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COMMENTARY

Ischemic Brain Damage and Memory Impairment: A Commentary

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ABSTRACT: Studies in humans and monkeys have identified structures in the medial temporal lobe essential for memory (the hippocampal region, i.e., the dentate gyrus, the hippocampus, and the subicular complex, and the adjacent perirhinal, entorhinal, and parahippocampal cortices). Additional work has revealed that for both species, damage limited to the hippocampal region produces less severe memory impairment than damage that includes additional structures within the medial temporal lobe. This work has been based on both neurosurgical lesions and on lesions produced by global ischemia or anoxia. An important issue about ischemic damage is whether the damage identifiable in histopathological examination provides an accurate estimate of direct neural damage or whether additional direct damage might be present that is sufficient to disrupt neuronal function in areas important for memory and sufficient to impair behavioral performance, but not sufficient to progress to cell death and to be detectable in conventional histopathology. This commentary explores the issue of ischemic damage and memory impairment. Although few studies have addressed this issue directly, the currently available data from global ischemia in rats, monkeys, and humans are consistent with the hypothesis that the detectable neuronal damage is responsible for the severity of the observed behavioral impairment. Yet it is also true that this hypothesis has not been the target of very much systematic work. We encourage additional experimental work, especially in rats, that could further illuminate how to evaluate the behavioral effects of ischemic lesions. © 1996 Wiley-Liss, Inc.

KEY WORDS: ischemia, anoxia, covert damage, hippocampus, medial temporal lobe, human amnesia, nonhuman primates

INTRODUCTION

The study of memory impairment has a long tradition in neurology and neuropsychology (Ribot, 1881; Scoville and Milner, 1957; Talland, 1965). Once brain structures important for memory functions were identified, it became possible to consider in a systematic way how the severity of memory impairment varied as a function of the locus and extent of damage. Two developments were especially important for clarifying these relationships: 1) the development of an animal model of human amnesia in the monkey (Mishkin, 1982; Squire and Zola-Morgan, 1983), which led to the identification of structures in the medial temporal lobe important for memory (Squire and Zola-Morgan, 1991; Mishkin and Murray, 1994); and 2) cases of human amnesia in which extensive neuropsychological data have been related directly to detailed, postmortem neuropathological information (Mair et al., 1979; Zola-Morgan et al., 1986; Mayes et al., 1988; Rempel-Clower et al., 1996) or to high-resolution brain images (Squire et al., 1990; Corkin et al., 1996).

This work has shown that the structures in the medial temporal lobe essential for memory include the hippocampal region (i.e., the dentate gyrus, the hippocampus, and the subicular complex) and the adjacent perirhinal, entorhinal, and parahippocampal cortices (Fig. 1; for reviews, see Squire and Zola-Morgan, 1991; Murray, 1992; Zola-Morgan and Squire, 1993; Mishkin and Murray, 1994). For example, in monkeys a mild, albeit long-lasting memory impairment results from either ischemic lesions (ISC group; Zola-Morgan et al., 1992) or radiofrequency lesions (H group; Alvarez et al., 1995) of the hippocampal region (Fig. 2). More severe memory impairment results from lesions that include adjacent cortex as well as the hippocampal region (Fig. 2, the H^+ and H^{++} groups; Zola-Morgan et al. 1993).

Similar findings have been obtained in humans (Table 1). Amnesic patients with damage apparently limited to the hippocampus or hippocampal region (Zola-Morgan et al., 1986; Rempel-Clower et al., 1996, 1995) are impaired, but less impaired than patients with damage that includes adjacent cortex of the medial temporal lobe memory system (e.g., patient H.M.), (Scoville and Milner, 1957; Corkin et al., 1996). Thus, data from both monkeys and humans suggest that the hippocampus itself, together with the dentate gyrus and the subic-

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ular complex, are critical for memory function. Damage limited to this region is sufficient to cause significant memory impairment, and more extensive damage that includes adjacent cortex produces more severe impairment.

