Commentary

New approaches to amnesia

Karim Nader¹

Department of Psychology, McGill University, Montreal QC H3A 1B1, Canada

Our colleagues have raised a number of interesting points concerning our study that claims to provide a new framework for testing the nature of amnesia. We initially reasoned that any attempt to create a paradigm to test the nature of amnesia must meet three criteria. First, we needed a paradigm that could make a positive prediction for the absence of a memory. If amnesia is a storage impairment, the only prediction that this view makes in the recovery from amnesia paradigm is no change in performance (no recovery from amnesia), a negative prediction. A negative finding is not proof for a memory no longer existing. This scientific shortcoming in the ability to prove the absence of a memory using the recovery from amnesia paradigm was plainly described by Professor Miller in 1974: "The experimental amnesia paradigm is such that, . . . , the consolidation-failure position is behaviorally *untestable*. That is, . . . lack of recovery would not prove that recovery is impossible" (Miller and Springer 1974; see Table 1A). Given the depth of the descriptions of the molecular and cellular mechanisms proposed to mediate this putative consolidation process (Kandel 2001), it is remarkable that to this day there is no positive evidence that amnesia is due to a storage impairment of a memory.

Our second criterion for a new paradigm is that it makes different predictions for the retrieval and storage impairment views of amnesia. The recovery from amnesia paradigm failed to do so after 1973. In 1973, Professor McGaugh's group published an elegant experiment that allowed for interpretations of recovery from amnesia as being consistent with the memory that was not being stored (Gold et al. 1973). Specifically, amnesia is never 100%; commonly there is residual performance on the range of <50% of control responding. Therefore, recovery from amnesia was seen as new learning adding onto a residual memory trace (Gold and King 1974). Thus, after 1973 any finding from the recovery from amnesia paradigm was consistent with both views of amnesia (see Table 1B). This is part of the reason why this paradigm could not resolve this issue. Even by 2006, 30 years later, there remains no agreement among a series of memory scientists on the nature of amnesia (see special section The Neurobiology of Amnesia in *Learn Mem*, Vol. 13, Issue 5, 2006).

Our third criterion was for a paradigm that did justice to the historical complexities of the issue. With the rediscovery of reconsolidation (Nader et al. 2000) there was a resurgent interest in the nature of amnesia. Unfortunately, in the rush to test the nature of amnesia induced by reconsolidation blockade, many of the issues that plague this field were trivialized such that interpretations of recovery from amnesia that predated 1973 were used to interpret their findings (Vianna et al. 2001; Fischer et al. 2004; Lattal and Abel 2004; Power et al. 2006).

The logic we developed was to exploit the fact that some tasks have different behavioral or neurobiological signatures engaged in the first and second time the animals learn a task. Thus, logically, if amnesia for the memory of the first learning is not stored, then the second time animals learn a task the brain should use mechanisms

that are engaged by first learning. This is a positive prediction for the absence of a memory. If amnesia is a retrieval impairment, then the memory for the first learning would be consolidated into the brain, and therefore engage either behavioral or neurobiological mechanisms normally engaged by second learning. Part of the appeal of this logic is that any type of amnesic treatment (whether systemic or local) can be employed on any behavioral response measured, the neurobiological mechanisms mediating the amnesia is irrelevant, and no knowledge of how the brain detects whether a learning session is the first or second time animals learn is required. Thus, it has wide applicability.

The second learning effect was first demonstrated in the watermaze by Morris' group (Bannerman et al. 1995) and then extended to contextual fear conditioning in conjunction with intradorsal hippocampus (dH) infusions of NMDA receptor (NMDAR) antagonist by AP5 by Sanders et al. (2003). We replicated the basic effect by Fanselow's group demonstrating that AP5 blocks the acquisition of the first, but not second, contextual fear task (Table 2; Sanders et al. 2003). Thus, we used the sensitivity of the second learning to intra-dH AP5 as an assay to let the brain tell us if it thinks there is a prior memory there or not. The a priori predictions are that, if anisomycin-induced amnesia is a storage impairment, then during the second learning the brain should treat it as the first time it has learned this task, and be blocked by AP5 infusions. Conversely, if amnesia is a retrieval impairment then, during the second learning, the brain should know that there is an existing memory such that second learning will be AP5 insensitive. We found that anisomycin caused second learning to be blocked by AP5 infusions into the dH, a mechanism that is normally engaged by first learning.

