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Invited review

Taking memory beyond the brain: Does tobacco dream of the mosaic virus?

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ABSTRACT

Memory is typically defined through animal behavior, but this point of view may limit our understanding of many related processes in diverse biological systems. The concept of memory can be broadened meaningfully by considering it from the perspective of time and homeostasis. On the one hand, this theoretical angle can help explain and predict the behavior of various non-neural systems such as insulin-secreting cells, plants, or signaling cascades. On the other hand, it emphasizes biological continuity between neural phenomena, such as synaptic plasticity, and their evolutionary precursors in cellular signaling.

1. Introduction

While not a disputed fact in the scientific community, it comes as a surprise to many non-scientists that simple animals like the marine mollusk *Aplysia* "have memory." It is worth contemplating this reaction: what specifically seems unusual about *Aplysia*'s memory from an everyday perspective? It does not surprise anyone that sea hares remember to withdraw their body parts faster after painful stimulation – that, in fact, is very intuitive. What would have been surprising is if *Aplysia* had *human* memories, and this is exactly what many people are trying to imagine. Their surprise is therefore an expression of a self-centric metaphor for memory: *memory is what I remember*.

The scientific metaphor for memory, by contrast, is grounded in behavioral science. Essentially, memory is what remains after experience to change future behavior (Eisenstein, 1997; Kukushkin & Carew, 2017; Schacter, Addis, & Buckner, 2007; Skinner, 1950). Science thus accepts conceptual equivalence between *Aplysia* and human memory at the level of defining what memory is. A non-scientist may be found unconvinced by this expanded definition of memory, but there are strong arguments supporting the behavioral metaphor: namely, the deep molecular-level similarities between learning in *Aplysia* and mammals, and the evolutionary homology of many components of their nervous systems (Kandel, 2013). From a modern scientific standpoint, a shared metaphor for human and *Aplysia* memory is justified by the existence of a shared *mechanism*.

It may be informative to take another conceptual step in the same direction: a more abstract idea of memory, detached from both the subjective self, and from animal behavior. But what is memory if not those two things? Any experiment involving memory involves behavior: whether a human is tested for memorization in an fMRI scanner, or a mouse is conditioned to fear the sight of an electrified arena, the fact that physiological changes in their brain correspond to memories can only be established through movement: a keystroke made by the human, freezing by the mouse. Subjectively it is obvious that memory should extend beyond movement. Yet any attempt to externalize this information will involve movement. Is the scientific concept of memory then meaningless without behavior?

2. Homeostasis and temporal hierarchy

We have recently advanced a theory of "temporal hierarchy", which uses time and homeostasis to define memory as a biological phenomenon (Kukushkin & Carew, 2017). Homeostasis refers to the tendency toward a stable state in a system, such as an organism, cell, or even an ensemble of molecules. By definition, if a homeostatic system is disturbed, it *eventually* returns to equilibrium. Such disturbance, triggered by a preceding stimulus, can be viewed as a bell-shaped curve of the state-time plot centered at homeostasis (Fig. 1A). In our theoretical account (Kukushkin & Carew, 2017), we have termed these events "time windows". A "time window" thus refers to the temporal properties of a homeostatic disturbance: when does the change start, when does it end, how rapidly it builds and decays. It is dependent on the onset of stimulus, but it can be maintained for a longer time before it decays – hence the critical word, "eventually", that unifies return to homeostasis with memory.

Even after the initial stimulus decays, a disturbance in homeostasis may persist, such as in the case of a protein kinase that remains activated even when neurotransmitter that triggered its activation is washed away. A disturbance in homeostasis can modify a response to a new stimulus (Fig. 1A), but also cause additional disturbances in

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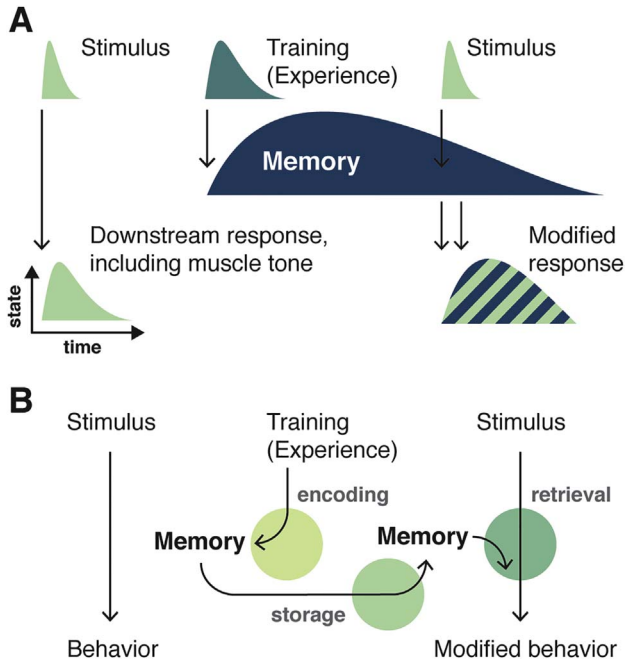

Fig. 1. Conceptualizing memory. (A) Memory can be defined as a homeostatic disturbance, or "time window", A perturbation of the system persists after the cessation of training that triggered it, constituting a memory. Upon coincidence with another stimulus, the "time window" of memory produces emergent downstream "time windows" that include, but are not limited to, modified behavioral responses. (B) Memory is typically defined through animal behavior, i.e. movement of the organism in response to a given stimulus. After training, the response changes, resulting in modified behavior. Training is thus thought to lead to the encoding of a behavior-modifying memory, which is stored for various periods of time and retrieved during stimulation.

homeostasis. These will also coincide with new and ongoing disturbances, forming a hierarchy of increasing scale and duration. For example, coincident "time windows" of elevated intracellular calcium produce a more persistent "time window" of activated CaMKII, which in some cases can produce an even more persistent "time window" of altered gene expression and epigenetic change. We have provided many examples of such hierarchy of "time windows" and proposed that it is the vast repertoire of homeostatic variables ranging in their time constants from momentary to lifelong that allows the organism to simultaneously represent various timescales of past experience (Kukushkin & Carew, 2017).