The findings in humans and monkeys have depended on two kinds of lesions, neurosurgical lesions (e.g., H.M. Scoville and Milner, 1957; and monkeys with H^+ or H^{++} lesions, Zola-Morgan et al., 1993); and lesions produced by global ischemia or anoxia[1] (e.g., patients R.B., Zola-Morgan et al., 1996, and patients L.M., G.D., and W.H., Rempel-Clower et al., 1996; and monkeys with ISC lesions, Zola-Morgan et al., 1992). The fact that two kinds of lesions have been used has raised the important issue of how neurosurgical lesions are to be compared with ischemic or anoxic lesions. In the case of neurosurgical lesions, one presumes that the direct damage caused by the lesion can be identified in histopathology. In the case of ischemic or anoxic lesions, there are two difficulties. First, the damage is virtually never limited to one brain region. For example, even though the hippocampus is the structure most sensitive to global ischemia and is the site of the most extensive cell loss, hippocampal damage is invariably accompanied by a loss of cerebellar Purkinje cells. Second, one cannot assume that all the direct neuronal damage caused by the lesion is detectable in histopathological examination. In other words, it is possible that ischemia or anoxia causes abnormalities that are sufficient to disrupt neuronal function in areas important for memory but not sufficient to progress to cell death and be detected in histopathology. This possibility is referred to here as the possibility of covert damage, i.e., any abnormality sufficient to impair behavioral performance but not detectable in neuropathological examination. It is an important issue because if covert damage commonly occurs, then the findings from monkeys and humans who have memory impairment in association with ischemic or anoxic damage cannot be interpreted with confidence. For example, ischemic or anoxic lesions apparently limited to the hippocampal region could not be taken as strong evidence that the hippocampal region itself is important for memory.

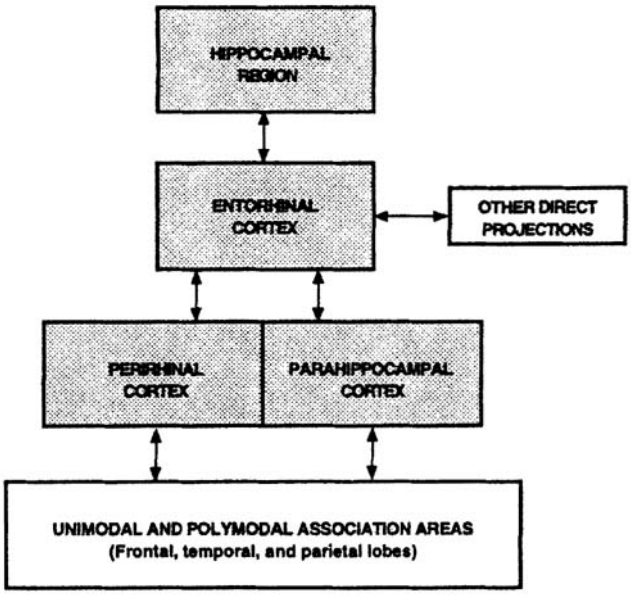

FIGURE 1. Schematic view of the medial temporal lobe memory system. The entorhinal cortex is a major source of projections to the hippocampal region (which includes the dentate gyrus, the cell fields of the hippocampus, and the subicular complex). Nearly two-thirds of the cortical input to the entorhinal cortex originates in the adjacent perirhinal and parahippocampal cortices, which in turn receive projections from unimodal and polymodal areas in frontal, temporal, and parietal lobes. The entorhinal cortex also receives other direct inputs from orbital frontal cortex, cingulate cortex, insular cortex, and superior temporal gyrus. All these projections are reciprocal.

The idea that covert damage might be an important issue was raised in the context of a study in monkeys that compared the effects of damage to the medial temporal lobe made by surgical lesions (similar to what was described above as the H^+ lesion) with the effects of damage produced by an ischemic procedure, i.e., bilateral permanent blockage of the posterior cerebral artery (PCA; Bachevalier and Mishkin, 1989). The damage identified in the PCA group was reported to be substantially less than the damage identified in the surgical group. Yet the PCA group was reported to have more severe memory impairment than the surgical group. One explanation offered for these results was that covert damage occurred in the PCA group, beyond what could be detected in the neurohistological analysis, and that this covert damage contributed to the memory deficit.

