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Locating the engram: Should we look for plastic synapses or information-storing molecules?

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ABSTRACT

Karl Lashley began the search for the engram nearly seventy years ago. In the time since, much has been learned but divisions remain. In the contemporary neurobiology of learning and memory, two profoundly different conceptions contend: the associative/connectionist (A/C) conception and the computational/representational (C/R) conception. Both theories ground themselves in the belief that the mind is emergent from the properties and processes of a material brain. Where these theories differ is in their description of what the neurobiological substrate of memory is and where it resides in the brain. The A/C theory of memory emphasizes the need to distinguish memory cognition from the memory engram and postulates that memory cognition is an emergent property of patterned neural activity routed through engram circuits. In this model, learning re-organizes synapse association strengths to guide future neural activity. Importantly, the version of the A/C theory advocated for here contends that synaptic change is not symbolic and, despite normally being necessary, is not sufficient for memory cognition. Instead, synaptic change provides the capacity and a blueprint for reinstating symbolic patterns of neural activity. Unlike the A/C theory, which posits that memory emerges at the circuit level, the C/R conception suggests that memory manifests at the level of intracellular molecular structures. In C/R theory, these intracellular structures are information-conveying and have properties compatible with the view that brain computation utilizes a read/write memory, functionally similar to that in a computer. New research has energized both sides and highlighted the need for new discussion. Both theories, the key questions each theory has yet to resolve and several potential paths forward are presented here.

1. Introduction

In the contemporary neurobiology of learning and memory, two profoundly different conceptions contend: the associative/connectionist conception and the computational/representational conception; we will refer to these as the A/C perspective and the C/R perspective, respectively. These conceptions share a commitment to the hypothesis that a purely material account of mental processes is in principle possible. That is, both schools of thought take it for granted that the brain is the physical realization of the mind and that the brain is a machine, a purely physical entity. The two schools differ in their assumptions about the level of neurobiological structure at which we should search for the material realization of cognitive processes. The A/C school assumes that we should look at the level of neural circuitry; hence the term connectionism. The C/R school suggests that we should look intracellularly, at molecular level structures, which are known to be capable of storing information, in Shannon's (1948) sense of the term 'information', which is the only scientific sense. Thus, in the decades since Lashley's (1950) lesion studies the search for the engram has moved from gross anatomy to cellular and molecular structures.

An A/C account of memory is built on a three-level hierarchy:

(i) Information: The informational endowment of a neuron is a property of the neuron's inputs and activity and is not symbolically-dependent on cellular change
(ii) Combination of information: Learning combines information by using cellular change to form associations between active neurons
(iii) Activation of learned combinations to influence behavior: Associations enable information conveying patterns in brain activity to be reinstated by cues

Conversely, a C/R account of memory assumes:

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(i) Information as defined by Shannon is stored in molecularly realized number-like symbols that encode quantitative facts gleaned from experience
(ii) Learning is mediated by computational operations on those symbols, operations that generate new symbols that encode computationally derived facts
(iii) Innate strategies read facts stored in memory to inform behavior

2. Basics of associative/connectionist (A/C) and computational/representational (C/R) perspectives

In the A/C perspective, learning is the formation of associations and memory is the associations that have been formed. Thus, learning and memory are conceptually inseparable, and the core learning mechanism is the association-forming mechanism. Associations forged during learning control the path and pattern of activity in the brain and allow for the transformation of inputs to memory and behavior.

It is almost universally thought that the neurobiological mechanism (s) that realize changes in associative strengths (also called connection weights) is/are those that change synaptic conductances. A synaptic conductance is the magnitude and/or duration of change in post-synaptic membrane potential produced by a presynaptic action potential. Because there is variability in these mechanisms and the conditions that govern their operation we will refer to them generically as plastic synapse mechanisms; Hebbian synapses are a kind of plastic synapse (Hebb, 1949; Levy & Steward, 1979).

A fact of crucial importance is that plastic synapses are not symbols. The weights in a connectionist network are not thought to refer to quantities out there in the world. In connectionists models, a plastic synapse is represented by a single number, a connection weight, denoted by w. The sign $(+/-)$ of w determines whether the effect of a presynaptic action potential is to transiently decrease $(+)$ or increase $(-)$ the polarization of the post-synaptic membrane, while its absolute value determines the magnitude and/or the duration of the transient change in membrane polarization. Connectionist models sometimes assume that synaptic inputs can be represented by a single number (the population rate code assumption, see Gerstner, Kistler, Naud, & Paninski, 2014). This number seen by postsynaptic processes is wr, the product of the input (r for rate) and the conductance (w for weight).

The A/C perspective is rooted historically in empiricist philosophy, connectionist modeling, and systems neuroscience (McClelland, 1989). In its contemporary form, this view contends that the brain does not process information in the way a computer computes, because it does not have a read/write memory (Koch, 1999; McClelland, Rumelhart, & Hinton, 1986). A read/write memory is a memory into which number-like symbols generated in the course of a machine's computations are written and from which they are read when needed in subsequent computations. It is a foundational component of computing machines (Turing, 1947, 2004; von Neumann, 1945, 2011). The A/C perspective adheres to the notion that a serious psychological theory should be neurobiologically plausible. That is, it should honor the materialist commitment by including or even resting on some neurobiological postulates that are broadly in line with what contemporary systems neuroscience understands about how the brain works. An example of such a postulation is that concepts consist of the activation of cell assemblies, created by the effects of learning on Hebbian synapses. Activation of associations between cell assemblies forms phase sequences, which are thought to underlie complex cognition (e.g. perception and thought) and behavior (Hebb, 1949).

The computational theory of mind, as understood by many cognitive scientists, is that the mind/brain computes in roughly the same sense as a computer does (Fodor, 1975; Gallistel & King, 2010; McCulloch & Pitts, 1943; Newell, Shaw, & Simon, 1958; Putnam, 1975; Sloman, 1978; Turing, 1950; von Neumann, 1958). This C/R version of the computational theory of mind is rooted historically in computer science, mathematics, information theory, cognitive science, linguistics, rationalist philosophy, cognitive psychology (particularly psychophysics), ethology and, more recently, in molecular biology. This school of thought is skeptical about the relevance of contemporary systems neuroscience to understanding how the brain works, because contemporary neuroscience does not have a theory of memory as memory is understood in computer science[2]. In the C/R view, it is more important for a psychological theory to comport with the basics of computer science than for it to comport with what neuroscientists maintain about how brains learn and remember. Computer science knowledge has been used to construct computing machines with extremely widespread practical applications. There are currently several efforts to build computing machines that rest to varying degrees on contemporary neuroscience (Furber, 2016), but these machines are still under development; they have yet to prove their worth. They have yet to demonstrate how well they perform when they are not coupled to conventional memories that provide their inputs and store their outputs.

While the A/C approach says memory relies on the formation and activation of associations in neural circuits, the C/R view proposes that memories reside in information-conveying and processing intracellular molecular structures. These structures are more than a trillion times smaller than circuit level structures, and have many other properties of interest to those who believe that computations in brains depend in a fundamental way on a read/write memory just as do computations in computers (Gallistel, 2017b). Computation is the composition of functions (feeding the output of one computation to the input of another computation). The read/write memory in a computing machine makes this unbounded composition possible: the output of any operation is written to memory, from which it may be retrieved as input to any other operation. The retrieval may occur at any point in the indefinite future and under circumstances utterly unrelated to those that initiated the first computation. Thus, the read/write memory liberates computation from the tyranny of time and circumstance.

In short, the A/C perspective maintains that current neuroscience knowledge trumps computer science knowledge when it comes to theorizing about how brains compute, while the C/R perspective holds that current computer science knowledge trumps neuroscience knowledge.

3. The associative/connectionist theory of memory

3.1. Separating the engram from memory cognition

The A/C view contends that the brain's ability to learn depends on the formation of associations. In his seminal work, Hebb (1949) described the mechanisms of cellular plasticity through which associations form. Hebb hypothesized that coupled neuronal activity causes cellular changes that strengthen associations between co-active neurons. Strengthened associations increase the likelihood that neurons co-activate again, just as they did during learning (Hebb, 1949). The cellular change deposited with learning is defined as the engram (Poo et al., 2016). The engram is embodied by engram cells and reroutes activity through what becomes the engram circuit; this organization is shown in Fig. 1.

The memory engram must be distinguished from the phenomenological experience of memory, herein termed memory cognition.

[2] Koch (1997) writes: "And what of memory? It is everywhere (but can't be randomly accessed). It resides in the concentration of free calcium in dendrites and the cell body; in the presynaptic terminal; in the density and exact voltage-dependency of the various ionic conductances; and in the density and configuration of specific proteins in the postsynaptic terminals." By contrast, in computer science, memory is where facts (distances, durations, directions, numbers, probabilities, images, etc) are stored so that they may be retrieved in the indefinite future for use in computations and for use by the strategies that implement machine output (behavior). This is the conception of memory embraced by the C/R view.

