**Why NMDA-receptor-dependent long-term potentiation may not be a learning and memory mechanism, or is it Memorex?
A reply to Morris, Gallagher, and Staubli**

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In our paper, we offered another perspective on the findings reported by Morris, Anderson, Lynch, and Baudry (1986), Robinson, Crooks, Shinkman, & Gallagher (1989), and Staubli, Thibault, DiLorenzo, and Lynch (1989). In doing so, we called into question the NMDA-memory hypothesis. Here we address some of the points made in the comments on our paper by the authors Morris, Gallagher, and Staubli.

**It's Heads We Win and Tails He Loses:
Response to Morris**

Morris makes a number of interesting points, and we agree with some of them. He characterizes our critique as a "cunning attack" on the NMDA-memory hypothesis. We view it as simply an articulation of some of the limitations and implications inherent in the NMDA-receptor blockade strategy as a means of connecting LTP to behavior. If NMDA receptors are blocked, so too should be the learning and memory that depend on their activation. Our reading of the literature is that when one takes into account the nonassociative influences of the NMDA antagonists, one is more impressed that the animals learn than that they don't learn. So we questioned the NMDA-memory hypothesis. Morris agrees that one has to be concerned that the impairments produced by NMDA antagonists may reflect nonspecific sensorimotor effects, but he argues that we have prematurely rejected the NMDA-memory hypothesis, providing his own data published since 1986 to make the point.

Morris also discusses an observation from his laboratory that in our view significantly weakens the NMDA-memory hypothesis. In a footnote, we suggested that it would be instructive to compare the effects of AP5 on rats trained with a hidden platform that was always in a fixed location in the pool with rats trained with the platform location randomly varied. When platform location varies randomly on each trial, spatial information is of no value to the animal in solving the problem. So if AP5 blocks the processes needed to learn spatial information, then rats trained on the fixed location version of the task should behave like rats trained on the random location version. However, if AP5 does not block the processes needed to use spatial information, rats trained on the fixed

platform should be better than rats trained on the random platform task.

According to Morris, in his laboratory, AP5-treated animals trained on the fixed location task are much better than those trained on the random location task. So AP5-treated animals did learn the spatial location of the platform, and this finding scores against the NMDA hypothesis. Yet, rather than accept this straightforward interpretation of the data, Morris questions the value of the random control task.

The problem he notes is that his pool (200 cm in diameter) is very large compared to the size of the platform (10 cm in diameter), with a ratio of surface areas of 400:1. Because of this ratio, he says "that rats trained in the random platform condition have a very low *chance* [emphasis ours] of finding the platform. Unfortunately, they react to this failure by returning to their initial 'strategy' of swimming thigmotactically against the sidewalls of the pool and thereby collect a large number of (maximal) 120-sec latency scores (the mean escape latency in the random control procedure was circa 85 sec)" (Morris, 1990, p. 264).

We may have missed something, but unless the AP5-treated rats trained with the platform in a fixed location can learn spatial information, their *chance* of locating the platform is the same as it is for the animals trained with platform location varying randomly. So they too should return to the wall and collect a large number of 120-sec latency scores. But they do not. So the AP5-treated animals must have learned spatial information, and this finding scores against the NMDA-memory hypothesis.

Pool size to platform size is an irrelevant consideration, but if Morris thinks this is a serious problem, then we suggest he use a smaller pool. He assumes that a large pool amplifies small differences in spatial learning abilities. We suspect otherwise—that a large pool amplifies the effects treatments have on the nonassociative processes essential to performance on this task.

Morris also agreed with our views of the problems associated with MK-801. In fact, he noted complications that were omitted in our paper, and his assessment was at least as negative as ours. So we were surprised that he considered our use of the term "gratuitous" as unfriendly, ill-judged, and insulting. We should also like to note that we did not say MK-801 has no interesting properties, and agree that it is worthy of investigation irrespective of whether or not it blocks LTP (see Whishaw & Auer, 1989, for an interesting case in point).