To consider this possibility, it is necessary to examine the study in more detail. Three monkeys sustained ischemic damage that appeared to be restricted bilaterally to portions of the hippocampal formation and parahippocampal gyrus. The behavioral performance of these three monkeys (PCA 4–6) was compared to the performance of five monkeys with surgical removals of the hippocampal formation and parahippocampal cortex (H1–5). Monkeys H1–5 consisted of two subgroups. Monkeys H1–3 were from a previous study (Mishkin, 1978), and monkeys H4 and

[1]Ischemia refers to a reduction in normal blood flow to a level that is insufficient to meet metabolic demands (Garcia and Conger, 1981; Nunn and Hodges, 1994). During an ischemic episode, oxygen delivery may fall below critical levels, producing an anoxic state. Anoxia refers to a reduction in the normal oxygen availability to tissues (Stys et al., 1992). The dramatic susceptibility of cell fields of the hippocampus, particularly the CA1 cell field, to both ischemia and anoxia is well established in work with humans (Brierley and Cooper, 1962; Siesjo, 1981; Plum, 1983; Zola-Morgan et al., 1986) and experimental animals including monkeys (Zola-Morgan et al., 1992) and rodents (Pulsinelli and Brierley, 1979; Volpe et al., 1992; Nunn et al., 1994). The neuropathology that occurs in the hippocampus following an ischemic or an anoxic episode can be quite similar (Brierley and Graham, 1984; Ng et al., 1989). Perhaps for this reason, the literature on clinical case studies typically refers to patients as having "hypoxic/ischemic" damage. Nevertheless, depending on the causes and duration of the ischemia or anoxia, the effect on the central nervous system can be different (Richardson et al., 1959; Seisjo, 1981; Auer et al., 1984). It is not within the scope of this commentary to consider the different neuropathological consequences of ischemia and anoxia.

H5 were prepared at the same time that the PCA monkeys were prepared. However, the two subgroups were not the same in their preoperative learning ability on the delayed nonmatching-to-sample task that served as the behavioral measure. Monkeys H1–3 required an average of 93 trials to learn the nonmatching task preoperatively, whereas monkeys H4 and H5 required more than twice as many trials on average (190 trials) to learn the task preoperatively ($P = .06$). Following surgery, monkeys H4 and H5 required numerically more trials (mean = 120) and errors (mean = 27) to relearn the nonmatching task than monkeys H1–3 (mean trials = 73, mean errors = 19). Finally, monkeys H1–3 obtained an average score of 90% on the postoperative performance test, and monkeys H4 and H5 obtained an average score of 85% ($P = .06$). Thus, there appears to have been a systematic difference between the two subgroups of monkeys, and including monkeys H1–3 from the earlier study served to increase the apparent difference between the H and PCA groups.

