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Where memory resides: Is there a rivalry between molecular and synaptic models of memory?

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Abstract

Recent proposals that the substrate of memory is molecular raise questions about where this molecular model stands in relation to the dominant synaptic model of memory. In this article, we address the perceived rivalry between these models and ask whether they can be integrated. We argue that addressing rivalry or integration requires delineating the explananda of synaptic and molecular models, as well as revisiting assumptions about how these models account for their explananda. The perceived rivalry between these models exemplifies epistemic costs that arise when we try to pit explanatory models as rivals or integrate them.

1. Introduction

In recent years, scientists (Langille and Gallistel 2020; Levin 2021; Gold and Glanzman 2021) have argued that the substrate of memory is molecular. Some proponents of this molecular model take it to challenge the dominant synaptic model of memory, according to which synaptic efficacy is the substrate of memory formation and storage (Poo et al. 2016). This rivalry might appear odd to philosophers. Is there a real challenge to this dominant model? Likewise, is there incompatibility, let alone a rivalry, between molecular and synaptic models, given philosophical commitments to physicalism, reductionism, or mechanistic explanation?

Rather than taking sides in this debate, we argue that assessing whether these models are rivals or can integrate requires that we first delineate what these models explain (the explanandum). Proponents of each model take the rivalry to reflect empirical and conceptual disagreements: what counts as memory, what it means for an organism to store information, and how memory tracks over an evolutionary scale. Further, we argue that relating these models requires determining how each model explains, and if integration is pursued, additional explananda must be explained. Together, these features of the perceived rivalry make this situation a valuable case

study of the epistemic costs that arise when we try to pit explanatory models as rivals or integrate them.

2. Two families of models and their critics

The synaptic model of memory refers to a widely accepted family of models of the mechanisms underlying memory in animal nervous systems. According to this model, changes in the strength of synaptic connections between neurons are the substrate of memory formation and storage. This model posits that the process of memory formation involves the conversion of newly acquired information into a stable format dependent on enduring synaptic changes. This process is thought to be mediated by mechanisms like long-term potentiation (LTP) and long-term depression (LTD), which alter the capacity of a presynaptic input to influence postsynaptic output.

The synaptic model is supported by a wealth of evidence from behavioral tasks, phylogenetic analysis, and neural circuits, establishing it as the dominant model of memory. Illustrating its widespread acceptance, Poo and colleagues state that "there is now general consensus that persistent modification of the synaptic strength via LTP and LTD of pre-existing connections represents a primary mechanism for the formation of memory" (2016, 1). This acceptance has led philosophers to take this model as a paradigm of neuroscientific explanation (Bickle 2003; Craver 2007).

Despite the popularity of the synaptic model, a growing group of researchers propose an alternative: the molecular model, in which intracellular molecular mechanisms are the substrate of memory. What are these molecular mechanisms? The options considered by the model's proponents include modifications of DNA, RNA, and chromatin methylation. Gallistel (2017) proposes that symbols are molecularly stored in neuronal RNA or DNA, basing his proposal on computational considerations. Namely, polynucleotides compactly store large amounts of information for long periods, and their coding properties are generally understood. Gold and Glanzman (2021) argue that long-term memory storage is mediated by changes in the genome. Jablonka (Bronfman et al. 2014) argues for the role of methylation in storing memories. DNA methylation can repress gene transcription, inhibiting the synthesis of proteins required for synaptic efficacy.

Molecular models have been posited, but why should we take them seriously in the face of the dominant synaptic model? Proponents of the molecular model cite a bundle of empirical findings that they use to criticize the synaptic model and legitimize the molecular one. The first criticism levied at the synaptic model is its inability to account for memory storage on the order of a human's life span. There is a worry that synaptic mechanisms do not occur at the timescales needed to both encode memory over long periods and store it for this time. Gershman notes that for encoding memory, "these mechanisms can extend the timescale of synaptic plasticity from milliseconds to seconds, but they cannot explain how learning is possible over longer timescales" (2023, 3). Further, he notes that for the storage of memory, "even over relatively short retention intervals (on the order of cellular time constants), information stored in persistent activity is quickly degraded due to noise" (ibid., 4). Likewise, Gold and Glanzman highlight that the stability of synaptic connections seems inadequate for the "permanent storage" of memory (2021, 111). Molecular models, by contrast, seem sufficiently stable for long-term storage.