Another Look at Robinson et al. (1989)

In response to our criticisms of the Robinson et al. (1989) behavioral studies of the effect of MK-801, Gallagher raised several issues that we are obliged to consider. One issue is that we ignored their finding that MK-801 produced impaired place learning at a dose that

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had no detectable effect on relevant performance indices. This outcome presumably counters our assertion that MK-801 may have influenced behavior by impairing non-associative processes. A second issue concerns whether or not MK-801 actually blocks NMDA-dependent LTP. Our position was that in the absence of evidence that MK-801 blocks the induction of NMDA-dependent LTP, the claim that behavioral impairments induced by this drug support the NMDA-memory-mechanism hypothesis is gratuitous. Gallagher challenges our conclusion that MK-801 does not block LTP.

On the first issue, Gallagher is partially correct. We did ignore their place-learning results, but not for the reason that she implies—that the data were inconvenient for our position. We saw no need to address the experiment, because if, as we concluded, MK-801 does not block LTP, then, whatever the outcome, the results were not relevant to the NMDA-memory hypothesis. We still see no reason to change our position on this issue (see below), but we certainly are willing to give this experiment another look.

First, this experiment (Robinson et al., 1989, Experiment 1) was designed well. It was used to assess the effects of three doses of MK-801 (.01, .05, and .08 mg/kg) on two versions of the Morris water task: the place-learning task (where the platform is hidden), and its cued version (where the platform is visible). The cued version was included as a control task for the nonselective effects of MK-801. A single dissociation was produced by the .05-mg/kg dose. It disrupted performance on the place but not the cued task. Yet there is more to the story. Specifically, the .01-mg/kg dose did not impair performance on either task, whereas the .08-mg/kg dose significantly impaired performance on both tasks.

Gallagher concluded that the single dissociation obtained with the .05-mg/kg dose is sufficient grounds for rejecting the hypothesis that MK-801 was merely exerting its influence in some nonselective way: "Although a steep dose-response effect was observed, the behavioral data suggest that, within a narrow dose range, MK-801 produces a place-learning impairment that is not confounded by a sensorimotor performance deficit" (Robinson et al., 1989, p. 159). But this result should not be viewed in isolation from the rest of the data. When the implications of the entire data set are considered, her conclusion becomes unwarranted.

Assume that there is a process common to both the cued and the place task and another process that is unique to the place task (e.g., performance on it depends on NMDA-dependent LTP, whereas performance on the cued task does not). Gallagher wishes to conclude that the .05-mg/kg dose exerted its influence on the place task by selectively influencing the unique process. But the complete data set reveals that performance on both the cued and the place task monotonically deteriorated as the dose of MK-801 increased.

So the drug does impair a process common to both tasks. All that differs is that MK-801 disrupted performance on the place task at a lower dose (.05 mg/kg) than

was needed to disrupt performance on the cued task (.08 mg/kg). That the place task was disrupted by the lower dose is not surprising, because it is more difficult than the cued task. So this pattern of data is quite consistent with the hypothesis that a process common to both the place and the cued task is disrupted by MK-801 but the threshold level of impaired function of this process needed to disrupt performance on a difficult (place) task is lower than is needed for it to influence an easy (cued) task. There is no need to assume that MK-801 selectively impaired a process unique to the place task, in order to explain the data set. A recent paper by Dunn and Kirsner (1988) provides a useful discussion of the general issues that surround the interpretation of dissociations.

Gallagher also discusses another aspect of their data, in order to argue against the nonselective interpretation of MK-801's effect. She says, "Finally, animals trained under the drug had persistent deficits when tested on a free swim in the absence of the drug" (Gallagher, 1990, p. 258). So even in the absence of the drug, animals that were trained on the place task displayed no evidence of having learned the location of the platform while on the drug. What should be noted is that the animals to which she refers in the above quotation were animals trained under the high dose (.08 mg/kg). At this dose, animals were also significantly impaired in swimming to a visible platform. So it comes as no surprise that they failed to learn the location of the hidden platform.

