Neuroscience and Biobehavioral Reviews 137 (2022) 104664

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Neuronal metabolism in learning and memory: The anticipatory activity perspective

Yuri I. Alexandrov [a,b,*], Mikhail V. Pletnikov [c,d,e,**]

[a] V. B. Shvyrkov Laboratory for the Neural Bases of the Mind, Institute of Psychology, the Russian Academy of Sciences, Moscow, Russia
[b] Department of Psychology, Institute for Cognitive Neuroscience, HSE University, Moscow, Russia
[c] Department of Physiology and Biophysics, Jacobs School of Medicine and Biomedical Sciences, State University of New York, University at Buffalo, Buffalo, NY 14203, USA
[d] Solomon H. Snyder Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA
[e] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA

ARTICLE INFO

Keywords:
Learning
Memory
Neuronal metabolism
Goal-directed behavior
Predictive activity

ABSTRACT

Current research on the molecular mechanisms of learning and memory is based on the "stimulus-response" paradigm, in which the neural circuits connecting environmental events with behavioral responses are strengthened. By contrast, cognitive and systems neuroscience emphasize the intrinsic activity of the brain that integrates information, establishes anticipatory actions, executes adaptive actions, and assesses the outcome via regulatory feedback mechanisms. We believe that the difference in the perspectives of systems and molecular studies is a major roadblock to further progress toward understanding the mechanisms of learning and memory. Here, we briefly overview the current studies in molecular mechanisms of learning and memory and propose that studying the predictive properties of neuronal metabolism will significantly advance our knowledge of how intrinsic, predictive activity of neurons shapes a new learning event. We further suggest that predictive metabolic changes in the brain may also take place in non-neuronal cells, including those of peripheral tissues. Finally, we present a path forward toward more in-depth studies of the role of cell metabolism in learning and memory.

1. Introduction

A major goal of neurobiology is to determine the mechanisms of learning and memory. Most research efforts have focused on learning-induced plastic changes at synapses according to the "stimulus-response" viewpoint, which we refer to as the reactivity paradigm (Kandel et al., 2014; Langille and Brown, 2018). Such studies rarely consider the predictive activity of neurons, which is emphasized in contemporary cognitive and systems neuroscience (Aleksandrov, 2006; Buzsáki, 2019; Pezzulo et al., 2021; Raichle, 2015). In this review, we consider this intrinsic activity of neurons in a broader context of the activity paradigm and argue that it is essential for understanding the mechanisms of learning and memory. We believe the disconnect between the molecular research based on the reactivity paradigm and the systems neuroscience research increasingly centered on the activity paradigm is a major roadblock to further progress in the field of learning and memory.

Recent studies have begun to demonstrate the significance of cellular metabolism, including cell bioenergetics, for the intrinsic activity of neurons (Mann et al., 2021; Styr et al., 2019). However, we still do not know if and how neuronal metabolism determines intrinsic neuronal activity during a new learning event and what metabolic changes are involved in the formation of a memory "engram." We hypothesize that some neurons "experience" a mismatch between their current metabolic state and the metabolic requirements imposed during learning. We propose that this metabolic mismatch initiates spiking activity of those neurons (i.e., predictive activity) to generate a new adaptive behavior that resolves the mismatch. In this review, we use the activity paradigm as a conceptual framework to critically evaluate the current molecular studies of learning and memory and propose new directions to test our hypothesis of the metabolic needs and their resolution during acquisition of new adaptive behaviors (Aleksandrov, 2006; Anokhin, 1974; Shvyrkov, 1990).

* Corresponding author at: V. B. Shvyrkov Laboratory for the Neural Bases of the Mind, Institute of Psychology, the Russian Academy of Sciences, Moscow, Russia.
** Corresponding author at: Department of Physiology and Biophysics, Jacobs School of Medicine, University at Buffalo, Buffalo, NY 14203, USA.
E-mail addresses: yuraalexandrov@yandex.ru (Y.I. Alexandrov), mvpletni@buffalo.edu (M.V. Pletnikov).

https://doi.org/10.1016/j.neubiorev.2022.104664
Received 16 November 2021; Received in revised form 30 March 2022; Accepted 10 April 2022
Available online 16 April 2022

