prenatal exposure through drinking water, pups were exposed to Pb-containing food when they were 2 days old. It is possible that the concentration of lead accumulated in the Pb-exposed animals’ hippocampi was insufficient to impair the formation and stabilization of long-term spatial memory. Further studies are needed to elucidate the exact relationship between hippocampal lead concentration and its cognitive consequence on different components of learning and memory, including acquisition, consolidation and retrieval.

It could be argued that since Pb-exposed animals performed equally well with controls in both probe trials, any observed differences in the escape latency during training sessions should not be attributed to learning deficits; instead they are likely to be caused by more general effects of the chemical. However, several reasons may explain why this is not the case. First of all, non-specific effects of lead were well controlled in this experiment. The weighing data did show that animals on the lead diet were significantly lighter than those on the control diet up to PND 20. However, on PND 25, there was no longer a significant difference between the two diet groups. Considering the fact that behavioral testing was conducted between PND 24 and 27, it is more reasonable to assume that weight is not a contributing factor to animals’ escape latency. Also, among MK-801-treated rats, those on lead diet performed even slightly better than the controls. Therefore, factors other than physical weight should account for the observed behavioral differences. Activity levels of animals were also controlled in this study. In contrast to what previous studies suggest, lead exposure in the present study did not lead to hyperactivity in animals [24]. In fact, Pb-exposed animals exhibited similar activity levels with control animals. This may be due to the lower concentration of lead used in this experiment. Moreover, lead exposure had no impairing effect on animals’ cued trial performance. Since Pb-exposed animals showed longer escape latency only in the absence but not in the presence of cue, slower learning caused by lead exposure should not be attributed to either visual problems or lower motivation level. After excluding the several non-cognitive effects that may possibly influence the performance of Pb-exposed animals, it is reasonable to assume that any behavioral impairment is probably an outcome of cognitive deficits associated with lead exposure. Secondly, it should be emphasized that although spatial learning/memory appears to be one unified phenomenon, it actually consists of a few distinct phases, namely the acquisition, consolidation and retrieval. Impairment could possibly occur at one single phase without affecting other phases. It is true that Pb-exposed animals eventually acquired as
robust a memory as the control animals, but a significant difference in the escape latency on the first training day and a significantly prolonged overall mean escape latency undeniably pointed to an observable deficit in the acquisition of spatial memory, no matter how small the deficit is and how closely the overall trend in daily escape latency matched with the controls.

Since NMDA receptors are critically involved in learning and memory, they are proposed to be the target site where lead exerts its neurotoxic effect [1,14-15]. The NMDA receptor antagonist MK-801 was therefore used in the current study to probe for the possible mechanisms of lead action. Consistent with previous experiments, the administration of MK-801 seemed to result in significant impairment of animal's spatial learning [19-20]. One may attribute the impairment to the significantly higher activity levels induced by MK-801 injection. However, since MK-801-treated rats spent a significantly longer time to find the hidden platform, hyperactivity, which tends to increase the probability of finding the platform by chance, would not account for their poorer performance. Moreover, there was no correlation between the activity levels and water maze performance. Unfortunately, MK-801-treated rats showed significantly longer escape latency than saline treated rats in the cued trial as well, suggesting severe visual problems caused by the drug. The data analysis also illustrates a significant correlation between cued trial escape latency and normal trial escape latency, implying that animals which had longer escape latencies during normal trials may not be cognitively impaired after all, and perhaps it is their visual problem that affected their performance. This interpretation should be taken seriously especially owing to the fact that 31% of MK-801-treated rats while 0% of saline-treated rats were unable to find the visible platform within 60 s. Therefore, one should not be making blunt claims that MK-801 impairs spatial learning and memory, because in the current study, the effect of MK-801 on higher-order cognitive processing, such as the ability to associate external cues with the platform location, was masked by perceptual deficits. In other words, since the behavioral test heavily relies on animals’ visual system to pick up external cues, it does not allow for a fair judgment on animals’ ability to learn and memorize when some of them developed poor vision. It is worth mentioning that factors other than visual problems, such as altered motivational level, may also contribute to a general increase in the escape latency during both cued and normal trials.