We would have been more impressed had animals that were trained under the .05-mg/kg dose displayed no evidence of place learning when subsequently tested in the absence of the drug, but evidently Robinson et al.'s (1989) animals trained under the .05-mg/kg dose were not tested in the absence of the drug. We note again (see also Morris, 1990), however, that Halliwell and Morris (1987) did report that animals which were impaired while being trained under the influence of MK-801 were just as good as controls when tested in the absence of the drug—a result that supports the hypothesis that MK-801 can impair performance on the place task without impairing learning.

We turn now to the second general issue. Gallagher has challenged our conclusion that MK-801 does not block LTP in doses that permit learning to be assessed. In reaching this conclusion, we noted that Halliwell and Morris (1987) reported that MK-801 failed to block LTP altogether and Abraham and Mason (1988) found that MK-801 blocked LTP only when very large doses were given. Gallagher argues that because both Abraham and Mason (1988) and Halliwell and Morris (1987) used anesthetized animals, their results are not relevant to this debate, and that in unanesthetized rats MK-801 (0.1 mg/kg) blocks LTP (Gilbert & Mack, 1989).

In making her first point, she assumes that the NMDA-receptor activation is not occurring normally in the anesthetized animal. This issue has already been addressed by Abraham and Mason (1988), who argued just the opposite—that NMDA-receptor activation does occur nor-

mally in the anesthetized animal. We will not repeat their arguments here (but see Abraham & Mason, 1988, p. 45). With respect to Gallagher's second point—that MK-801 (0.1 mg/kg) blocks LTP in unanesthetized animals (Gilbert & Mack, 1989)—we make two points. First, Gallagher and her colleagues (Robinson et al., 1989) found that animals that received a 0.08-mg/kg dose of MK-801 were impaired on both the place and the cued version of the Morris task (i.e., the non-hippocampal-dependent task). So even if Gilbert and Mack's (1989) result is accurately interpreted, its significance for Robinson et al.'s (1989) behavioral results is debatable, because it is reasonable to expect that the nonselective behavioral effects of a 0.1-mg/kg dose of MK-801 would be even greater than those produced by the .08-mg/kg dose. Second, in the Gilbert and Mack (1989) abstract to which Gallagher refers, only the effect of MK-801 on the population spike was reported, not its effects on the EPSP (except in their kindling-induced potentiation study). So it is impossible to determine whether or not MK-801 actually blocked synaptic enhancement. The reader is referred to Bliss and Lynch (1988) for a discussion of this issue.

Finally, Gallagher has claimed that we argued "that the effect of MK-801 on LTP observed by Abraham and Mason is *not meaningful* [emphasis ours] because it was obtained at a dose that diminished the population spike response to test pulse stimulation of the perforant path" (Gallagher, 1990, p. 259). On the contrary, that MK-801 reduces the population spike to a test pulse is extremely important. It means that, unlike AP5, MK-801 interferes with normal neural transmission in the hippocampus and elsewhere (i.e., the brainstem). That MK-801 blocks normal neuronal transmission may be why it produced the behavioral impairments Robinson et al. (1989) observed.

Finally, we also recognize that Abraham and Mason (1988) performed the proper controls, and we agree with their conclusion that very high doses of MK-801 (1.0 mg/kg) block LTP. We also agree with their conclusion that "before any behavioral effects (of NMDA antagonists) can properly be attributed to an altered ability to produce LTP, physiological 'side effects' such as the reduction of the population spike amplitude and changes in complex spike activity in the hippocampus plus any change in the function of other structures need to be considered" (Abraham & Mason, 1988, p. 46). The reader is referred to Morris's (1990) commentary for another assessment of the problems associated with the use of MK-801 to evaluate the NMDA-memory hypothesis.

