consistent with those of Graf-Radford *et al.* Thalamic nuclei are often small and densely packed so the precise extent of lesions is hard to ascertain, so resolution of this issue will probably require post-mortem analysis of patients with very selective lesions.

Does our partial knowledge of amnesia's anatomy reveal anything about the functional deficit(s) that underlie the syndrome? It is currently disputed whether one or several independent processing deficits are associated with amnesia. Both Mishkin's view of the syndrome's anatomy and the view derived from the work of Zola-Morgan and his colleagues strongly suggest that at least two processing deficits are involved although these are of a different nature. From Mishkin's view one could postulate one process mediated by a hippocampal circuit and one by an amygdalar circuit. From the view derived from Zola-Morgan *et al.*'s work one could postulate one process mediated by a cortico–hippocampal–cortical loop, and another process mediated by a cortical–medial diencephalic–cortical loop. This latter interpretation denies any role to the hippocampal input into midline diencephalon, however, and may underplay the role of polysensory association cortices. There is, for example, evidence that hippocampal lesions only cause a mild retrograde amnesia in humans extending back at most a few years before the onset of brain damage (case R.B., see Zola-

Morgan *et al.* 1986) whereas, in medial temporal lobe amnesics with lesions that perhaps extend into the parahippocampal cortex and possibly other polysensory association cortices, retrograde amnesia can extend back for decades, perhaps because these are long-term storage regions (Squire *et al.* 1989). In humans, this possibility can now be investigated using MRI in living patients (Press *et al.* 1989). Interestingly, in monkeys, lesions that include only the hippocampus and part of the parahippocampal cortex have been reported to cause a retrograde amnesia that extends back only four weeks prior to the lesion (Zola-Morgan & Squire, 1990) whereas monkeys with more extensive parahippocampal and perirhinal cortex lesions, show a much more extensive retrograde amnesia (Salmon *et al.* 1987). Temporal association cortex lesions may therefore cause temporally extensive retrograde amnesia although it remains uncertain whether similar deficits are not also caused by selective midline diencephalic lesions.

Can knowledge of amnesia's anatomy guide our thinking about the nature of the processing deficits that cause the syndrome? Two rival views about the nature of one such deficit are currently influential. One view postulates a deficit in consolidation of all those types of information for which amnesics show impaired recall and recognition and the other view postulates that there is a consolidation impairment selective to contextual information and failure to retrieve this information causes a secondary, less severe deficit in recall and recognition of target information (Mayes, 1988). It is known that the main structures implicated in amnesia receive processed sensory information from the polysensory association cortices, process this information further, and then probably feed the product back to the cortical regions from which the information came and where the long-term memory may be stored eventually. Most is known about the hippocampus, a structure with a fairly well-understood microcircuitry and which displays a long-lasting form of plasticity. Neural network modelling of the hippocampus that pays attention to biological detail has already begun (Rolls, 1989) and future work will provide a powerful constraint on our thinking about the functional deficits that underlie amnesia. Such anatomically guided modelling will need to explain the pattern of preserved, impaired and disproportionately impaired memory shown by amnesics. Models like this will help resolve whether amnesics suffer from a consolidation deficit specific to contextual information, one that applies equally to all episodic and factual information, or from a different kind of deficit.

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