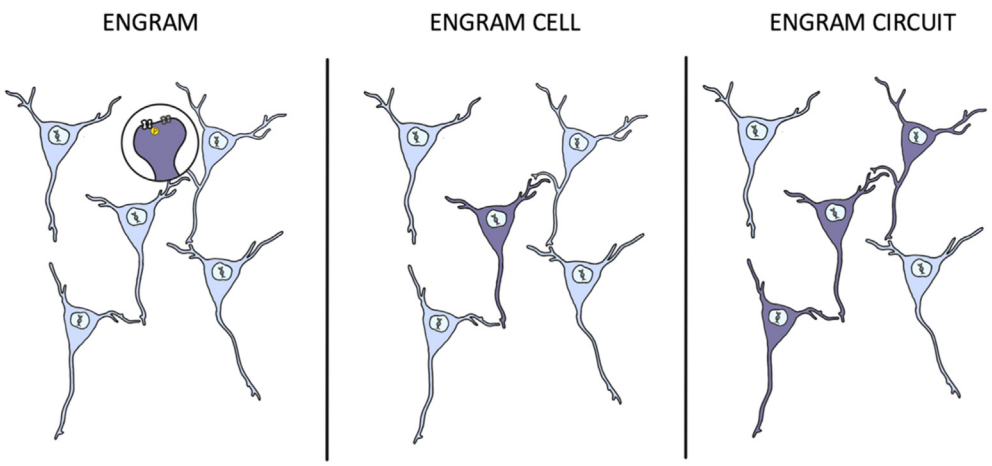

Fig. 1. Neurobiological organization of memory in the brain. Left: A partial trace of learning in form of cellular change (shown as new receptors (grey) and receptor phosphorylation (yellow 'P' circle)) at a synaptic process (shown magnified); engram. Middle: The neuron containing this part of the trace of learning or engram; engram cell. Right: The ensemble of engram cells associated during learning; engram circuit. Each organizational level is labeled above and shown in dark purple. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Memory cognition is an emergent property of neural activity and functions to guide behavior. Crucially, in an A/C model neural activity is symbolic and synapse change stores information only indirectly, as commands for the path and pattern of neural activity; this is in contrast to theories that contend that synapses contain information (Grant, 2019; Zhu et al., 2018). Thus, engram formation is the neurobiological correlate of learning and determines between what neurons and in what patterns neural activity moves and this guided activity is the neurobiological correlate of memory cognition.

3.1.1. Memory cognition as patterned activity in engram circuits.

The emergence of memory from patterned brain activity can be understood through principles of neuronal information processing. A neuron sees only the information its input sees, and this information is only realized via connections to other neurons and ultimately to output centers that generate behavior or mental experience (Buzsáki, 2010). In this way, single neurons represent variable units of information (e.g. an oriented bar of light in primary visual cortex (Hubel & Wiesel, 1959), a tonal frequency in primary auditory cortex (A1) (Recanzone, Guard, & Phan, 2000) or a place in the specialized cells of the medial temporal lobe (Aronov, Nevers, & Tank, 2017)). This notion is supported by experimental observations and theoretical conceptions, this is discussed below.

A classical study from Roe, Pallas, Kwon, and Sur (1992) demonstrated that when visual signals were made to ultimately end up in A1 the information represented by A1 neurons became visual. Similarly, amputations cause brain areas that got their inputs from the lost tissue to become reallocated to process information also processed by nearby areas (Elbert et al., 1997), presumably because these nearby areas come to provide active inputs (Florence, Taub, & Kaas, 1998). Finally, single cells in the medial temporal lobe that represent place can also represent time (Salz et al., 2016) or sound information (Aronov et al., 2017), indicating that what information a cell can see is not fixed.

While experimental observations support the concept that a neuron sees only what its input sees, the idea that this information requires connections to output centers for its realization fits with theoretical notions for how memory works in the brain. While the hippocampus is inextricably linked to memory, hippocampal indexing theory (Teyler & DiScenna, 1986; Teyler & Rudy, 2007) suggests that the neurons of the hippocampus do not have the capacity to represent memories directly. Instead, this theory indicates that neurons in the hippocampus provide an index of the cortical neurons active during learning. Reactivation of these cortical neurons is thought to be what triggers memory sensations (Yassa & Reagh, 2013).

If a neurons informational content is a product of its inputs, then this information should not be of uniform complexity throughout the brain. Consistent with this, the information that a neuron represents often changes across information processing networks as consequence of circuit convergence and lateral inhibition (e.g. retina (points of light), primary visual cortex (bars of light), inferior temporal cortex (objects) (Leibovic, 1990; Ungerleider & Bell, 2011)). This hierarchical organization allows the activity of single or small ensembles of neurons to represent a range of information, from simple quantities (Hubel & Wiesel, 1959) to complex concepts (Quiroga, 2012). Thus, independent lines of experimentation and theory backup the notion that the information a neuron is privy to is at least partially determined by the inputs to said neuron.

Inputs interact with connection weights to shape single neuron and ensemble activation patterns and various qualities of this activity are thought to link to stimulus qualities and be symbols of memory cognition. The neural code appears to be two tiered, with stimulus semantics being captured by both the ensemble of cells active and by properties of the activity within these cells. Intra- and inter-neuronal spike dynamics are complex, offering many dimensions and grades of variation for symbolizing information. These include the timing and shape of individual spikes (Juusola, Robinson, & de Polavieja, 2007; Panzeri, Petersen, Schultz, Lebedev, & Diamond, 2001), the first spike onset latency (Chase & Young, 2007), inter-spike interval (Lundstrom & Fairhall, 2006), burst coding (Zeldenrust, Wadman, & Englitz, 2018) more generally and spike count (Romo & Salinas, 2003) as well as noise correlation (Franke et al., 2016), population (Panzeri, Macke, Gross, & Kayser, 2015), oscillation phase (Watrous, Deuker, Fell, & Axmacher, 2015) and rate coding (Groh, 2001). In comparison, the order of information may be represented in the temporal organization of spike and ensemble dynamics (e.g. in oscillations and the order of cell assembly activations, termed phase sequences (Hebb, 1949; Buzsáki, 2010; Lisman & Jensen, 2013)).

The hierarchy of information representation in the brain can be understood using Buzsáki's idea of neural letters, words and sentences (Buzsáki, 2010). Neurons often represent limited units of information and thus can be thought of as "neural letters", these are the basic components of a language and are on their own relatively uninformative. An ensemble of neurons, firing in a patterned manner forms Hebbian cell assemblies and organizes these neural letters into "neural words". Words, like the individual concepts thought to be represented by cell assemblies, have meaning but are still relatively low in informational content in isolation. It is when many cell assemblies associate to form more elaborate ensembles or phase sequences that neural words join into "neural sentences" and the emergent phenomena of memory sequences, ongoing perception and monologues of thought come to be; the characterization presented here is simplified and Buzsáki (2010) indicates groups of neurons and sequences of these groups best characterize neural letters and words/sentences. Consistent with assemblies of neurons associating to mediate complex phenomena (Buzsáki, 2010; Hebb, 1949), Ghandour et al. (2019) find multiple smaller assemblies make up the broader ensemble of neurons involved