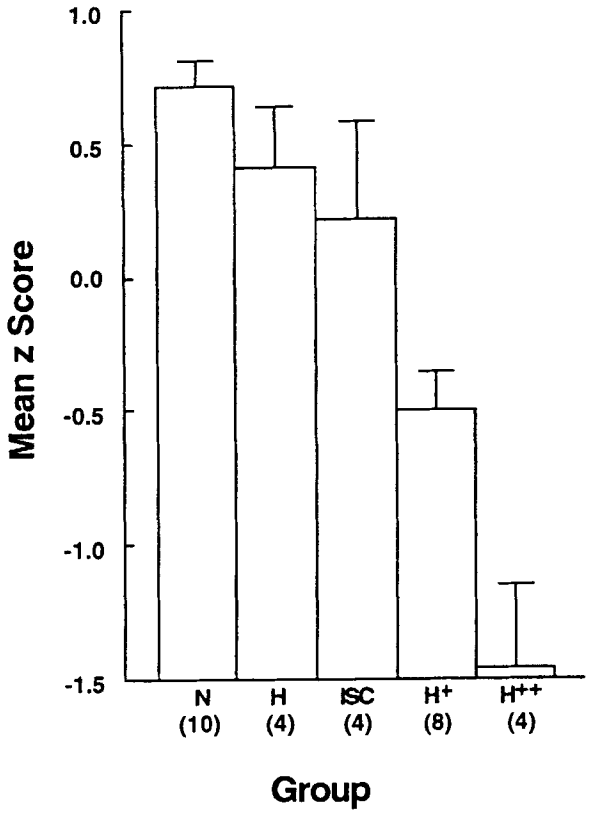

FIGURE 2. Mean z scores based on data from four measures of memory for ten normal monkeys (N), four monkeys with surgical damage limited to the hippocampal region (H: the dentate gyrus, the cell fields of the hippocampus, and the subicular complex), four monkeys with ischemic lesions of the hippocampal region (ISC), eight monkeys with damage that also included the adjacent entorhinal and parahippocampal cortices (H^+), and four monkeys in which the H^+ lesion was extended forward to include the anterior entorhinal cortex and the perirhinal cortex (H^{++}). Conversion of the data from the four behavioral measures into z scores permitted tasks that used different performance measures (e.g., trials to criterion, percent correct) to be compared with each other. The H and ISC groups performed similarly, and both performed better overall than the other operated groups. See footnote 2 for a comparison of the H and ISC groups on the four measures used in the z score analysis. Error bars indicate standard errors of the mean (adapted from Zola-Morgan et al., 1994).

A related, and more important point is that one of the three PCA monkeys (PCA4) was not trained preoperatively on the delayed nonmatching-to-sample task. Yet it is now clear that monkeys trained preoperatively on the nonmatching rule of the delayed nonmatching task perform better on postoperative delay tests than monkeys trained only postoperatively (Zola-Morgan and Squire, 1986; Ringo, 1988). Thus, including monkey PCA4 in the PCA group would have been expected to lower the average postoperative test score of this group and to disadvantage the PCA group relative to the H group. If monkey PCA4 is excluded from the data analysis, then the difference between monkeys H1–5 and the remaining two PCA monkeys does not reach statistical significance (average score for monkeys H1–5 across all delay and list conditions = 88%; average score for monkeys PCA5 and PCA6 = 80%; ($P = .07$). Moreover, if one excludes monkeys H1–3, who were from an earlier study and who performed better than monkeys H4 and H5, and if one instead compares only monkeys H4 and H5 with monkeys PCA5 and PCA6 (these are the animals that were tested concurrently and that had similar preoperative training scores), then the group scores are even more similar (PCA = 80%; H = 85%; $P > .10$).

Thus, when only monkeys with similar testing histories are compared, the results do not support the idea that it is the group with less visible damage (the PCA group) that had more severe memory impairment. The two lesion techniques appear to have produced approximately similar levels of impairment. This conclusion would agree with findings from rats. Partial lesions of the hippocampal region have been found to produce either less memory impairment or similar memory impairment, in comparison to larger lesions, but not more memory impairment than larger lesions (Davis and Volpe, 1990; Moser et al., 1993; Nunn and Hodges, 1994; Moser et al., 1995). In short, the study of PCA monkeys provides no basis for proposing that the PCA procedure produced covert damage that impaired memory performance.

A second study in monkeys attempted to address directly whether covert damage is an important issue in interpreting the effects of ischemic damage (Zola-Morgan et al., 1994). This study asked how monkeys with global ischemic lesions of the hippocampal region (produced by a noninvasive technique involving carotid occlusion and pharmacologically induced hypotension; Zola-Morgan et al., 1992) perform on memory tasks in comparison to four other experimental groups (an unoperated group, a group with surgical damage limited to the hippocampal region [H], a group with surgical damage to the hippocampal region plus underlying parahippocampal and entorhinal cortex [H^+], and a group with surgical damage to the hippocampal region plus underlying parahippocampal, entorhinal, and perirhinal cortex [H^{++}]). The ischemic group sustained detectable damage primarily in the CA1 and CA2 cell fields of the hippocampus and in the hilar region of the dentate gyrus. There was possible minor damage in the mammillary nuclei, mediodorsal nucleus, and ventral putamen, and there was patchy loss of cerebellar Purkinje cells. The behavioral result was that the ischemic group performed

TABLE 1.