My colleagues have suggested that this study raises many issues and complications. Although our paradigm might not seem straightforward at first glance, our aim was to develop a new and reliable way of testing the nature of amnesia that may be induced by any amnesic agent. For example, Matzel and Miller (2000) correctly indicate that the nature of the representation being affected by intrahippocampus infusions is still debated. However, the logic of the paradigm can still be applied regardless of whether we have agreement on what representation is stored in a given brain site. This paradigm addresses the nature of amnesia which does not require a complete understanding of the exact representations being challenged. In the same manner, my colleagues correctly indicate that the effectiveness of anisomycin's ability to inhibit protein synthesis was not examined and correlated with the depth of amnesia induced. However, the aim of this study was not to examine the mode of action of the amnesic agent. The aim of this study was to develop a paradigm to test the nature of amnesia, regardless of its mode of action, whether it is a local versus a global treatment such as electroconvulsive shock (ECS), genetic such as a transgenic mouse, or a pharmacological manipulation. The logic of the experiment is not challenged by any of these differences. We see this as an advantage, not a complication, of the paradigm.

Another complication correctly identified by Matzel and Miller (2000) is that there must be some residual memory trace outside of the hippocampus for the first training that may

¹Corresponding author.E-mail karim.nader@mcgill.ca; fax (514) 398-4896.Article is online at <http://www.learnmem.org/cgi/doi/10.1101/lm.1598209>.

Table 1A. The specific arguments invoked to explain the nature of amnesia before 1973 in the recovery from amnesia paradigms that led to a conceptual stalemate on the issue

Recovery from amnesia observed?	Storage impairment view	Retrieval impairment view
Yes	Inconsistent	Consistent with overcoming retrieval impairment
No	Consistent with storage impairment	Consistent, as proper parameters to overcome the retrieval impairment have not been found

confound the mechanisms engaged by second learning. If this were a critical factor, then regardless of what experimental manipulation was administered during first learning, there would remain a residual memory outside of the hippocampus to influence the mechanisms mediating second learning. However, extinction of the first learning engaged different learning mechanisms during second learning as AP5 and ANISO. These findings rule out the suggestion that a residual memory outside of the hippocampus is a significant confound.

I agree with my colleagues that we do not understand how the brain knows whether it is first or second learning, which is a very important issue. However, as these experiments demonstrate, the paradigm can be used to ask questions concerning the nature of amnesia without having to wait for an understanding of this process.

The main thrust of their concern is that perhaps one could make the post-hoc interpretation: An anisomycin-induced retrieval impairment caused the second learning to be acquired by mechanisms that are normally engaged by first learning. Speaking against this possibility are the results of the ability of AP5 to block second learning after either AP5 infusion prior to first learning or extinction of first learning. NMDARs are almost universally considered to block encoding/consolidation of information (Martin et al. 2000) and not play much of a role in the retrieval of consolidated memories. Therefore, the ability of AP5 to block first learning is commonly viewed as blocking the acquisition or storage of first learning. Therefore, what was found was second learning, in this case, should be mediated by NMDAR; the same effect as anisomycin. Extinction is also universally known to be new learning which inhibits the expression of an existing memory (Pavlov 1927; Rescorla 2001; Bouton 2002). Therefore, extinction of first learning should lead to second learning being NMDAR independent, again what was found. This demonstrates that the expression of a memory is inhibited to the level of anisomycin-induced amnesia; the brain still knows there is existing prior memory and engages mechanisms that are appropriate to second learning, the opposite of what was found for AP5 and anisomycin.

Thus, by comparing anisomycin's effects on second learning to the effects of what are universally accepted manipulations that block the acquisition/storage of a first memory (NMDA receptor antagonists), or inhibits an existing memory (extinction), we find that anisomycin impairment causes this system to act as if the animals had AP5 prior to first learning. This clearly demonstrates this case of amnesia is a storage impairment and cannot be explained as a retrieval impairment as suggested by my colleagues.