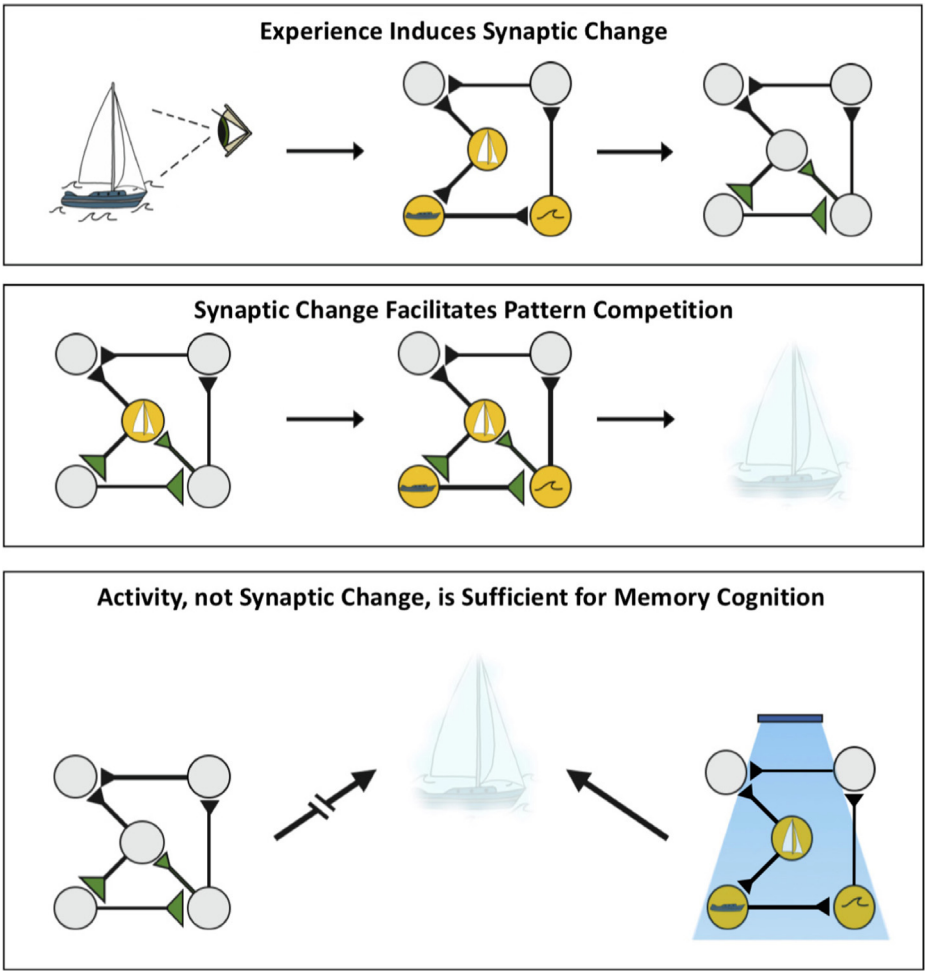

Fig. 2. The A/C model of memory. Top panel: Sensory stimulation (left) activates an ensemble of neurons and the activity of each neuron represents a stimulus element (middle). Activity in ensemble neurons causes strengthening (shown larger and in green) and growth (entire neurite shown in green) of synapses between ensemble neurons (right). Middle panel: synaptic change allows stimulus elements (left) to pattern complete (middle) and produce memory cognition (right; shown faded and in haze). Bottom panel: synaptic change (left) is not symbolic and does not, independent of activation, cause memory cognition (middle) while optogenetic activation of ensemble neurons (right), independent of non-structural synaptic change, may. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

in a memory.

To summarize in terms perhaps most familiar to the computer scientists, the brain uses patterned activity in the form of guided, electrical reverberations as software programs and biological networks (engram circuits), built up from single neurons (engram cells) and the cellular modifications at their synapses (engrams), as the hardware on which the software is run. The physical substrate provides a medium for and guides, via synapse association strengths, the path and pattern of activity, from which memory cognition arises.

3.1.2. Experimental evidence for the necessity of synaptic change and neuronal activation for memory cognition

Learning changes synapses (Whitlock, Heynen, Shuler, & Bear, 2006), and experimental intervention at any level of the engram system alters memory performance. At the engram level, Navabi et al. (2014) demonstrate that synapse strengthening (long-term potentiation (LTP)) or weakening (long-term depression (LTD)) can bi-directionally control memory performance. These researchers used low and high frequency optogenetic stimulation patterns to reverse, re-produce, reverse again or re-produce again plasticity associated with learning. As a result, memories forged by learning or reinstated by LTP were weakened by LTD of regional synapses. Building on these findings, Kim and Cho (2017) demonstrate learned behavior is lost when synapse weakening is limited to those connections engaged by training. Similarly, Hayashi-Takagi et al. (2015) observe that weakening only synaptic spines that formed with learning impairs later performance on the learned task. These findings directly implicate synapse change in memory.

At the engram cell level, only a fraction of neurons produce synapse change during learning (Butler et al., 2018) and it is these neurons that are thought to control memory (Choi et al., 2018). What neurons come to underpin memory is determined by variations in cell excitability (Zhou et al., 2009); increases in excitability preference which neurons underpin memory while restricting excitability may hinder such involvement (Park et al., 2016; Yiu et al., 2014; Zhou et al., 2009). This variation may shape the cell assemblies and phase sequences underpinning memory by modulating the activation of engram forming pathways (Lisman, Cooper, Sehgal, & Silva, 2018; Murphy et al., 2004; Viosca, Lopez de Armentia, Jancic, & Barco, 2009). Taken together, these results suggest the neurons that come to embody a memory are those that produce synaptic change.

At the engram circuit level, light stimulation of hippocampal or retrosplenial neurons modified to express light sensitive channels in a learning-dependent manner causes evidence of fear memory recall (Cowansage et al., 2014; Lacagnina et al., 2019; Liu et al., 2012). When these manipulations are reversed such that putative hippocampal engram cells have their activity repressed, memory recall is less evident (Denny et al., 2014; Tanaka et al., 2014). These findings suggest that neuronal activation may be the critical factor for memory cognition. In line with this interpretation, Ryan, Roy, Pignatelli, Arons, and Tonegawa (2015) demonstrate that later, artificial activation of neurons that were active during experience can cause adaptive behavior indicative of memory recall even in the absence of the synaptic change necessary for natural memory recall; anisomycin was used in these experiments to suppress synapse changes and weaken learning. The authors interpret these results as suggesting that it is structural connectivity, and not synapse change, that is most important for memory (Ryan et al., 2015).

If synapse changes are normally required to allow pattern

completion through an engram circuit from a partial stimulus, then under the experimental conditions described above (Ryan et al., 2015) either: (i) All engram neurons are activated by light and synaptic changes are not necessary as memory cognition is an emergent property of neural activity or; (ii) light stimulation is stronger than natural cues to the extent that light activation of even part of the engram ensemble causes sufficient activity to spread and reactivate the entire engram circuit or pathways that cause behavior, without a need for facilitation by synaptic changes. Research on monocular deprivation supports the latter claim and suggests that remnant structural change may cause memory to be available but less accessible in the absence of further synaptic change (Hofer, Mrsic-Flogel, Bonhoeffer, & Hubener, 2009). Reduced accessibility may result from weak synapses, which lack the biochemical machinery to meaningfully activate under natural conditions (Isaac, Nicoll, & Malenka, 1995), or from non-synaptic properties (Pignatelli et al., 2019). In Ryan et al. (2015) experiments, while anisomycin caused weak synapses light stimulation bypassed this restraint, appearing to make an otherwise relatively inaccessible memory accessible; a schematic of the A/C model is included as Fig. 2.

Opposite to the findings discussed above, Abdou et al. (2018) found that following LTD, light activation of engram cell synapses was insufficient to produce evidence of fear memory recall. LTD can cause the removal of spines (Sanders, Cowansage, Baumgartel, & Mayford, 2012) and the loss of these synaptic structures may breakdown the engram circuit. Even strong light stimulation cannot drive activity across connections that do not exist and for this reason would be incapable of reinstating the neuronal activation necessary for memory expression. LTD stimulation can also cause the excessive removal of AMPA receptors from the cell membrane (Ma et al., 2016), perhaps rendering synapses unable to produce signals necessary for the expression of memory or behavior (Abdou et al., 2018).

In the experiments carried out by Abdou et al. (2018), two fear memories recruited many of the same cells but were distinguishable by their synaptic associations. Despite using similar cells, directed synapse weakening led to the disruption of only one of the two memories. In the A/C model, information is shaped by a cells inputs and this offers an explanation for why similar memories use many of the same cells. When considering memory cognition, the semantics of a memory are thought to be represented in part by the neurons recruited to an engram circuit while memory uniqueness manifests in the pattern these cells are activated in and in the firing of each engram cell. The order, pattern and intensity with which an engram cell is recruited to a reactivating engram circuit is shaped by synapse properties. In sum, recent experiments concerning the neurobiology of memory support the A/C model and suggest that synapse change may permit neuronal activations necessary to express learned behavior.

3.1.3. Patterned activity candidate

A neurons reaction to a stimulus is short-lived. To line up with behavioral timescales and activate synapse strengthening pathways, neuron activity patterns need to reverberate (Hebb, 1949; Johnson, LeDoux, & Doyere, 2009). To do this, the brain appears to use attractors (Amit, 1995). In neural networks, attractors may manifest as Hebbian cell assemblies and phase sequences (Buzsáki, 2019; Hecht-Nielsen & McKenna, 2012; Lansner, Fransen, & Sandberg, 2003). Attractor dynamics in cell assemblies and phase sequences provide neurobiologically and mathematically sound manifestations of Hebbian "reverberatory activity" and "alternating reverberations" (Hebb, 1949).

In addition to offering a description for how neural activity can be guided into attractors, Hebbian theory may also provide a neurobiological mechanism for architecting circuits that can reinstate these attractors. During learning, new attractors are established in the brains networks, presumably by activating engram forming pathways (Lundqvist, Herman, & Lansner, 2013; Miller, 2016). Once formed, engrams reside, at least partially, in modified synapses, which when cued pattern complete towards activity patterns that are similar to those present during learning (Horner, Bisby, Bush, Lin, & Burgess, 2015; Jackson, 2013). Similar to neurobiological ensembles, attractors can be reinstated by an incomplete stimulus (Carrillo-Reid, Yang, Bando, Peterka, & Yuste, 2016; Tang et al., 2018). Thus, the engram may serve as an increased ease and likelihood of moving the brain's activity towards an attractor, which once in, is memory cognition.