I argue here that our theory might also provide a new meaning for the concept of memory, free from the constraint of animal behavior. In a traditional stimulus-response behavioral framework, memory is viewed as a discrete object or state that modifies behavior, i.e. movement in response to a stimulus (Fig. 1B). The encoding, storage, and retrieval of memory are seen as independent phenomena. From the perspective that we have advocated (Kukushkin & Carew, 2017), memory should be seen as a disturbance in homeostasis (Fig. 1A). Rather than anchoring memory in behavioral patterns, memory can be measured against the system's basal state with much broader applicability (Fig. 1). Any system can be said to have memory as long as its boundaries are clearly defined, and as long as influences outside the boundary lead to deviations from homeostasis inside the boundary.

Could there be memory without homeostasis? A memory that lasts a lifetime by itself is not necessarily non-homeostatic, since the time it takes to decay may well exceed the lifetime of the individual. A permanent change in a system that alters its behavior, such as a severed limb or a genomic rearrangement in response to a mutagen, could in some sense be considered memory, but it would fall outside the homeostatic definition. An interesting case to contemplate is immunological memory. During their maturation, B- and T-lymphocytes undergo a random and permanent reassortment of gene fragments, known as V(D)J recombination, that greatly expands the diversity of antibodies and T-cell receptors (Schatz, 2004). Mature lymphocytes that have encountered and responded to an antigen proliferate and become long-lived memory cells, which allows for a faster immune response in the future (Gourley, Wherry, Masopust, & Ahmed, 2004). The change in DNA is not a homeostatic change. But useful immunological information is not encoded in the DNA at the cellular level, but rather in a specific pattern of altered cellular states at the systemic level, and the permanent changes in DNA only supply variables that can be used by the immune system for representing this information. It is certainly a possibility, however, that some information-bearing changes in living systems are truly permanent, which establishes the falsifiability of our theory of temporal hierarchy (Kukushkin & Carew, 2017). The information capacity of such permanent changes would be severely restricted since the change can only happen once, but is not inconceivable that a brain, for example, may have a large number of "disposable" modules that accumulate experiential information non-homeostatically, or permanently store physical particles sampled from the environment. I theorize, however, that the vast majority of behavioral effects of memory are consistent with the proposed homeostatic definition.

The behavioral metaphor for memory defines it through past sensory sources of future motor behavior. The homeostatic metaphor allows for a broader outlook. The internal hierarchy of "time windows" in a nervous system, its "repertoire" or homeostatic variables of many scales, is extraordinarily large (Kukushkin & Carew, 2017), and animals' capacity for abstraction and memory is therefore unprecedented. Yet from the standpoint of time and homeostasis, the brain is not the only biological system capable of memory, and behavior, as expressed in the movement of an organism, is not the only consequence of memorizing. Just as the self-centric metaphor on memory omits from consideration an immense number of clearly related processes in diverse animals, the behavioral metaphor may restrict understanding of a much wider biological phenomenon.

3. Memory as metaphor

The new metaphor of memory will only be useful inasmuch as it predicts and explains biological mechanisms. It could be reasonably applied, for example, to the regulation of insulin production. Secretion of insulin by pancreatic β-cells is regulated similarly to the secretion of neurotransmitters by neurons. In other words, plasticity of insulin production strongly resembles synaptic plasticity (Hinke, Hellemans, & Schuit, 2004). For example, short-term regulation of the exocytosis machinery by Ca^{2+}- and cAMP/PKA-dependent mechanisms is a hallmark of both processes (Ammala, Ashcroft, & Rorsman, 1993; Hatakeyama, Kishimoto, Nemoto, Kasai, & Takahashi, 2006; Kandel, 2013; Kandel & Schwartz, 1982; Moens et al., 1996; Takahashi et al., 1999). Furthermore, both cases involve activity-dependent increases in the synthesis of specific proteins (Graber et al., 2013; Havik, Rokke, Bardsen, Davanger, & Bramham, 2003; Lee, Lee, & Kaang, 2015; Permutt, 1974; Richter, 2015; Welsh, Nielsen, MacKrell, & Steiner, 1985; Welsh, Scherberg, Gilmore, & Steiner, 1986). Both can be controlled specifically by the coincidence of multiple inputs. For example, just as the action of neurotransmitters on neurons depends on other modulatory factors, in β-cells, the effects of glucose on insulin release depend on the presence of GI hormones incretins, acting through a cAMP-dependent mechanism typical of several neuromodulators (Hinke et al., 2004; Jia, Brown, Ma, Pederson, & McIntosh, 1995; Moens et al., 1996). Incretins can have short-term and long-term effects, the latter of which can involve enhanced transcription of genes including preproinsulin (Hinke et al., 2004). The control of gene transcription can be exerted via pre-existing transcription factors such as CREB (Jansson et al., 2008), and additionally by the production new transcription factors such as C/EBP (MacDougald, Cornelius, Liu, &