For 40 years the issue of amnesia has been held hostage at the end of Ockham's razor. Also known as the law of parsimony, it states: It is preferable to choose the interpretations of data that require the fewest number of variables to explain the data. This guiding principle, of

course, is central to science. However, if this principle is applied with too much zeal, it creates hypotheses that are too simple to explain complex issues. This can prevent fields from evolving because the more complex theories with more variables that could make novel predictions are criticized as having too many variables. The latter situation seems to be the state of affairs for the nature of amnesia. For 40 years, amnesia has been seen as a global entity that is always

either a retrieval impairment (Spear 1973; Miller and Matzel 2000; Riccio et al. 2002; Sara and Hars 2006) or a storage impairment (Glickman 1961; McGaugh 1966; Gold and King 1974; Davis and Squire 1984) for all cases of amnesia, including all amnesic agents, species, and paradigms.

But why must this be the case? Why cannot some cases of amnesia be a storage impairment and some a retrieval impairment? There are many kinds of clinical amnesias, including Korsakoff's Syndrome; why should they all be either retrieval or storage impairments? Even within the domain of molecular neurobiology that has seen such success identifying molecules involved in memory consolidation, there are kinases and receptor mechanisms that seem to have a role in retrieval. For example, using similar inducible knockout technology to examine the role of CaMKII signaling in learning and memory processes, it was reported that expression of the mutated CaMKII-ASP²⁸⁶ gene during training led to an impairment in cued and contextual fear conditioning (Mayford et al. 1996). When the transgene was turned off prior to test, the behavior returned. These data are consistent with the idea that CaMKII is involved in the expression of acquired fear. Other molecules traditionally associated with consolidation but that also have roles in retrieval include β -1 adrenergic receptor (Murchison et al. 2004), PKA, and MAPK (Szapiro et al. 2000, 2002).

Every student of learning and memory agrees that there are psychological/neurobiological processes that mediate learning and consolidation and others mediating retrieval. Therefore, there must be mechanisms responsible for the storage of a memory in the brain and some that mediate retrieval. It would seem reasonable, then, that we should be able to induce different kinds of amnesia by targeting the mechanisms that mediated either storage or retrieval of the memory.

The most reasonable statement concerning the nature of amnesia was stated by Lewis in 1969. Early theories of memory consolidation all viewed amnesia as a storage impairment (e.g., Glickman 1961; McGaugh 1966). To them, Lewis said "The typical procedure for retrograde amnesia experiments has been to have an animal experience a simple learning task, wait varying time intervals, and administer an amnesic agent. Any resulting amnesia has commonly been attributed to the failure of the memory trace

Table 1B. The specific arguments invoked to explain the nature of amnesia after 1973 in the recovery from amnesia paradigms

Recovery from amnesia observed?	Storage impairment view	Retrieval impairment view
Yes	Consistent with storage impairment. Recovery reflects new learning added onto residual memory	Consistent with overcoming retrieval impairment
No	Consistent with storage impairment	Consistent, as proper parameters to overcome the retrieval impairment have not been found

Notice all possible outcomes can be explained by all positions.

Table 2. Predictions, results, and interpretations of our findings

	Predictions for AP5's effect on second learning	Our findings of AP5 on second learning	Our interpretation of the sensitivity of second learning to AP5 infusions	Matzel and Miller's ^a interpretation of the sensitivity of second learning to AP5 infusions
V/AP5	No effect (NE)	NE	Memory 1 still present	Memory 1 still present, cannot be retrieved
AP5/AP5	Block	Block	Memory 1 absent	Memory 1 still present
Ani/AP5	Block/NE	Block	Memory 1 absent	Memory 1 still present
Extinction/AP5	NE	NE	Memory 1 still present	Memory 1 still present

^aMiller and Matzel (2000).

to fixate (Glickman 1961; McGaugh 1966), to a failure in learning. But there is no necessary reason always to attribute a response decrement following learning as an amnesic agent to failure at the input end. There is a great deal going on subsequent to fixation as the learning-performance distinction has always made clear. And there is nothing in the design of amnesia experiments that demands that a response (output) failure be always attributable to a failure to fix the input" (Lewis 1969).

Today, I would put Lewis' (Lewis 1969) question to Miller and Matzel (2000), with the following modification: There is a complex neurobiology mediating learning and subsequent stabilization/consolidation of the memory. So there is no reason to attribute all amnesia to the retrieval side of the spectrum. If we can agree that some cases of amnesia are due to a storage impairment, then the next logical question is how we can test this? Although the authors state that they can imagine a scenario where some amnesias are due to a storage impairment, they do not tell us what behavioral criteria they would use to differentiate those amnesia from retrieval impairments.