3.2. An A/C theory of memory is compatible with observations in psychology and cognitive neuroscience research

Memory cognition differs qualitatively from natural, live experience. Known properties of synaptic plasticity and transduction can offer several, notional explanations for the 'haziness' of recalled memory, relative to live experience; the term haziness is used here to describe the psychologically perceived lack of tessellation, vividness and veridicality in retrieved memory. (i) Cognition is at least partially digital (e.g. patterns of all-or-none spikes) (McCulloch & Pitts, 1943) while plasticity uses non-binary mechanisms (Enoki, Hu, Hamilton, & Fine, 2009). Though other research indicates some cognition is analog and synapse strength changes digitally (O'Connor, Wittenberg, & Wang, 2005; O'Reilly, 2006; Petersen, Malenka, Nicoll, & Hopfield, 1998). In any case, the transformation of complex spike codes into, out of and back into synaptic change during memory encoding, recall and reconsolidation may cause information to be lost or distorted. (ii) During natural experience, psychological activity may be an amalgam of all the different activity taking place in the brain at a given moment. During memory recall, cognitive resources are busy tending to stimuli in the environment and peripheral thoughts. Accordingly, attempts to recruit similar neural machinery weakens memory (Edmiston & Lupyan, 2017). This may be because the firing rate or pattern of assembly cells in memory recall is different than during the original experience; separate evidence suggests recall engages a subset of the neurons active during learning (Denny et al., 2014). Firing rate could provide a means of representing information along degrees of vividness, ranging from strong firing and high vividness during experience to weak or interrupted firing and hazy mental representations during memory recollection. In support of this, work by Thiele and Bellgrove (2017) suggests that attractor firing rates vary and that this variation relates to changes in cognition. (iii) Not all information represented by activity in the brain comes to be stored as meaningful change at synapses. Of the information that does trigger plasticity pathways, only that which activates high-threshold, protein synthesis-dependent processes will be lastingly useful (Huang, 1998). Therefore, not all information encountered during a learning episode contributes to the synaptic change blueprint for reinstating said learning. An incomplete blueprint will cause a portion of the neural code originally present during learning to not recollect. (iv) Synaptic change involves proteins and structures that are vulnerable to turnover (Attardo, Fitzgerald, & Schnitzer, 2015; Crick, 1984; Mongillo, Rumpel, & Loewenstein, 2017), this too may result in an imperfect blueprint. Thus, an A/C view predicts properties of memory cognition observed by psychologists and cognitive neuroscientists.

3.3. Addressing proposed shortcomings of an A/C theory

An A/C view has many strengths but is not without challenge, challenges for this view include the coding problem and recent research on non-associative learning. The coding problem references the difficulty in explaining how the brain stores individual indispensable facts. These facts include quantities such as weight, distance and direction (Gallistel, 2017a). While there are cells in the brain that encode basic facts (e.g. place cells), these cells may encode more than one basic fact or lack meaningful detail. In the case of location, place cells are known to "re-map" and change the position they represent (Miota, Rosis, Zhou, LeDoux, & Blair, 2004). Additionally, place cells can have different scales (Brunec et al., 2018) and represent non-place information

(Aronov et al., 2017; Salz et al., 2016). Therefore, many place representing cells may be required to convey reliable information about position (Park, Dvorak, & Fenton, 2011). Consistent with a need for associations between place representing cells, synapse plasticity is important for forming lasting place representations (Cobar, Yuan, & Tashiro, 2017).

Even if individual cells can represent individual facts, in an A/C perspective memory involves the formation of associations and a single, unassociated basic fact (e.g. six meters) may not constitute a memory. An animal cannot adaptively guide its behavior, the given definition of memory cognition, simply by remembering a distance. Instead, information about distance, direction, position, context and other elements of experience must be encoded and expressed together, a feat achieved by the formation of associations between implicated neurons.

The combination of many pieces of information is important for dead reckoning, the process by which an animal keeps a record of its travels (Burak & Fiete, 2009). Though, the energetic cost of the kind of circuit level mechanisms described by an A/C model makes an account of dead reckoning difficult; this is discussed further in the C/R section below. The universality of an A/C model is also called into question by the observation that at least one quantitative fact, the duration of a conditioned stimulus (CS)-unconditioned stimulus (US) interval, is less dependent on synaptic associations for its representation (Jirenhed, Rasmussen, Johansson, & Hesslow, 2017). The idea that some types of learning employ non-synaptic plasticity mechanisms is supported by research demonstrating memory uses cell excitability changes (Mozzachiodi, Lorenzetii, Baxter, & Byrne, 2008; Zhang & Linden, 2003). Consistent with a mechanism of this kind being involved in memory, Rao-Ruiz et al. (2019) observe that learning impacts the expression of genes important for controlling cell excitability. Though, it is not clear that excitability changes could offer the complexity necessary to represent all information. Instead, these changes may function to influence the selection and initial or later stabilization of engram circuit neurons (Lisman et al., 2018; Zhang & Linden, 2003), to help store temporal relationships, or to help with recall (Pignatelli et al., 2019; Sehgal et al., 2018; Silva, Zhou, Rogerson, Shobe, & Balaji, 2009).

As with the learning of some simple quantitative facts, non-associative learning may be less dependent on synaptic associations. Chen et al. (2014) find that in Aplysia, memory can withstand protein synthesis and protein kinase M inhibitors that reduce synaptic associations and learned responses. In interpreting these findings, Chen et al. (2014) suggest memory may employ a nuclear process—others have since found evidence that learned information may be contained in epigenetic material that can be transferred to offspring or experimentally to other animals (Bédécarrats, Chen, Pearce, Cai, & Glanzman, 2018; Moore, Kaletsky, & Murphy, 2019; Posner et al., 2019)—and note that it is at least unclear how this kind of mechanism would manage in more advanced cases. Nonetheless, theories of lasting memory usually list as a requirement synaptic associations that are dependent on protein synthesis and then protein kinase Ms and the finding that memory can be independent of these features questions the basic premise, or at least the universality, of a synaptic theory of memory.

In light of Chen et al. (2014) research, it is important to note that an A/C approach does not deny or discount the importance of nuclear changes for memory, as these alterations may function to shape the expression or expressibility of synapse proteins (Kyrke-Smith & Williams, 2018; Miller & Sweatt, 2007). Taken together, the experiments and writings discussed here suggest that ancillary aspects of memory (e.g. engram selection/production, stabilization, association, maintenance and recall) as well as simpler and inherited types of learning (e.g. interval length measurements and stimulus guided behaviors, respectively) rely on non-synaptic mechanisms (Chen et al., 2014; Jirenhed et al., 2017; Kyrke-Smith & Williams, 2018; Lisman et al., 2018; Miller & Sweatt, 2007; Moore et al., 2019; Park et al., 2016; Pignatelli et al., 2019; Posner et al., 2019; Sehgal et al., 2018; Viosca et al., 2009) while more complex memory (e.g. rodent associative learning) ordinarily depends on synapse change (Navabi et al., 2014). Though, if intracellular information-carrying molecules or changes in cell excitability, and not neuronal discharges, are the symbolic elements of memory then synapses are still needed to acquire, use or exchange stored knowledge with centers used for perception, cognition or behavior (Langille & Brown, 2018).

Additional critiques of a theory of memory implicating synaptic change include: (i) The tendency for synaptic proteins and structures to turnover (Attardo et al., 2015; Crick, 1984; Mongillo et al., 2017). (ii) Evidence that can be interpreted to suggest learning may be distinct from memory (Saucier & Cain, 1995) and; (iii) evidence indicating memory requires only one trial (Barot, Chung, Kim, & Bernstein, 2009; Bevins, McPhee, Rauhut, & Ayres, 1997; Gallistel & Balsam, 2014; Trettenbrein, 2016). These critiques are challenged by research demonstrating a resistance of synapse proteins to breakdown, multiple plasticity maintenance molecules and regular memory reactivations (Fauth & van Rossum, 2019; Gao, Goodman, Sacktor, & Francis, 2018; Heo et al., 2018; Lisman, 1985), by the existence of diverse plasticity mechanisms (Anwyl, 2009; Nicoll & Schmitz, 2005; Petrovic et al., 2017) and by neuromodulator effects (Hu et al., 2007), respectively; these critiques are discussed in additional detail elsewhere, see Langille and Brown (2018).