2. Molecular mechanisms of learning and memory: origin and status quo

The science of learning and memory has predominantly been shaped by the reflex theory developed by the French philosopher René Descartes (1596–1650), who applied the laws and principles of physics and mechanics to biology and psychology (Corson and Corson, 1985). The reflex theory explained animal behavior as "reactive," with external stimuli as the primary cause. British empiricism further promoted this with the idea that our knowledge is acquired through experience based on the ability of the brain to perceive and interpret the outside world (Buzsáki, 2019) (Fig. 1A). The physiological studies by Sir Charles Sherrington supported the view that brain function is reactive to the environment (Sherrington, 1951). The reactivity paradigm is highly popular among neuroscientists because stimuli and responses can be experimentally controlled. This section presents an overview of the current understanding of learning and memory from the molecular neuroscience perspective.

2.1. Synaptic plasticity

The leading concept among neuroscientists to explain the brain mechanisms of learning and memory is Hebbian synaptic plasticity, in which the response to a synaptic input is strengthened when the activity of the presynaptic neuron co-occurs with activity of the postsynaptic neuron (Hebb, 1949; Sejnowski, 1999). Thus, learning reflects a synaptic modification resulting from the simple temporal association between two inputs (Blair et al., 2001; Pare, 2002; Sah et al., 2008). In addition to this remodeling, new synapses form during long-term memory formation, which requires protein synthesis in the body of the neuron and at the synapse (Davis and Squire, 1984; Martin and Morris, 2002; Silva, 2003; Tully et al., 1994). Although experimental evidence does not contradict the molecular and synaptic theories corresponding to the reactivity paradigm (Josselyn and Tonegawa, 2020; Langille and Brown, 2018), they are not universally accepted (e.g., Trettenbrein, 2016). In fact, there is a growing appreciation of the non-synaptic mechanisms of learning, including epigenetic modifications within individual neurons as a mechanism of storing acquired information (Abraham et al., 2019a; Arshavsky, 2006, 2017).

2.2. Neuronal metabolism in learning and memory

The adult brain consumes ~20% of the body's energy, and 60–75% of this energy is used for generating and propagating action potentials and synaptic transmission. The remainder is spent on anabolic metabolism for neuronal maintenance, such as for ion channels, receptor turnover, cytoskeletal remodeling, lipid metabolism, and protein synthesis for signal transduction pathways (Attwell and Laughlin, 2001; Bauernfeind et al., 2014; Bordone et al., 2019; Hyder et al., 2013). Additional energy requirements to accommodate changes in brain activity are proposed to be $< 5\%$ of baseline levels of consumption (Raichle, 2015; Raichle and Mintun, 2006). Thus, there appears to be little energy allocated for "externally driven" actions (for further details, see Fünfschilling et al., 2012; Magistretti and Chatton, 2005; Pellerin and Magistretti, 1997; Raichle, 2015).

Mitochondria are the key energy-producing organelles of the cell (Mattson et al., 2008; Raefsky and Mattson, 2017). Mitochondrial electron transport generates the ATP that is essential for the excitability and survival of neurons and for the phosphorylation of proteins that mediate synaptic signaling and related long-term changes in neuronal structure and function. Mitochondrial responses also address the bioenergetic challenges faced by neurons, such as Ca^{2+} and redox signaling and Ca^{2+} buffering, and contribute to developmental and synaptic plasticity, including the formation and maintenance of dendritic spines (postsynaptic structures) (Kann and Kovács, 2007). Neurons can also utilize glutamate, lactate, ketone bodies, and fatty acids as alternative sources of energy (Attwell and Laughlin, 2001; Bordone et al., 2019).

Glucose is metabolized during task-induced increases in aerobic glycolysis that are observed as changes in blood flow (i.e., blood-oxygen-level-dependent signals in functional magnetic resonance imaging). Synaptic proliferation and pruning are also linked to aerobic glycolysis (Raichle, 2015; Raichle and Mintun, 2006). When rats perform various