So after another look at the Robinson et al. (1989) paper and a consideration of the points Gallagher raised in her commentary, we see no reason to alter our position.

The Animal Psychologists Reply to Staubli

In our paper, we argued that the Staubli et al. (1989) findings on the effects of AP5 on odor discrimination learning go against the NMDA-memory hypothesis. This assessment was based on the following facts: Under two of the three training conditions (normal odor intensity with

10-min intertrial interval, and low odor intensity with 2-min intertrial interval), AP5 had no effect on the rate of discrimination learning; and where an effect of AP5 was observed (low odor intensity, 10-min intertrial interval), it was quite small and could easily be explained as an effect of the drug on the sensory or motor side.

In response to our view, Staubli says, "In brief, what we see in Keith and Rudy's complaint are two sets of preconceptions coming into collision: our notions about the properties of LTP . . . as opposed to Keith and Rudy's expectations, which are based on behavioral experiments with rats and on the history of animal psychology. What seems to be a substantial impairment from one perspective apparently is not seen as such from the other" (Staubli, 1990, p. 267). We are not sure what the history of animal psychology has to do with the matter, but we disagree with this assessment of our complaint. We had no preconceptions about how AP5 should effect the learning and memory processes involved in odor discrimination learning. We asked whether or not there were sufficient grounds in the data for rejecting the null hypothesis—that AP5 has no effect on learning and memory. We concluded that the null hypothesis could not be rejected.

First, we saw no reason a priori why the effect of AP5 on odor discrimination learning should depend on the concentration of the odors or on the intertrial interval (although ad hoc accounts of why it did are easy to imagine). Second, the observed effect with the low odor concentrations and long intertrial interval was small. The AP5 animals' performance improved significantly over the 20 training trials, and as best we can estimate from Staubli et al.'s Figure 2 (bottom left), the AP5-treated animals made on the average only .9, 1, and .5 fewer correct responses on Trial Blocks 2–5, 6–10, and 11–15, respectively, than did control animals. Third, the entire data set was statistically evaluated with an unprotected *t* test, so we are not even convinced that there was a statistically significant effect of AP5, even in the low intensity, 10-min intertrial interval condition. So given that AP5 blocks NMDA-dependent LTP, we concluded that the fact animals learned argued against the NMDA-memory hypothesis. We encourage readers to consult the data to see if they agree with Staubli's assessment: "We are, however, reasonably confident that human beings showing the type of failure of rapid acquisition that we have observed in our animal studies would be judged as having a severe memory impairment" (Staubli, 1990, p. 267).

The second point Staubli raised was in response to our attributing the effects of AP5 on behavior to nonspecific sensorimotor effects. We agree that such interpretations can be difficult to rule out. That alone does not, however, exclude their validity. Nor does the fact that we failed to identify "a few studies in which sensorimotor impairments *had* been 'convincingly' controlled" (Staubli, 1990, p. 268) make the criticism go away.

Finally, we would correct the erroneous statement that "it is misleading of Keith and Rudy to pretend that we

or any others have claimed that pharmacological work alone is sufficient to evaluate the role of LTP in memory" (Staubli, 1990, p. 268). Nowhere in our paper did we make such an assertion. We appreciate that NMDA-dependent LTP has properties that make it an attractive memory-mechanism candidate and that pharmacological evidence goes into the same evaluative bin as other evidence. We part company with Staubli, however, in how we evaluate her pharmacological data (Staubli et al., 1989). So our complaint is with neither her particular paradigm nor her approach. It is with how the data are interpreted.

Conclusion

The reader might have the impression that we initiated this debate because of some a priori bias against the NMDA-memory hypothesis. In fact, just the opposite is true. We initially read the papers of Morris et al. (1986) and Staubli et al. (1989) with the expectation that these behavioral experiments were going to add significantly to the case linking NMDA-dependent synaptic changes to memory. The data changed our minds.

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