3.4. Outstanding questions for an A/C theory of memory

At least three questions remain unanswered, or have yet to be understood, using an A/C theory:

(i) Causality problem: Do synapses use intracellular changes or do intracellular changes use synapses? As is suggested in Langille and Brown (2018), if synapses store information then intracellular change is required to produce it and if intracellular change stores information then synapses are required to use it. In either case, the functionally relevant site of memory is, directly or indirectly, the synapse.
(ii) Information identity problem: Does the brain store information only indirectly, as non-symbolic synaptic change? If so, is there a language of synaptic change that identifies, and when deciphered translates out to, a particular pattern of symbolic neuronal signals?
(iii) Activity coding problem(s): How does electrical activity in a neuron amount to information? And how do the inputs to a neuron summate to represent information of increasing complexity?

3.5. Summary of an A/C theory of memory

An A/C view separates the cognitive process of memory from its storage in the brain. In this model, active cells represent information which is stored indirectly as non-symbolic synaptic change. Synaptic change functions to enable later reactivation of learned attractors, the instructions for which are silently embedded in engram circuits. Thus, the A/C view builds on cellular theories of memory to provide a conception capable of beginning to bring together those with support for a synaptic theory (Choi et al., 2018; Yang, Pan, & Gan, 2009) and those indicating a synaptic theory lacks a complete explanation of this cognitive process (Arshavsky, 2016; Bédécarrats et al., 2018; Gallistel & Balsam, 2014; Trettenbrein, 2016).

4. The computational/representational perspective

4.1. Brain has the architecture of the internet

The C/R version of the computational theory of mind is rooted historically in computer science, mathematics, information theory, cognitive science, linguistics, rationalist philosophy, cognitive psychology (particularly psychophysics), ethology and, more recently, in molecular biology. It is skeptical about the relevance of contemporary

systems neuroscience to understanding how the brain computes, because contemporary neuroscience does not have a theory of memory that makes possible the unbounded composition of functions.

A mathematically idealized computing machine (the Turing machine) has two components, a transition table and a read/write memory. The transition table is a set of basic functions that operate on data read from memory and write the results of their operations back to memory. In practical computing machine, the transition table is a few central processing units (CPUs) or a largish number of graphical processing units (GPUs), while the memory is random-access and address-addressable. At least two of the founding figures of mathematical computer science and practical computer engineering stressed that the memory was the most important part: the larger, more compact, faster and more energy-sipping the memory was, the better the resulting machine (Turing 1947/2004; von Neumann, 1945, 2011). Although there has been much progress in the practical application of neural nets, secondary accounts of this progress often do not make it clear that all neural nets that currently do anything are embedded in a conventional computer with a read/write memory. That memory plays a fundamental role in providing the net with its input vectors and storing its outputs.

A finite state machine is a Turing machine that cannot read what it has written. Therefore, it cannot feed the results produced by one function to another function (or back into the first function) at some indefinite future time. In more mathematical terms, it cannot do the temporally unbounded composition of functions.

The neuroscience theory of memory is that the brain is a finite state machine that rewires itself so that its functions are better adapted to its environment. Memory resides in the altered wiring, the plastic synapses. These rewirings alter the animal's behavioral dispositions, but they do not encode experiential facts; at least no one is willing to suggest how they encode even simple facts like the duration of an interval or the distance to a goal. Synapses are signal conductors, not symbols. They do not stand for anything. They convey information-bearing signals between neurons, but they do not themselves convey information forward in time, as does, for example, a gene or a register in computer memory. No specifiable fact about the animal's experience can be read off from the synapses that have been altered by that experience. More interestingly, neural net models do not store specifiable facts in the notional synapses in these models, even though they could in principle do so, because the weights that represent the synaptic conductances in these models are assumed to be real valued variables; any real valued variable can represent another real-valued variable.

The lack of an addressable read/write memory is explicitly assumed in neural net modeling and in neurobiological theorizing about memory (Koch, 1997; McClelland, 1989; Smolensky, 1986). This assumption justifies the claim that the brain does not compute in the way that computers compute. However, it also brings the theory into conflict with the implications of a variety of behavioral phenomena, phenomena that imply that brains routinely perform the temporally and circumstantially unbounded composition of functions.

The computational/representational view asserts that brains do the unbounded composition of functions because they have the addressable read/write memory that makes it possible. In this view, the close parallel between computer memory and genetic memory strongly suggests that memory is implemented at the molecular level inside neurons—and so is the computational machinery (the transition table). Neuron-intrinsic molecular structures do the computations. The primary function of inter-neuronal signaling is updating the large memory stores inside each neuron. On this view, the brain has the architecture of the internet. It is robust for the same reason as the internet: the same information and the same computational machinery are preserved and present in many different sites.

The argument for this perspective rests on the following considerations: (i) Recent evidence that the engram for a simple quantity—the durations of the interval between the onset of a CS and the onset of the US—is intrinsic to the cerebellar Purkinje cell (Johansson, Jirenhed, Rasmussen, Zucc, & Hesslow, 2014). (ii) Storing the symbols for quantities is 15 orders of magnitude more volumetrically efficient than storing them in cell assemblies (Gallistel, 2017b). (iii) The numbers (symbols for quantities) in any computing machine capable of navigation must be generable on the fly in the course of its computations. Molecules are rapidly and massively generable and modifiable by intracellular metabolic machinery; whereas neurons and neural circuits are not. (iv) Genetic memory has the same bipartite structure as computer memory: an address part and a coding part. It does so because such a structure is essential in a computing machine. It enables variable binding and the creation of hierarchical data structures. (v) Binary logic gates, which are the foundations of conventional computing machinery, are implemented by the molecular machinery that reads the genetic code. (vi) Computation implemented at the molecular level is 13 orders of magnitude more energetically efficient than computation implemented at the circuit level (Gallistel, 2017b). (vii) There is no mystery about how brains implement the temporally and circumstantially unbounded composition of functions if they have the requisite kind of memory.

In developing this perspective, we focus on the phenomena of insect navigation because: (i) Navigation is computationally well understood and easily explained. (ii) The fact that these phenomena are observed in all the genera whose navigation has been studied, including insects, implies that they are not the result of a uniquely mammalian brain. Any theory about the neurobiology of navigation cannot rest on details of uniquely vertebrate neural circuitry, such as that found in the hippocampus. The explanatory power of the C/R approach is not limited to navigation, however. For C/R models of the Pavlovian fear conditioning that figures prominently in the literature on the neurobiology of memory, see (Balsam, Fairhurst, & Gallistel, 2006; Gallistel, Craig, & Shahan, 2019; Gallistel, 1990; Wilkes & Gallistel, 2016, 2017). A C/R account of fear conditioning begins with the observation that fear isn't a fact gleaned from experience; it's an emotional reaction engendered by the memory of the quantifiable facts that comprise a fearful experience: the location, the intensity of the pain, its duration; its latency, the duration of the exposure to the experimental chamber, etc.

4.2. Dead reckoning

Dead reckoning, or path integration, is the foundation of navigation in both human and non-human animals. Fig. 3A shows tracks of Cataglyphis ants foraging in a salt pan in the Tunisian dessert. This species does not lay odor trails. These foraging journeys may last more than an hour and cover more than 1200 m–420 km when scaled by the human/Cataglyphis body-length ratio. They are conducted by dead reckoning, as shown in Fig. 3B, where foraging ants were displaced as they started the homeward leg. The range and bearings of the courses run by the displaced ants (yellow traces in Fig. 3B) would have taken them to the near vicinity of the nest had they not been displaced, but what they saw on these post-displacement runs was not what they would have seen had they in fact been headed back toward their nest; this proves that the course was run by dead reckoning, not by piloting (steering by recognized landmarks).

Dead reckoning requires functions that compute direction and speed from diverse sensory inputs to generate a velocity vector. A velocity vector on the plane is a string of two numbers that represent how fast the animal is moving in each of two orthogonal directions. Feeding it to an integration function produces a position vector. The position vector represents the animal's net displacement along each of the two orthogonal dimensions.