The second criticism is that the synaptic model fails to account for memory phenomena where synaptic connections are unstable or absent. For instance, moths can learn to avoid odors as caterpillars. This learned response persists into adulthood, even though the insect's nervous system undergoes a radical transformation during metamorphosis (Levine 1984). Likewise, rodents can retain learned responses despite their dendritic spines undergoing measurable retraction during hibernation (Magariños et al. 2006). Proponents of the molecular model also argue that memory occurs in organisms that lack synapses. They cite empirical evidence that memory phenomena occur in "aneuralians" like single-celled organisms (Gershman et al. 2021) and slime molds (Sims and Kiverstein 2022).

Proponents of the molecular model also highlight cases where molecular interventions result in memory change, such as memory transfer. These studies involve (1) the training of a donor organism, (2) the transfer of molecular material (often RNA) from donor to a recipient, and (3) the demonstration of the learned behavior in this recipient. Though widely considered a failed research program (see Colaço 2018), this research has been revived, with new studies suggesting that transfer using molecules is possible. In one example, noncoding RNAs from trained Aplysia were injected into naïve Aplysia, leading the naïve animal to express the learned behavior (Bédécarrats et al. 2018). This research suggests that RNA molecules can serve as catalyzers for memory storage, constituting a case in which molecular but not synaptic interventions result in changes in memory behavior. However, memory transfer research is controversial for both empirical and conceptual reasons (see Colaço 2022), so embracing this empirical "support" requires clarifying what memory is and how we demonstrate it.

Prima facie, appealing to memory in simplistic organisms or even aneuralians might seem like shifting the goalposts. Molecular and synaptic models, however, do not disagree on the nature of memory phenomena under investigation. The concept of memory allows for broad definitions (ibid.; Najenson Forthcoming). Whether these organisms exhibit memory phenomena is a question about what we can demonstrate, but it is also a question of how we conceptualize memory. Nevertheless, despite the various ways one might conceptualize memory, molecular and synaptic models share an inferential space. By "inferential space," we mean the set of phenomena that studies investigate and to which the results of these studies apply. Both models agree that phenomena like habituation and Pavlovian conditioning are paradigmatically memory. These models generally agree on how to elicit and measure these phenomena. Thus, the fact that the molecular model applies to organisms outside the scope of the synaptic model does not in itself constitute a deviation from mutually accepted memory phenomena.

3. The evolutionary argument

Given the contested support for the molecular model, its proponents supplement their claims with an evolutionary argument, which begins with the idea that a molecular substrate that is present in aneuralians might be conserved in humans. Gershman and colleagues note:

> A cellular-level mechanism for storing acquired information with delayed behavioral consequences is exciting from an evolutionary perspective because it suggests that the mechanisms for memory storage in complex multicellular organisms may have been inherited from much simpler organisms, possibly even protozoa . . . . [If] evolution hit upon a way to implement learning in these organisms, it is natural to conjecture that such a mechanism would be conserved across phyla, given its computational and energetic advantages. (2021, 2)

If organisms akin to protozoa, evolutionary precursors of animals, possess mechanisms that underwrite memory phenomena, these mechanisms might be present in their evolutionary successors, including humans. This claim is supported by evidence that suggests that memory phenomena occur in protozoa, along with the speculation that memory functions are entrenched due to their conferral of evolutionary fitness.

Other molecular model proponents support this argument. Gold and Glanzman "believe it unlikely that successful mnemonic mechanisms that had been in place for possibly billions of years would have been jettisoned by the possessors of the first nervous systems" (2021, 110). Likewise, Lyon and colleagues claim that "the molecular infrastructure for capacities typically associated with brains long predated the evolution of neurons" (2020, 2). From this, they conclude that "organisms today are the beneficiaries of this inheritance" (ibid.).

The evolutionary argument suggests that neuralians have inherited something related to memory. However, it is unclear what a supporter of this argument commits to being conserved. Presumably, this argument amounts to more than the conservation of the molecular components of these mechanisms, where "conservation" captures the genetic information shared between neuralians and their ancestors, which codes for these components. Even if these components are inherited, this fact alone does not entail that they underwrite memory phenomena. Many molecular components are inherited but play functionally distinct roles in ancestors when compared to contemporary species (Plattner and Verkhratsky 2018).

If the evolutionary argument supports the molecular model, it must entail that neuralians have inherited a molecular memory mechanism whose original function, or a function relevantly like the original, is inherited. These molecular mechanisms underwrite memory phenomena in neuralians as they did in our ancient ancestors. Construed in this way, the evolutionary argument posits that the fact that molecular mechanisms underwrite memory in our ancestors provides reason for us to believe that these mechanisms underwrite memory in neuralians as well.