*Memory Performance of Amnesic Patients With Medial Temporal Lobe Damage and Operated Monkeys With Medial Temporal Lobe Damage**

	Extent of damage from neurosurgery			Extent of damage from ischemia		
	H	H^+	H^{++}	H	H^+	H^{++}
Severity of memory impairment in amnesic patients			+++[a]	+[b]	++[c]	
Severity of memory impairment in operated monkeys	+[d]	++[e]	+++[f]	+[g]	++[h]	

*Three extents of damage are indicated (H = damage limited to the hippocampal region; H^+ = damage to the hippocampal region together with damage to entorhinal and/or parahippocampal cortices; H^{++} = the H^+ lesion extended forward to include perirhinal cortex). Three levels of severity of memory impairment are also indicated (+, ++, and +++; the larger number of + signs indicates increased severity of memory impairment). Note that the severity of impairment is meant to reflect overall memory ability, not the score on a particular test. For the filled cells in the table, the relationship between extent of damage and level of memory impairment appears similar for humans and monkeys. Moreover, the relationship between the extent of damage and severity of memory impairment appears similar following ischemic lesions and neurosurgical lesions.

[a]Patient H.M., Scoville and Milner (1957).

[b]Patients R.B. and G.D., Zola-Morgan et al. (1986). Rempel-Clower et al. (1996).

[c]Patient W.H., Rempel-Clower et al. (1996).

[d]Alvarez et al. (1995).

[e]Zola-Morgan et al. (1989).

[f]Zola-Morgan et al. (1993).

[g]Zola-Morgan et al. (1992).

[h]Bachevalier and Mishkin (1989).

similarly to the H group and significantly better than each of the other lesion groups (Fig. 2).[2] This result suggested that covert damage did not occur in the ischemic group to the extent necessary to impair memory beyond what would have been expected from the damage that could be detected histopathologically.

At this time, only these two studies are available in monkeys to address the issue of whether covert damage is rare or typical following ischemia and to what extent it might affect behavior. Yet this issue has become important with the increasing number of reports of well-studied human amnesic cases with damage limited largely to the hippocampal region (e.g., Zola-Morgan et al., 1986; Victor and Agamanolis, 1990; Rempel-Clower et al., 1996). Do these cases demonstrate that the hippocampal region itself is critical for normal memory function, or should one suppose that the amnesia in these cases might be due to the presence of covert damage in areas outside the hippocampal region?

Table 1 summarizes current information concerning how much memory impairment occurs in humans and monkeys following medial temporal lobe damage produced by ischemic or neurosurgical lesions. Table 1 makes several points. First, damage to the medial temporal lobe memory system in monkeys can produce different levels of memory impairment. Second, the severity of impairment corresponds to the locus and extent of damage to the components of the medial temporal lobe memory system, i.e., H, H^+, or H^{++}. Third, for amnesic patients the level of memory impairment also depends on the locus and extent of medial temporal lobe damage. For example, patient H.M. (Scoville and Milner, 1957), who sustained a large bilateral neurosurgical lesion of the medial temporal lobe, was more severely impaired than patient W.H. (Rempel-Clower et al., 1996), who had an ischemic lesion that damaged bilaterally the hippocampal region and caused some cell loss in the entorhinal cortex. In turn, patient R.B. (Zola-Morgan et al., 1986) and patient G.D. (Rempel-Clower et al., 1996), who had bilateral ischemic lesions limited essentially to the CA1 field of the hippocampal region, was less impaired than patient W.H. Accordingly, for both monkeys and humans, ischemic damage seems to produce a level of memory impairment similar to what is produced by comparable neurosurgical lesions. At the same time, there are empty cells in Table 1, and there are only a few observations in the filled cells so that, despite the orderly and systematic relationship illustrated in Table 1, additional work could usefully address this issue.