The essential requirements in a machine designed to carry out this computation are a memory capable of preserving the current position vector indefinitely and a sum-to-memory mechanism. The sum-to-memory function updates the position vector by computing the sum of the position vector in memory and the latest displacement vector. In the

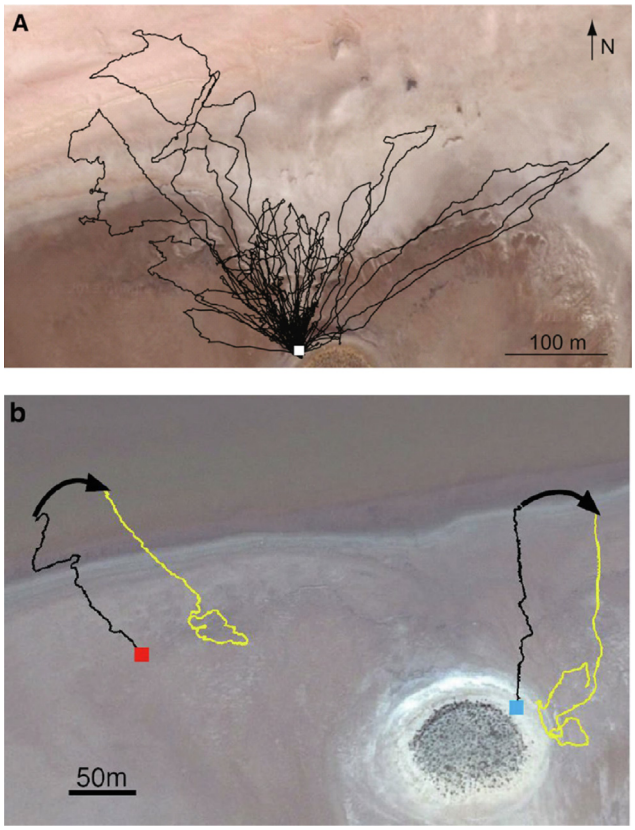

Fig. 3. A. Tracks of Cataglyphis ants foraging on a salt pan in Tunisia. Note the scale bar. (Buehlmann, Graham, Hansson, and Knaden (2014) used by permission of authors and publisher). B. Tracks of two ants displaced from a food source at the beginning of the homeward leg. Black traces are the outward journeys; yellow, the homeward journeys. The red and blue squares mark the nest entrance. The arrows indicate the displacement (Huber & Knaden, 2015, used by permission of authors and publisher). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

keeping of this running sum, the sum-to-memory function is recursively composed with itself over and over again.

Because the memory in a conventional computer makes possible the unbounded composition of functions, dead reckoning is trivially implemented in a machine with a conventional read/write memory and a mechanism for adding the numbers stored in that memory and putting the results of the addition back into that memory.

Implementing dead reckoning in a machine without a memory is far from trivial (Burak & Fiete, 2009; Samsonovich & McNaughton, 1997). A means must be found to maintain a representation of the animal's current position, a representation that endures indefinitely, even when the animal is sitting still. The standard approach is to exploit recurrent connections between neurons to create a continuous attractor network. The animal's location is represented by which neurons are firing and which are not. Incoming velocity signals nudge the network from a cell assembly that represents one location to a cell assembly that represents an adjacent location. The firing pattern representing the current position is maintained by trains of spikes circulating in recurrent loops within the network. From an engineering perspective, this way of preserving the sum is spectacularly and needlessly wasteful of physical resources:

Volumetric inefficiency. A position is a string of two numbers that refer to two orthogonal distances. Vectors may be materially realized in polynucleotides (DNA and RNA), which is why researchers are exploring the use of bacterial DNA as the memory in conventional computers (Scudellari, 2015). A polynucleotide string occupies a volume roughly 15 orders of magnitude smaller than a cell assembly (Gallistel, 2017b). A recent paper reports the implantation of a sensitization engram in Aplysia by RNA injection (Bédécarrats et al., 2018), which is evidence that polynucleotides may be the material realization of the engram.

Energy inefficiency. Maintaining the position vector in dead reckoning requires the neurons in the cell assembly to fire several times a second, even when the animal is not moving. Spikes are energetically very costly. Restoring the energy consumed by the transmission of a single spike, the ensuing release of transmitter substance, and the reuptake of the released transmitter requires the hydrolyzation of almost 10^9 (one billion) ATPs (Laughlin, de Ruyter van Steveninck, & Anderson, 1998; Laughlin, 2001, 2004). The number of spikes circulating per second in one of the most sophisticated connectionist models of dead reckoning (Burak & Fiete, 2009) is about 10^4 spikes per second (personal communication from Ila Fiete, email Nov 5, 2018). Thus, keeping the representation of position in this way consumes about 10^13 ATPs per second. By contrast, keeping the position vector in a molecule as thermodynamically stable as a polynucleotide reduces the ongoing energetic cost to essentially 0.

Lack of thermodynamic stability. When patterns of firing are maintained by spikes circulating in attractor networks, they are subject to noise that degrades the pattern, destroying its usefulness as a symbol. Burak and Fiete (2009) varied the parameters of their integrate-and-fire attractor models for dead reckoning within a biologically plausible range of values and concluded that when the animal was sitting still the circulating activity pattern representing its position would degrade in somewhere between 1 and 11 min. They also found that the fewer the neurons in which spikes circulated, the shorter this survival interval became. This degree of stability is not sufficient to explain the behavioral facts (see Fig. 3 and accompanying text).

Immediate purpose specificity. Maintaining the current position vector by recirculating activity in a continuous attractor network solves only the immediate problem of maintaining a representation of the animal's current position. It does not explain the fact that the foraging ant remembers the location of the newly discovered food source and returns directly to it later. Conventional computer memory allows the output delivered by a function operating now to be fed to the inputs of many different functions, for equally many different purposes, at many different times in the indefinite future, under circumstances completely different from those in which this output was generated. This is the key difference between a finite state machine and a conventional computer. The construction and utilization of the cognitive map illustrate this difference and its implications:

4.3. The cognitive map

A map is a set of vectors in a 2- or 3-dimensional vector space, on which navigation-relevant vector functions are defined. A vector is an ordered string of numbers, e.g. [52.1 4.5]. A vector space is a frame of reference that establishes the relation between the number strings and some aspect of the experienced world, e.g., color (Cornsweet, 1970), odor, and faces (Chang & Tsao, 2017; Le Chang, Pinglei, & Tsao, 2017; Stevens, 2018). In the cognitive map, the frame of reference is spatial; the vectors represent locations.

Constructing the map. Assume for the sake of illustration that the location of the ant's nest is represented by the vector [0 0]. The ant measures distances in 1 mm paces (Wittlinger, Wehner, & Wolf, 2006, 2007). Thus, a kilopace is 1 m. When the foraging Cataglyphis discovers a dead scorpion 90 m north and 20 m east of its nest, its current position vector reads [90 20], where the first element in the vector represents latitude and the second longitude, measured in kilopaces from an origin at the nest. We know that the ant makes a copy of this vector and stores it in memory, because the ant returns directly back to the scorpion on its next foraging journey. The current position vector of the ant will change the moment it moves away from the scorpion, but the copy of

that vector, made when the ant was at the location of the scorpion, does not change. The copy represents the location of the scorpion. The making of this copy is an example of the generative nature of computation. Computations constantly generate new numbers. The plastic synapse view of memory offers no account of how this generativity is possible.

The vector that represents the nest location and the vector that represent the location of the scorpion together establish a *frame of reference*. A frame of reference anchors a vector space to the world. Specifying those two vectors and the locations to which they refer fixes the mapping from all other locations within reach of the foraging ant to the vector that represents that location in that frame of reference, whether or not the ant has visited those other locations. As it gains experience, the ant records in that frame of reference the locations of other food sources, the locations of landmarks surrounding them and the locations of landmarks it encounters en route to and from them. In each case, it does so by making a copy of its position vector and its heading vector when viewing the landmark (Freas & Cheng, 2018) and leaving those copies in memory. Each time it does this, it generates new numbers in its memory, numbers that represent the locations, numbers that represent the headings, and numbers that represent (encode) the view.

Generability. The physical realization of the computations that construct the cognitive map is not mysterious when the numbers are physically realized by molecules with the properties of the polynucleotides. As Watson and Crick famously remarked at the conclusion of the paper in which they reported the structure of DNA, "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material." How these computations might be physically realized if memory consists of cell assemblies held together by plastic synapses is mysterious. An essential property of the numbers in any computing machine is that they be generable (Gallistel, 2017c). Every operation in a computing machine generates a new bit pattern. Cells and neural circuits are not rapidly generable; molecules are.

Utilizing the cognitive map. An experiment by Menzel and his collaborators further demonstrates the temporally and circumstantially unbounded composition of functions in map-based navigation (Menzel et al., 2011). They trained one platoon of bees to forage at one feeder (denoted FT in Fig. 4) about 650 m from the hive and a second platoon of bees from the same hive to forage at a different location (denoted FD in Fig. 4) at a similar distance from the hive. Foragers returned from a good food source do a dance in the hive that signals the range and bearing of the source from which they have returned. Other foragers follow behind the dancing bees to learn the map coordinates of that source (Frisch, 1965; Kiya & Kubo, 2011; Riley, Greggers, Smith, Reynolds, & Menzel, 2005). The Menzel team observed the dances that the returning foragers performed in the hive to be sure that the bees foraging at FT had observed the dance of the bees foraging at FD on many occasions. The next day, they removed the artificial nectar from the FT table. When members of the platoon that foraged at the FT table arrived and found no food, some of them set a course for the FD table. Two examples are in Fig. 4.