4. Is integration viable?

With an understanding of the molecular model and the motivations behind it, we ask whether we can integrate this model with the synaptic model. This case involves models, so we ask whether explanatory integration, or "the fusion of explanatory frameworks" (O'Malley and Soyer 2012, 61), is achievable. If we can integrate the models, then it is unfair for us to call them rivals: the models jointly explain memory phenomena.

The evolutionary argument leaves open the possibility for explanatory integration. It is consistent with several possibilities for how intracellular molecular mechanisms and synaptic mechanisms interrelate when underwriting memory phenomena. By implication, this argument alone does not suggest that there is any in principle incompatibility between molecular and synaptic models of memory.

We address three avenues for integrating the molecular and synaptic models. The first avenue is that these models stand in part-whole compositional relation to one another, suggesting that they can be integrated using levels. We show that this avenue is unsatisfactory in this case. We then shift to avenues that we argue have more promise. The second avenue is that these models represent mechanisms that underwrite memory phenomena at different temporal or spatial scales. The third is that these models represent mechanisms that underwrite different stages of memory encoding, storage, and retrieval.

4.1. Integration using levels

An influential view of explanatory integration involves an appeal to levels (Craver 2007; Potochnik and McGill 2012). If molecules and synapses belong to distinct levels, any apparent conflict between these models dissolves. Can these models be integrated by sorting the targets of the molecular and synaptic models into distinct levels of organization?

Adopting a level approach is central to reductionist and mechanistic explanatory views. According to reductionist accounts, memory phenomena are reducible to their molecular mechanisms (Bickle 2003). Bickle, for example, argues that memory consolidation reduces to the PKA-cAMP-CREB molecular pathway. On the standard mechanistic construal (Craver 2007), by contrast, mechanisms at the molecular level are a component of mechanisms at the synaptic level. For instance, NMDA receptors are components in neurons undergoing LTP. This assumption contrasts a strict division between the molecular and synaptic levels. If one adopts either of these views, then one might be skeptical of the idea that there is a genuine disagreement between molecular and synaptic models. Any perceived rivalry between the two is not an insurmountable problem, as these models might operate at different levels of organization.

However, the mechanisms proposed in the synaptic model do not reduce to those proposed in the molecular model. Proposals like RNA or DNA methylation are intended to supplant synapses as a relevant storage site rather than reclassify them as a higher-level phenomenon. Additionally, the entities described by the molecular model are not components of, for instance, LTP mechanisms that underwrite synaptic plasticity phenomena. For example, some proponents of the molecular model argue that components like NMDA receptors are not required to explain learning phenomena (Langille and Gallistel 2020). Consequently, the synaptic and molecular models are not candidates for explanatory integration according to either reductionist or mechanistic accounts of integration in terms of a level-relation.

Part-whole compositional integration does not speak to the alleged rivalry between the two models. While synaptic mechanisms are made of molecules, these mechanisms do not stand in a part-whole hierarchical relation to one another, and therefore accounts of integration using levels are not relevant for capturing how

integration might be achieved in this case. This compatibility must be something more than the idea that molecules compose the entities that underwrite synaptic activity. All interlocutors in this debate are operating within a biological framework, meaning that, at the bottom, they all agree that molecules and their activities compose some level of explanation for memory phenomena. An integrative model must capture how molecular mechanisms play a role in underwriting memory that cannot be captured using synaptic connections alone.

4.2. Integration using scales

One could defend the viability of integration by appealing to spatial and temporal scales. Indeed, scales have been a central way to make sense of integration in philosophy of science (Wimsatt 2007). Some philosophers (Eronen 2013; Di Frisco 2017) argue that temporal scales are necessary to explain the dynamical interaction between distinct subsystems, a crucial factor given that molecular and synaptic processes need to connect and transmit information. When we consider claims that the mechanisms of memory storage should be investigated at different scales, from brain regions to a cell's nucleus (Josselyn et al. 2015), this notion of integration gains plausibility.

Consider what memory needs to function properly. Any physical substrate that retains memories should allow information to rapidly meet behavioral demands. However, this substrate should allow for the long-term preservation of information. Because the physical processes supporting memory need varying time scales—they must simultaneously allow for fast and stable processes—the time scales associated with the molecular and synaptic models are critical in understanding how information is accessed and retained.