We encourage additional experimental work, especially in the rat, in which systematic comparisons between the behavioral ef-

[2]The mean group scores for the four measures that were used in the z-score analysis and the results of two-tailed *t*-tests were as follows: trial-unique delayed nonmatching to sample, trials to criterion: H = 290 trials, ISC = 50 trials, $P = .043$ (note that the ISC group performed significantly *better* than the H group); trial-unique delayed nonmatching to sample, delays: H = 84% correct, ISC = 77% correct, $P = .063$; delayed retention of object discriminations: H = 85% correct, ISC = 85% correct, $P > .10$; trial-unique delayed nonmatching-to-sample retest, delays: H = 85% correct, ISC = 82% correct, $p = .37$.

fects of ischemic lesions and neurosurgical lesions could readily be carried out. Rats with ischemic lesions, and varying degrees of associated CA1 cell loss, have been found to be impaired on a wide range of behavioral tasks including delayed nonmatching to sample, the radial maze, and the water maze (Volpe et al., 1989; Auer et al., 1989; Wood et al., 1993; for additional references, see Nunn and Hodges, 1994). Behavioral deficits in rats with hippocampal damage caused by neurosurgical lesions have been reported on these same tasks (Mumby et al., 1995; Olton et al., 1979; and Morris et al., 1982). The useful studies that are now needed would compare, within the same study, the behavioral effects of different extents of surgical lesions of the hippocampal region (as in Moser et al., 1993; Moser et al., 1995) to the behavioral effects of an ischemic lesion. Surgical lesions have most typically been made by aspiration, a technique that necessarily damages overlying cortex as well as fibers of passage within the hippocampal region. Ischemic lesions do not appear to damage fibers of passage and, depending on the duration of the ischemia, can cause ostensibly focal damage. Accordingly, it would be important to use lesion techniques that produce relatively circumscribed lesions, e.g., stereotaxic radiofrequency lesions or lesions made by neurotoxins.

The ischemic procedure should be one that produces substantial detectable cell loss within the hippocampal region without producing detectable cell loss outside the hippocampal region. Several techniques have been developed for the rat that produce consistent patterns of damage. In the four-vessel occlusion method (Pulsinelli et al., 1982), the vertebral arteries are electrocoagulated, and 24 h later the carotid arteries are reversibly ligated for up to 15 min. This procedure results in loss of 80–90% of CA1 cells in dorsal hippocampus, and the extent of cell loss is related to the duration of occlusion. An alternative method (two-vessel occlusion) involves transient bilateral carotid ligation combined with pharmacologically induced hypotension or hypotension induced by exsanguination. This procedure results in loss of 50–60% of CA1 cells in dorsal hippocampus (Meldrum, 1990; see Nunn and Hodges, 1994, for discussion of these procedures). At the completion of behavioral testing, histological analysis can determine the extent of detectable damage in each group of animals. This analysis should include similar measures of damage for both kinds of lesions, e.g., the area or volume of spared CA cell fields.

Three studies in rats illustrate the difficulty of evaluating the behavioral effects of ischemia. Volpe et al. (1992) exposed rats to 30 min of ischemia using the four-vessel occlusion method. Other rats sustained low-dose or high-dose ibotenic acid (IBO) lesions of the dorsal hippocampus. Animals exposed to ischemia and to high-dose IBO were similarly impaired on a spatial delayed alternation task. Histological analysis demonstrated that performance was related to the amount of CA1 damage. Specifically, rats with high-dose IBO lesions had the most overall hippocampal damage, but these animals and the ischemic animals had comparable amounts of CA1 damage and similar behavioral impairment. In contrast, rats with low-dose IBO lesions performed significantly better than ischemic rats and had significantly less CA1 damage, although overall damage to the hippocampus in the ischemic and low-dose IBO animals was comparable. One interpretation of this study is that detectable CA1 damage predicts performance and that there is no covert damage in the ischemic animals relevant to performance. However, an alternative possibility is that the ischemic rats had covert damage throughout the hippocampus in the same regions damaged in the high-dose IBO rats, and this covert damage explains why the ischemic rats were as impaired as the high-dose IBO animals.