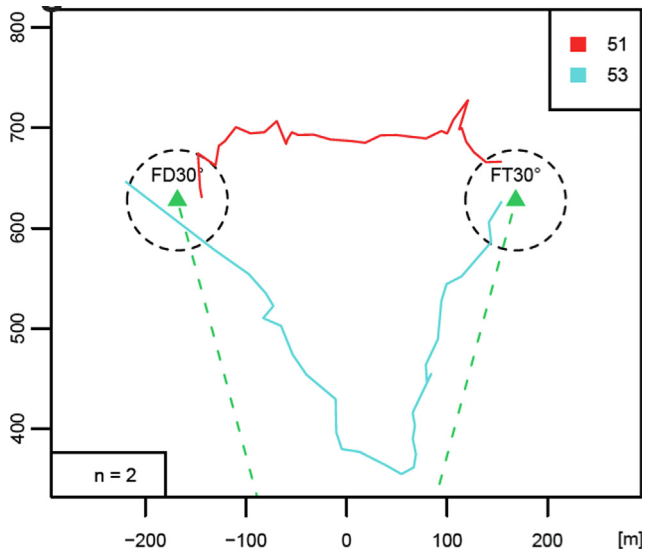

Fig. 4. The flight paths of two bees in the FT30° platoon who had observed the dances of the bees in the FD30° platoon, following the discovery by the former bees that there was no longer any food at the FT platform. (reproduced from Menzel et al., 2011 by permission of the authors and publisher).

The bees who set a course from FT to FD knew the location of FT from direct experience, but they knew the location of FD only by long-ago hearsay—by following dances in the hive the previous day. The course-setting observed in Fig. 4 requires a two-step composition of functions: The current position vector must be subtracted from the vector representing the location of FD. The resulting location-difference vector must be fed to the Cartesian-to-polar function to obtain the range and bearing of FD from the current position. The bearing controls the direction of the course, while the range determines the distance at which the navigator begins to look for the destination. One bee in Fig. 4 set its course directly from FT to FD; another started on the course back to the hive but midway there changed its mind and set a course from where it then was to FD.

An enduring characteristic of the A/C approach to learning and memory is that "memories" can only be activated by circumstances similar to those in which they were established. The behaviorists called this the principle of stimulus generalization. It is also called pattern completion (see A/C account above) and content-addressable memory. As the term pattern completion makes clear, the "memory" (cell assemblies) in a content-addressable memory must be activated by an input from the environment similar to the inputs that created those assemblies. It is called content-addressable because the full content of a complex memory is activated by an input specifying some part or parts of that content. An attractor state cannot be activated (settled into) by sensory inputs utterly unlike those that created the underlying pattern of synaptic weights. In the experiment by the Menzel team, the location of the FD source was learned by following the waggle dance of other foragers in complete darkness inside the hive far away from the FD platform. It was summoned from memory under radically different circumstances—when the bees were in the open air 650 m away from the hive on the following day with visual and olfactory inputs far removed from those that prevailed when they were following the dances of the foragers returning from the FD site. Conventional memory—random access address-addressable memory–allows facts to be retrieved whenever needed, regardless of current circumstances and the time elapsed since they were stored. Cell assemblies, by contrast, do not have this property; they can only be activated by inputs somewhat similar to those that forged the assembly.

4.4. Assembling the scraps: association without associations

The fact that insects record the smell of a given food source and compass-oriented views of the landmarks around it and of the horizon contour behind it raises the question how the position and heading vectors are associated with the appropriate snapshots and smells. To answer this question—the question of how separated scraps of acquired information are associated—the A/C framework posits the formation of associative bonds (plastic synapses). Computers and the gene-reading molecular machinery inside cells also summon up related scraps of information to realize overarching functional goals, but they do not do so by means of activation-conducting connections between the scraps. They assemble functionally related scraps of information by indirect addressing within an address-addressable memory.

Indirect addressing occurs when an item in memory is retrieved not

by specifying its address directly but rather by specifying an address where its address may be found or where numbers that permit the calculation of its address may be found. Indirect addressing solves the problem of binding variables to their values, a long-standing and still unsolved problem in A/C theorizing (D'Avila Garcez, Besold, De Raedt, & Foldiak, 2015; Garson, 1993; Kiela, 2011; Wolfe, 2012). In doing so, it makes possible the construction of hierarchical data bases of great complexity. An example of such system is the hierarchical system of translation factors that makes possible a gene for an eye (Gehring, 1998; Halder, Callaerts, & Gehring, 1995; Quiring, Walldorf, Kloter, & Gehring, 1994). Moreover, the system for reading genes realizes the Boolean logic gates that are the foundation of computational operations (Brophy & Voigt, 2014; Fernandez-Rodriguez, Yang, Gorochowski, Gordon, & Voigt, 2015). Thus, we know that there exists within every cell molecules that encode Shannon information within an address-addressable memory that is readable by intracellular molecular machinery. There is an entire scientific discipline—molecular biology—-devoted to the study of this intracellular machinery.

4.5. Neurobiological evidence for intracellular engrams

A problem within the A/C perspective on learning and memory is that the quantitative properties of plastic synapses revealed by electrophysiological experiments do not match any of the quantitative properties revealed by behavioral experiments (Gallistel & Matzel, 2013). Thus, the properties of plastic synapses do not explain any of the experimentally established properties of associative learning. The only cellular level Pavlovian conditioning phenomenon whose quantitative properties match those measured at the behavioral level is the conditioned pause in the spontaneous firing of the cerebellar Purkinje cell (Jirenhed & Hesslow, 2016, 2011a, 2011b; Jirenhed et al., 2017; Jirenhed, Bengtsson, & Hesslow, 2007; Wetmore et al., 2014). In this phenomenon, the duration of the conditioned pause is approximately the same as the CS-US interval used during the conditioning.

The conditioned pause in the firing of the cerebellar Purkinje cell is also the only cellular level phenomenon in which it is possible to specify a quantifiable experience that has been committed to memory. The duration of the CS-US interval is among the fragments that have been committed to memory in this phenomenon. That duration is an objectively definable and measurable experiential fact. A convincing case has recently been made that the mechanisms that time the CS-US interval, record it in memory, and read it out into a pause of appropriate duration are intrinsic to the Purkinje cell (Johansson et al., 2014; Johansson, Carlsson, Rasmussen, Yeo, & Hesslow, 2015; Johansson, Jirenhed, Rasmussen, Zucca, & Hesslow, 2018; Wetmore et al., 2014). The engram for the duration of the CS-US interval appears to reside somewhere within an intracellular biochemical cascade that begins with the mGluR7 metabotropic receptor on the postsynaptic side of the glutamatergic synapse between parallel fibers and the Purkinje cell (Johansson et al., 2015) and culminates in the inward rectifying Kir7 potassium channel (Johansson, 2015).

Recent advances in optogenetics have enabled researchers to visualize neurons activated in fear conditioning paradigms. Selectively activating these neurons evokes the learned behavior, even when treatment with protein synthesis inhibitors has rendered the memory of the conditioning experience behaviorally ineffective when the animals are simply returned to the conditioning environment (Josselyn, Kohler, & Frankland, 2015; Liu et al., 2012; Roy et al., 2016; Roy, Muralidhar, Smith, & Tonegawa, 2017; Ryan et al., 2015; Tonegawa, Pignatelli, Roy, & Ryan, 2015). These results tend to confirm the conclusion that the engram—the structural change that encodes the raw facts of experience—is intrinsic to those neurons.

4.6. Outstanding questions for the C/R theory of memory

(i) What is the physical medium in which the quantitative facts about the experienced environment are stored? From a research strategy perspective, this is the low hanging fruit. It should be the simplest to answer; and, the rest of the questions cannot be answered until this one has been answered (Gallistel, 2017). Johansson (2015) has identified the beginning and end of an intracellular biochemical cascade in the cerebellar Purkinje cell that appears to incorporate the engram. Gallistel (2017) has listed constraints on quantity-encoding engrams (numbers in the brain), which can guide subsequent experimental work. Experiments following up on Johansson's discoveries should look for changes in intracellular molecules—polypeptides, for example—that encode the CS-US interval in a readable way. Strong evidence that the quantity-encoding engram had been found would come from a demonstration that an experimenter blind to the conditioning parameters could read off the CS-US interval simply from knowledge of the nucleotide sequence in a polypeptide synthesized in the course of the conditioning. An even more compelling experiment would be to show that constructing polypeptides—or other molecular structures with similarly transparent information-storing capability—in accord with the presumed code for quantities and inserting them into appropriate neurons determines in the predicted way the direction and length of a homeward run in a foraging ant (or fruit fly).

(ii) How compact is the molecular engram—how many bits per m^{-18}?

(iii) How energy efficient is it— How many ATPs are required per bit stored during the generation of the engram that encodes an experienced quantity? And, how many ATPs/megabyte-year are required for the maintenance of the store?

(iv) What is the code, that is, what are the principles that describe the mapping from experiential quantities to the molecular structures that encode them? Knowledge of these principles would make it possible for cognitive neuroscientists to read-out the encoded quantities in the same way in which molecular biologists can read out protein structure from codon sequences. It would also make it possible to create synthetic memories.