We cannot use the recovery from amnesia paradigms because this was one of the main reasons the behavioral field of memory split and remains divided (see articles in *Learning & Memory* on this topic). Parsimony has been used by both camps to the point that it has prevented more complex theories of memory processing to evolve. Perhaps this is one reason why currently there is no field of amnesia. The numbers of papers that address it in a manner that considers its past are rare (e.g., de Hoz et al. 2004; Hardt et al. 2009). Within the domain of systems neuroscience, amnesia is simply a dependent measure to test whether a spectrum of molecular neurobiological candidate mechanisms contribute to a putative consolidation process. Retrieval impairments are viewed as nonspecific, trivial effects (Cahill et al. 2001; Lattal and Abel 2004), as opposed to interesting effects.

Thus, I would like to invite all scientists who propose global theories of amnesia (Glickman 1961; McGaugh 1966; Spear 1973; Gold and King 1974; Miller and Matzel 2000; Riccio et al. 2002; Sara and Hars 2006; Squire 2006) to either propose or develop paradigms that are independent of the recovery from amnesia approach, and meet the criteria that we set forth to meet: (1) a paradigm that makes a positive prediction for the absence of a memory, (2) can be used to make differential predictions for retrieval and storage impairments, and (3) respects the history and complexity of interpreting amnesia.

Pure amnesia presumably is a very rare entity. How much demonstration of 100% amnesia is seen in patients or the thousands of manuscripts examining the molecular mechanisms mediating consolidation? Today, amnesia is used in a more and more targeted manner, with most scientists targeting a memory system that is thought to control a particular response. Some of these systems likely store information concerning retrieval of a distributed memory, such as the hippocampus. Other systems, such as the amygdala, are thought to store emotional information.

Again there is no reason to think that all forms of amnesia are retrieval or storage impairments. Our paradigm can be applied to all the contemporary uses of amnesia for scientists to ask whether a particular molecule is involved in retrieval or storage in their paradigm and brain site.

Conclusions

My colleagues suggest that their interpretation of our impairment as a retrieval impairment is more parsimonious, as they claim the dominant view of amnesia is a retrieval impairment. However, this is simply Ockham's razor whose edge on this issue has dulled to the point of little deterrence. We hope the paradigm we developed will inspire others to use this paradigm or create others to the issue of the nature of amnesia. With sufficient data from other paradigms, amnesic treatments, memory systems, and species we can develop new theories of memory processing that include neurobiological mechanisms for memory storage and retrieval. In order for this to occur, we need to leave these global theories of amnesia behind. Perhaps these new theories of memory processing could be the future basis for unifying the behavioral and neuroscientific fields of memory.

Acknowledgments

This work was supported by grants from the Canadian Institutes of Health Research (CIHR), Steacie Foundation, and NSERC. The author thanks S. Josselyn, B. Balleine, O. Hart, and S.H. Wang for their comments on earlier drafts.

References

- Bannerman DM, Good MA, Butcher SP, Ramsay M, Morris RG. 1995. Distinct components of spatial learning revealed by prior training and NMDA receptor blockade. *Nature* **378**: 182–186.
- Bouton ME. 2002. Context, ambiguity, and unlearning: Sources of relapse after behavioral extinction. *Biol Psychiatry* **52**: 976–986.
- Cahill L, McGaugh JL, Weinberger NM. 2001. The neurobiology of learning and memory: Some reminders to remember. *Trends Neurosci* **24**: 578–581.
- Davis HP, Squire LR. 1984. Protein synthesis and memory. A review. *Psychol Bull* **96**: 518–559.
- de Hoz L, Martin SJ, Morris RG. 2004. Forgetting, reminding, and remembering: The retrieval of lost spatial memory. *PLoS Biol* **2**: 1233–1242.
- Fischer A, Sananbenesi F, Schrick C, Spiess J, Radulovic J. 2004. Distinct roles of hippocampal de novo protein synthesis and actin rearrangement in extinction of contextual fear. *J Neurosci* **24**: 1962–1966.
- Glickman S. 1961. Perseverative neural processes and consolidation of the memory trace. *Psychol Bull* **58**: 218–233.
- Gold P, King R. 1974. Storage failure versus retrieval failure. *Psychol Rev* **81**: 465–469.
- Gold PE, Haycock JW, Macri J, McGaugh JL. 1973. Retrograde amnesia and the "reminder effect": An alternative interpretation. *Science* **180**: 1199–1201.
- Hardt O, Wang SH, Nader K. 2009. Storage or retrieval deficit: The yin and yang of amnesia. *Learn Mem* **16**: 224–230.