A second study (Nunn et al., 1994) assessed spatial water-maze performance in rats that had undergone four-vessel occlusion (4VO) for 5, 10, 15, or 30 min. CA1 cell loss increased as a function of the duration of ischemia. However, according to the Abstract, the correlation between CA1 cell loss and behavioral performance on the spatial task was not significant (Nunn et al., 1994; p. 41). These results raise the possibility that no correlation between cell loss and behavioral impairment was obtained because of the presence of covert damage in the ischemic rats. Specifically, covert damage might have occurred to a similar extent in all the ischemic groups. If this covert damage was the main cause of impaired task performance, then no correlation should have been found between CA1 cell loss and behavior. Although the authors discount the possibility of covert damage as an explanation for their results, we suggest instead that the study does not permit an interpretation about the possible importance of covert damage. First, a separate surgical lesion group was not included for comparison with the ischemic group. Second, the report of no correlation between CA1 cell loss and behavior is not convincing. For several of the key correlational analyses that compared extent of CA1 cell loss with performance, the authors included only the animals that had undergone the 5-min and 10-min ischemic procedure. (They eliminated the 15-min and 30-min groups.) In a separate analysis, the CA1 cell loss estimates did not differ between the 5-min and 10-min ISC groups (Nunn et al., 1994; p47). Accordingly, it would not be surprising that analyses involving two groups with similar, submaximal CA1 cell loss revealed non-significant correlations between cell loss and performance. Third, when the authors do take into account the findings from the 15-min and 30-min groups, which sustained greater than 90% cell loss in the CA1 field, they state a conclusion different from what appears in their Abstract: "For some water maze measures, it would appear that prolonging the duration of 4VO (and therefore also increasing CA1 loss) increased behavioural impairments" (Nunn et al., 1994; p. 51).

A third study evaluated the separate and combined effects of ischemia (caused by two-vessel occlusion) and bilateral hippocampal ablation on object recognition (delayed nonmatching to sample, DNMS) in rats (Mumby et al., 1996). Rats that received ischemia alone exhibited severe deficits in DNMS, but rats that received hippocampal lesions 1 h after ischemia exhibited what was reported to be a milder deficit. It was proposed that ischemia exerts its behavioral effects through extrahippocampal damage and that this damage is produced by some pathogenic process that requires an intact hippocampus. However, the five rats given ischemia plus the hippocampal lesion did not in fact perform better than the ten rats given ischemia alone ($P > .10$). Additional data are needed to illuminate this key comparison.

None of these studies in rats settles the issue of whether covert damage is an important factor in understanding the behavioral effects of ischemia. We believe that the most promising approach would compare the behavioral performance of ischemic animals who have sustained substantial cell loss in the CA1 field of the hippocampal region, animals with partial neurosurgical lesions within the CA1 field, animals with more complete neurosurgical lesions within the CA1 field, and animals with more extensive neurosurgical lesions that involve other CA fields and even the entorhinal cortex. If covert damage is present in the ischemic animals, the ischemic animals should perform worse than animals with apparently similar or even larger neurosurgical lesions. If covert damage is not present to an extent that impairs memory, then the ischemic animals should perform at about the level predicted by their detectable damage, i.e., better than animals with larger neurosurgical lesions and worse than animals with smaller neurosurgically lesions.

The purpose of this commentary has been twofold. First, we suggest that there is no real conflict between the studies that have been carried out to date with nonhuman primates (Zola-Morgan et al., 1994; Bachevalier and Mishkin, 1989). The available data in monkeys are consistent with the notion that the neuronal damage relevant to behavioral impairment can be detected in histopathological examination following both ischemia and neurosurgical lesions, assuming sufficiently long survival times after injury. Second, the studies available to date in the rat do not resolve this issue. The time is ripe for a systematic experimental attack on this issue in the rat, in which one can compare the behavioral effects of ischemic lesions with the effects of several, different-sized hippocampal lesions made by electrolytic methods or by excitotoxins. Such an experimental program should make it possible to interpret unambiguously the cognitive deficits associated with ischemic damage to the hippocampal region.

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