Provided both lead and MK-801 have an impairing effect on water maze performance regardless of the actual nature of impairment, one might expect animals that are both Pb-exposed and MK-801-treated to perform the worst. Surprisingly, instead of exacerbating the deficits caused by MK-801, lead tended to alleviate the
Although MK-801-treated rats did not significantly differ between the two diet groups during normal training sessions, a significant drug by diet interaction demonstrates that MK-801 injection did affect Pb-exposed animal to a significantly lesser degree. One possible explanation which could not be dismissed is that there might be a ceiling effect among the MK-801-treated rats, so that further deficits were prevented from showing up in the data, and the slightly better performance of Pb-exposed animals was simply due to sampling errors. More sensitive measures, such as the direction of initial heading and the total path length, may be used in future studies to distinguish the performance of the two diet groups under MK-801 treatment. Nevertheless, a significant better performance of Pb-exposed animals within the MK-801 treatment group in probe trial 1 strongly suggests that lead does abate the deleterious effect of MK-801 to a measurable degree. No such difference showed up in probe trial 2 however, because all animals were tested under a drug-free condition. This suggests that any deficits caused by MK-801 do not have a prolonged effect.

Admittedly, since it is not entirely clear what actually caused the worse performance of MK-801-treated animals, it is difficult to determine whether lead actually has a mild protection effect on learning and memory in the special circumstance of MK-801 treatment or it simply tempers non-cognitive deficits induced by MK-801. Given that non-specific effects of MK-801 offer probable explanations for the observed behavioral deficits, this study provides no evidence of hippocampal involvement in the MK-801 induced deficits. Nevertheless, some kind of interaction between lead and MK-801 must have taken place somewhere in the brain if lead does alleviate the deleterious effects of MK-801. As discussed above, the observed deficits induced by MK-801 injection may likely due to visual problems, thus the interaction between lead and MK-801 could conceivably have taken place in the visual cortex of rats. Furthermore, what is unsure is just where in the brain MK-801 exerts an impairing effect but not how it exerts its effects, because any consequence of MK-801 administration always arises from it non-competitive binding to the NMDA receptors. Consequently, the possibility of non-specific effects of MK-801 should not deter one from making reasonable hypothesis that the key to the lead-MK-801 interaction lies at NMDA receptors. Previous studies failed to reach an agreement on whether lead increases or decreases NMDA receptor density [1,15-17]. Data from the present study would suggest that exposure to low-level lead more likely causes an increase in the NMDA receptor density at the affected brain region. The reasoning is as follows: a given dosage of MK-801 would affect a specific number of NMDA receptors; if the number of NMDA receptors now increases, due to the existence of more functional NMDA receptors, the same dosage of MK-801 would not cause as much impairment as before. This is exactly what the results demonstrated. However, this proposed molecular mechanism of lead action is highly speculative, because the existence of an interaction between lead and MK-801 is itself not conclusive from the present study.

If this speculation is true, one may then question why Pb-exposed animals showed slower acquisition than the controls under saline condition even though they have raised NMDA receptors density. A reasonable explanation is that although NMDA receptors play critical roles in learning and memory, more NMDA receptors do not always correspond to enhanced learning and memory. In fact, this explanation is supported by previous studies which demonstrated that most efficient learning requires an optimal instead of a maximum level of NMDA receptors ([25] Ingram et al., 1992; [26] Brooks et al., 1997). Perhaps in Pb-exposed animals, excess receptors disrupted normal synaptic plasticity, thus leading to impaired spatial learning.

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In conclusion, the present study shows that early postnatal exposure to even low-level lead can lead to observable impairment in the acquisition of spatial memory, and a Pb-induced alleviation of MK-801 associated deficits provides evidence for a possible alteration of NMDA receptor density by lead. Further experiments are necessary to verify the existence of an interaction between lead and MK-801 at the molecular level and also to explore the effects of low-level lead on other cognitive capacities.
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