Yet, the time scales of synapses and molecules are both virtues and vices when considering their role in memory formation and storage. The biophysical properties of synapses allow for the fast transmission of information necessary for learning and remembering, but synaptic links are highly volatile and characterized by a high rate of spine turnover (Mongillo et al. 2017). The molecular model faces the opposite situation. DNA, for instance, can preserve information for centuries. However, the rate at which these molecules are modified is too slow to meet behavioral demands.

This "fast synapses, slow molecules" characterization need not be a problem. The fact that these phenomena envelop in different timelines brings prospects of integration because both models are required for an explanation of how memory operates. The fast and slow dynamics allow for the two models to complement each other. While synapses are required to explain the shorter time scales that characterize the transmission of information, molecules are required to explain how information is stabilized and maintained over longer time scales.

While appealing, this way of integrating these models brings new problems. For one, reading synaptic and molecular models as describing phenomena at distinct time scales implies that they represent different functions: Each substrate's time scale cannot support what a mnemonic system would require for it to function properly. To reflect this possibility, neuroscientists who aim to integrate these models have suggested that synaptic and molecular models explain different functional roles, such as information storage versus retrieval, representational versus computational

memory functions, or different levels of accessibility to stored memories (see Gershman 2023).

This issue relates to the evolutionary argument. Organisms appearing earlier in evolutionary history might not have faced the behavioral demands of fast information transmission met by more complex organisms (Gold and Glanzman 2021). As a result, proponents of the synaptic and molecular models might have to recognize that they are dealing with different targets and that their models may not be applicable to all organisms. These models may only be effective for studying the mnemonic processes of certain phylogenetic groups.

Consequently, adopting a scale strategy for integrating these models would result in each camp ceding some of their explanatory goals. If one adopts this strategy, synaptic and molecular models are either explanations of different functions of the same system or explanations of entirely different kinds of entities.

4.3. Integration using stages

Some proponents of the molecular model offer a path to explanatory integration where the respective models differently underwrite the encoding, storage, and retrieval (ESR) of memory. The two models thus explain different phenomena, but these phenomena are related, and each is required for memory.

According to Schacter (2007), researchers must account for memory processes using three stages. The first stage, encoding, involves acquiring information about an internal state of the system or an external state of the world. In the second stage, storage, the change to a system's internal structure is maintained in a latent state. This internal change corresponds to an engram, a state or process that preserves encoded information. In retrieval, retained information is recovered and may be expressed in behavior.

Some proponents disentangle our explanations for these stages. Gershman argues that synaptic structures might underwrite memory retrieval but not storage (2023, 2). This claim aligns with research on caterpillar metamorphosis and rodent hibernation. Disruption of synapses might result in an inability to retrieve memories, where the restatement of these connections restores this ability. In both cases, the stored information persists despite synaptic disruption. Gold and Glanzman concur, speculating that "synaptic plasticity may mediate the rapid, but relatively short-term ... retention of learned information," where if a new memory's "significance surpasses some threshold value, the memory is then transferred to the nuclei of neurons for permanent storage" (2021, 110). Synaptic activation would then facilitate the retrieval and expression of these stored memories. Both claims highlight the idea that some memory stages are underwritten by synaptic mechanisms, as the speed at which these phenomena occur matches the efficacy of this kind of signaling. Storage, by contrast, need not occur quickly, but it potentially must persist for a long period, especially when considering human long-term memory.

Here, proponents of the molecular model argue for explanatory integration. This integration is achieved by recognizing that memory involves multiple stages, each of which is better explained by one of the models. Thus, accounting for memory requires a "fusion of explanatory frameworks," but this is not proposed so that we can account

for different levels or scales. Rather, this proposal accounts for different stages that jointly underwrite memory phenomena.

The evolutionary argument supports this reasoning. For instance, Gold and Glanzman state that it is likely that "the ancient memory apparatus would have been integrated into the more modern mechanisms for storing information provided by neurons" (2021, 110). Molecular memory storage is potentially more stable and less metabolically costly than synaptic storage. Paired with the idea that humans have these molecular storage mechanisms from a strong reading of the evolutionary argument, proponents of the molecular model argue that this division of memory stages in humans—encoding and retrieval underwritten by synaptic mechanisms; storage underwritten by molecular mechanisms—explains the examples that they argue cannot be adequately explained using the synaptic model alone.