(v) What is the code by which sequences of action potentials convey quantities to synapses?

(vi) What is the mechanism that translates the action potential code for quantities into the engram code (the write mechanism)?

(vii) What is the address mechanism? How does naturally arising synaptic input access (cause the reading of) the appropriate engram?

(viii) How does the architecture of the engram enable variable binding, hence the construction of hierarchical data bases?

(ix) What mechanism translates from the engram code into the action potential code and what are the principles by which it operates (the read mechanism)?

(x) What is the transcription speed, bits/s?

(xi) What is the evolutionary origin of the system for encoding acquired information? In speculating about this, the fact that the machinery for synthesizing and editing information-carrying polynucleotides and the logic gates for reading the information therein encoded have been present in cells since the early days of evolution looms large (Gallistel, 2017b). It is this machinery for maintaining, reading and editing and translating genetic memory that makes evolution possible. It is tempting to speculate that this information-processing machinery has been exapted for use in storing and operating on acquired information, as well as hereditary information.

4.7. Summary of a C/R theory of memory

In the C/R view, most researchers searching for the engram are looking for the wrong thing in the wrong place, guided by an erroneous conception of what memory is and the role it plays in computation.

Instead of looking for plastic synapses at the circuit level, guided by a conception of the brain as a finite state machine that rewires itself, they should be looking inside neurons for molecules inscribed with quantitative facts gleaned from experience, guided by a conception of the brain as a computing machine with the architecture of the internet (Gallistel, 2017b). In this conception, computation occurs intra-neuronally, and the primary function of inter-neuronal signaling in the central nervous system is the updating of massively shared memories. On this view, every neuron in the hippocampus, entorhinal cortex and associated structures may contain the complete cognitive map (Gallistel, 2017b).

5. Conclusions

There remain divisions in the contemporary neurobiology of memory. The A/C view contends that synaptic associations are central to memory, learning forms them and memory cognition uses them. This view reigns supreme in most teachings of memory neurobiology, but is not without challenge. Those advocating for a C/R view argue that intracellular information-carrying molecules and a computer-like read/write system are important parts of how memory operates in the brain. These views are not necessarily mutually exclusive, and a synergistic view of these theories may take at least one of three forms. Changes at synapses could enable symbolic activity patterns while those changes occurring intracellularly encode programs for the expression of genes and proteins necessary to maintain synapse change or modulate the selection, stabilization, association or reactivation of neurons in engram circuits (Kyrke-Smith & Williams, 2018; Lisman et al., 2018; Miller & Sweatt, 2007; Pignatelli et al., 2019; Sehgal et al., 2018; Silva et al., 2009; Zhang & Linden, 2003). This stance is increasingly accepted by A/C theorists. Alternatively, symbolic, intracellular changes may store information while changes at synapses regulate and allow for the communication or expression of this information. A third option is that both mechanisms are used, in different brain regions or types of learning (Abraham, Jones, & Glanzman, 2019). Going forward, progress in molecular biology will be crucial in teasing apart the relative contributions of plastic synapses and intracellular molecules to learning and memory. The search continues.

Author contributions

JJ Langille wrote the first half of the manuscript (A/C perspective) and CR Gallistel wrote the second half (C/R perspective). JJ Langille contributed Figs. 1 and 2, CR Gallistel contributed Figs. 3 and 4.

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Competing interests

The authors declare no competing interests.

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Glossary

Associative/Connectionist: A model for learning and memory, emphasizing the importance of associations between neurons

Computational/Representational: A model for learning and memory in which the brain computes symbolic representations of the experienced world and stores them in a read/write memory for use in the computational operations that direct and time future behavior

Shannon Information: A measure of the uncertainty in a probability distribution–$\sum p_i log(1/p_i)$—where p_i is the probability of the i^{th} possibility in a set of possible values for a variable. A neural signal or an engram conveys information about a behaviorally important variable (e.g., the distance to a food source or the duration of a CS-US interval) to the extent that receiving the signal or reading the engram reduces the a priori uncertainty about the value of that variable. For example, an amino-acid specifying codon in DNA conveys $\log_2(20) = 4.3$ bits of information because a priori there are 20 possible amino acids at any position in a polypeptide

Hebbian Synapse: The site of associative plasticity, detects and stores associations as coupled activity in pre- and post-synaptic neurons and strength increases, respectively

Read/Write Memory: The physical component of a computing machine where the outputs from computations are stored for use in later computations, some of which may control ongoing behavior

Cell Assembly: An ensemble of associated neurons

Phase Sequence: A chain of two or more cell assemblies

Composition of Functions: Feeding the output(s) of one or more functions to the input of another function. A physically realized function is a device that effects a specified mapping between its inputs and its outputs. For example the addition mechanism in a computer effects the mapping from two numbers to their sum. Recurrent neural nets may approximate any physically realizable function

Engram: the enduring change in some aspect of neurobiological structure that explains the effects of past experiences on subsequent behavior

Engram Cell: A cell that is activated during learning and contains part of an engram

Engram Circuit: An ensemble of engram cells, which collectively embody the cellular change associated with something learned

Memory Cognition: The processes that make use of previously molded plastic synapses to direct current behavior and thought

Neural Code: The signals used by the brain to represent information about an experience, such as the intensity of a pain stimulus, the color of an object, the duration of an interval, the direction of a food source from the hive, the face of a new friend, etc. Also, the mapping from experiences to the engram, the physical change that enables those experiences to inform subsequent behavior

Long-Term Potentiation (LTP): A lasting increase in an association between two neurons

Long-Term Depression (LTD): A lasting decrease in an association between two neurons

Optogenetics: An experimental tool for manipulating the activity of neurons; uses optical stimulation to open or close experimentally expressed, light sensitive ion channels

Pattern Completion: A process for activating an entire engram circuit from the activation of a subset of engram cells. Manifests as the activation of an entire memory from part of the original stimulus

Attractor: a stable pattern of activity in a dynamical system (such as a neural net), such that unstable patterns distinct from it but overlapping it to some extent evolve into it

Coding Problem: The problem of specifying the code (the principles) that map from a fact gleaned from experience (pain intensity, color of object, etc, see above) to the spike train that encodes that fact so that it may be transmitted from one location to another within the brain; or, that map to the enduring structural change that transmits the fact forward in time so that it may inform subsequent behavior

Dead Reckoning: Integrating velocity with respect to time so has to obtain position as a function of time; a foundational computation in traditional human navigation and in animal navigation

CS-US Interval: The latency at which the unconditioned stimulus (US) follows the conditional stimulus (CS) in a Pavlovian conditioning protocol

Eye Blink Conditioning: A form of Pavlovian (aka classical) conditioning in which a behaviorally neutral stimulus, such as a tone, warns of an impending threat to the eye at some fixed latency (the CS-US interval)

Central Processing Unit (CPU): the machinery that reads bit patterns from memory into one or two registers where they are operated on (added, subtracted, multiplied, divided, inverted, concatenated, copied, etc) to produce a result that is written back into memory where it is preserved for future use. A serial processor of information, because it performs one simple operation after the next

Graphical Processing Unit (GPU): A simple CPU-like piece of digital machinery that

performs mostly arithmetic operations on several bit patterns at once (often, but not necessarily, on the bit patterns from several neighboring pixels in a digital image) and writes the results to a memory that it shares with many other GPUs. Widely used to implement a form of parallel processing (many computational operations performed simultaneously)

***Random-Access Memory**:* A read/write memory so structured that any memory may be accessed as quickly as any other. Computer memory and genetic memory are examples

***Address-Addressable Memory**:* A memory in which every location has two parts, an address part, and a storage part. The address part enables the machine to read from and write to the storage part at that location (that address). Genetic memory is address-addressable, because genes have two parts, an encoding part (analogous to the storage part in a computer memory) and one or more promoter parts (analogous to the address part in a computer memory)

***Variable-Binding**:* The distance and direction back to home (aka the home vector) is an example of a variable; it changes as the forager progresses. The distance and direction at any one moment is the current value of that variable. In the course of computations, it is often necessary to move operations from the symbol for a variable to the symbol for its (current) value. An address-addressable memory solves the problem of getting from the symbol for the variable to the symbol for its value in a conventional computer, because, in the simplest case, the bit pattern (the symbol) for the variable is the address of its value. How to solve this problem in a neural net is a long-standing, unsolved problem

***Binary Logic Gates**:* Building blocks of the components that implement the built-in functions in a computing machine. A binary logic gate maps the four possible 2-bit input patterns (00 01 10 11) to a 2-bit output pattern. Dimerizing translation factors perform analogous functions in the reading and implementation of genetic (hereditary) memory. (For a diagram of the arrangement of logic gates that implements addition, see C. R. Gallistel, 2017a)

***Content-Addressable**:* A memory that is retrieved by specifying some of its constituents