- Kandel ER. 2001. The molecular biology of memory storage: A dialogue between genes and synapses. *Science* **294**: 1030–1038.
- Lattal KM, Abel T. 2004. Behavioral impairments caused by injections of the protein synthesis inhibitor anisomycin after contextual retrieval reverse with time. *Proc Natl Acad Sci* **101**: 4667–4672.
- Lewis DJ. 1969. Sources of experimental amnesia. *Psychol Rev* **76**: 461–472.
- Martin SJ, Grimwood PD, Morris RG. 2000. Synaptic plasticity and memory: An evaluation of the hypothesis. *Annu Rev Neurosci* **23**: 649–711.
- Mayford M, Bach ME, Huang YY, Wang L, Hawkins RD, Kandel ER. 1996. Control of memory formation through regulated expression of a CaMKII transgene. *Science* **274**: 1678–1683.
- McGaugh JL. 1966. Time-dependent processes in memory storage. *Science* **153**: 1351–1358.
- Miller RR, Matzel LD. 2000. Memory involves far more than "consolidation." *Nat Rev Neurosci* **1**: 214–216.
- Miller R, Springer A. 1974. Implications of recovery from experimental amnesia. *Psychol Rev* **81**: 470–473.
- Murchison CF, Zhang XY, Zhang WP, Ouyang M, Lee A, Thomas SA. 2004. A distinct role for norepinephrine in memory retrieval. *Cell* **117**: 131–143.
- Nader K, Schafe GE, Le Doux JE. 2000. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature* **406**: 722–726.
- Pavlov IP. 1927. *Conditioned reflexes*. Dover, New York.
- Power AE, Berlau DJ, McGaugh JL, Steward O. 2006. Anisomycin infused into the hippocampus fails to block "reconsolidation" but impairs extinction: The role of re-exposure duration. *Learn Mem* **13**: 27–34.
- Rescorla RA. 2001. Experimental extinction. In *Handbook of contemporary learning theories* (eds. R Mowrer and SB Klein), pp. 119–154. Lawrence Erlbaum, Mahwah, NJ.
- Riccio DC, Moody EW, Millin PM. 2002. Reconsolidation reconsidered. *Integr Physiol Behav Sci* **37**: 245–253.
- Sanders MJ, Wiltgen BJ, Fanselow MS. 2003. The place of the hippocampus in fear conditioning. *Eur J Pharmacol* **463**: 217–223.
- Sara SJ, Hars B. 2006. In memory of consolidation. *Learn Mem* **13**: 472–481.
- Spear N. 1973. Retrieval of memory in animals. *Psychol Rev* **80**: 163–194.
- Squire LR. 2006. Lost forever or temporarily misplaced? The long debate about the nature of memory impairment. *Learn Mem* **13**: 522–529.
- Szapiro G, Izquierdo LA, Alonso M, Barros D, Paratcha G, Ardenghi P, Pereira P, Medina JH, Izquierdo I. 2000. Participation of hippocampal metabotropic glutamate receptors, protein kinase A and mitogen-activated protein kinases in memory retrieval. *Neuroscience* **99**: 1–5.
- Szapiro G, Galante JM, Barros DM, Levi de Stein M, Vianna MR, Izquierdo LA, Izquierdo I, Medina JH. 2002. Molecular mechanisms of memory retrieval. *Neurochem Res* **27**: 1491–1498.
- Vianna MR, Szapiro G, McGaugh JL, Medina JH, Izquierdo I. 2001. Retrieval of memory for fear-motivated training initiates extinction requiring protein synthesis in the rat hippocampus. *Proc Natl Acad Sci* **98**: 12251–12254.

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Learn. Mem. 2009, **16**:

Access the most recent version at doi:[10.1101/lm.1598209](https://doi.org/10.1101/lm.1598209)

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