While accounting for memory in terms of stages underwritten by distinct mechanisms affords a form of explanatory integration, a rivalry between the molecular and synaptic models persists. This rivalry is not over memory; rather, it is over memory storage. Endorsing the molecular model comes with the implication that memory storage phenomena cannot be explained in terms of the synaptic model, despite any explanatory integration one can achieve when accounting more generally for the ESR framework. Proponents of the synaptic model can challenge this "integrative" model by arguing that it delegates synapses only to encoding and retrieval. Given that the evidence for this integrative model is limited at best, synaptic model proponents may be justified in pushing back against a molecular model of memory storage.

Further, integration using stages seems to be in tension with the evolutionary argument. According to this argument, aneuralians have the appropriate mechanisms for memory. However, if synapses play a role in encoding and retrieval, as integration using stages suggests, then we must ask how these stages occur in aneuralians that lack synapses. One might answer that synapses are only required for these stages in complex multicellular organisms, as encoding and retrieval require connections between perceptual, memory, and motor systems. Thus, a single-celled organism might be able to maintain these connections internally, without synapses. Nonetheless, an answer must be given for why, according to the evolutionary argument, humans have inherited molecular mechanisms for each stage, but, according to integration using stages, some stages are better explained synaptically.

4.4. The big picture of explanatory integration

Setting explanatory integration as the epistemic aim brings with it epistemic costs. Specifically, integrating synaptic and molecular models changes how we characterize both the explanandum and the explanans. Whether explaining different memory stages in terms of the synaptic or molecular model counts as integration or rivalry depends on what we take the explanandum to be. If these models operate at different time scales, they can be said to describe different functions. Synaptic models describe the rapid changes that occur during learning and remembering, while molecular models describe the long-term stabilization of storage. If the synaptic model is intended to explain all three memory stages, then arguing that a molecular model better explains one of them suggests a genuine rivalry between the two. Likewise, if

explanatory integration of models using stages is the aim, an additional explanandum is incurred. One must explain how encoding, storage, and retrieval relate. In other words, one now must explain how synapses and molecules causally interact.

Another way integration might change how we characterize the explanandum comes from motivations for the molecular model. The evolutionary argument, with its emphasis on aneuralians, highlights that these models track different explanatory targets. We might anticipate that the moment of integration between these models would mark a watershed in the evolutionary history of memory mechanisms. Finally, achieving integration by associating these models with different memory stages would strengthen the case that we are dealing with distinct memory phenomena, as the process can be decomposed into distinct mechanisms. In each case, endeavors by researchers to integrate suggest that we are dealing with distinct phenomena.

Distinguishing these avenues of integration also clarifies what evidence would support one avenue but not another. For instance, seeking double dissociations might generate evidence for stage integration. Previous research demonstrates that engrams can be activated when synaptic consolidation is inhibited (Ryan et al. 2015). Conducting a counterexperiment, where information storage is modified despite consistent synaptic changes, would challenge the assumption that synapses solely underwrite memory storage and allow further exploration into the specificity of synaptic manipulations. If double dissociation is not achievable, then stage integration is less promising. With this kind of evidence, we can determine when we can integrate models versus treating them as rivals, and what avenue of integration is most promising when we can.

Integration will not only change what we explain but also how we explain it. Combining phenomena at different time scales requires incorporating causal variables that are not currently accounted for in either model. For example, how do genetic and epigenetic information contribute to memory in behavioral time scales? Which causal factors ensure the productive continuity of these mechanisms when moving from learning to storing information? Answering these questions requires that we revisit the foundational assumptions regarding how these models account for their explananda.

5. Conclusion

While conclusive evidence remains forthcoming, available evidence and arguments for the molecular model demand that we consider how this model relates to the dominant synaptic model of memory. In this article, we have explored how these models might be rivals and how they might integrate. What is clear is whether integration is viable depends on what one takes the explanandum to be. Depending on how the explanandum is characterized, the molecular model might provide an explanatory grip that the synaptic model does not. More importantly, there is a real sense in which the two models are rivals, but there is equally a real sense in which the two can integrate into a single explanation.

Together, we argue that exploring whether explanatory models integrate requires delineating both explanandum and explanans, and it requires considering the epistemic costs that arise when relating these explananda and explanantia. For this reason, addressing the perceived rivalry between molecular and synaptic models

requires first answering two more basic questions. Which phenomena do these models purport to explain? And which phenomena should a model of memory explain? These two questions indicate that determining whether synaptic and molecular models are rivals or can integrate requires a reexamination of their explanatory aims and the possibility of revising some of their basic assumptions. In short, something's got to give.

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