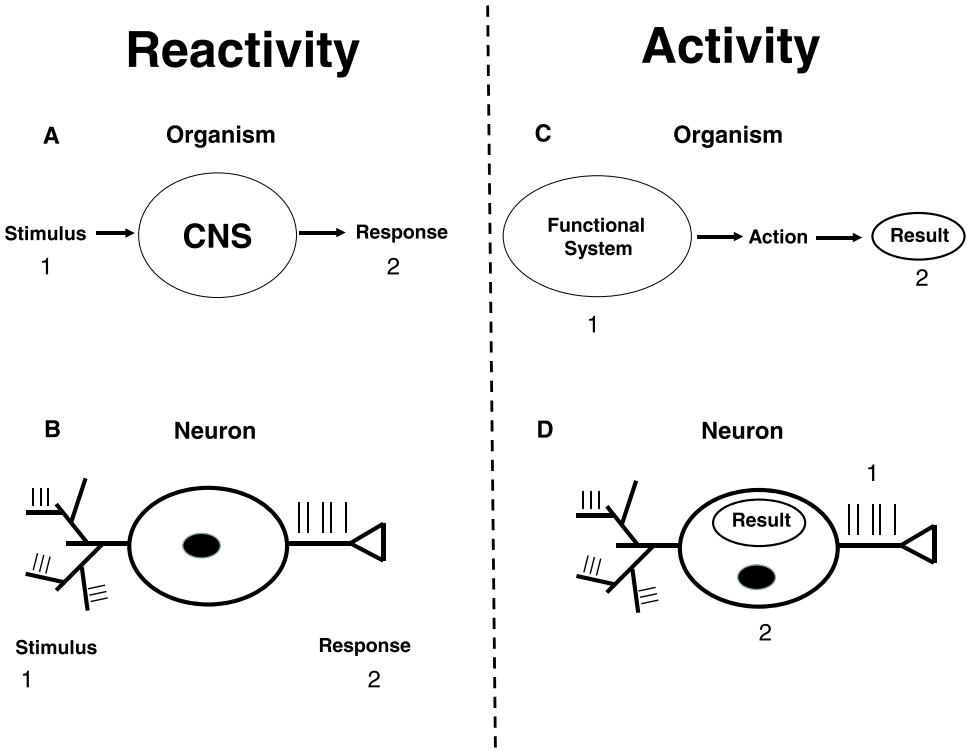

Fig. 1. Reactivity and activity paradigms. The numbers indicate the order of the events. **A–B**: According to the Reactivity paradigm, a stimulus (1) is followed by a response (2). This chain of events is observed at the levels of both the Organism (A) and the Neuron (B). At the neuronal level, the stimulus is the synaptic inputs (thin short lines) and the response is spiking activity of the neuron (thin long lines). **C–D**: According to the Activity paradigm, a functional system (1) is generated at the level of the Organism (C) to achieve an adaptive result (2). At the neuronal level (D), spiking activity is generated because of a mismatch between the basal metabolism and the metabolic requirements, e.g., as produced by a new learning event. Neuronal spiking is an action (1) that contributes to a newly established functional system. The functional system achieves an adaptive result that eventually eliminates the original metabolic mismatch (2). In this context, the adaptive result for the neuron is a new metabolic state that leads to cessation of neuronal activity. Thin short lines – synaptic inputs; thin long lines – spiking activity of the neuron.

cognitive tasks, the levels of glucose in the hippocampi decrease, suggesting that glucose consumption increases to provide neurons with additional energy metabolites (McNay et al., 2000, 2001; Newman et al., 2011; Suzuki et al., 2011). Glucose consumption may also increase to provide astrocytes with glycogen to produce lactate, which serves as a major energy metabolite during a learning event and/or the consolidation of a new memory. This notion is supported by evidence showing that knockout of glycogen synthase affects learning (Duran et al., 2013; Rich et al., 2019) and that learning-associated neuronal activity upregulates genes associated with the lactate shuttle, such as those encoding glucose and lactate transporters (Hirase et al., 2019; Rich et al., 2019; Tadi et al., 2015).

The launch of a new journal in 2019 (Nature Metabolism) reflects the growing appreciation that cellular metabolism not only provides energy in the form of ATP but also produces metabolites involved in signaling pathways and post-translational modifications, apoptosis (Green et al., 2014; Mason and Rathmell, 2011) and inflammatory processes (Zaslona and O'Neill, 2020). A possible role for neuronal metabolism as a "driver" of the predictive activity of neurons is also emerging. We believe that future research on cellular metabolism will elucidate how this activity serves as a mechanism of learning and memory.

3. Predictive mechanisms of learning and memory

3.1. Predictive activity of the brain

Modern concepts in cognitive and systems neuroscience related to learning and memory, such as "central pattern generators," "the restless brain," or "the inside-out program" (Buzsáki, 2019; Llinás, 2001; Raichle, 2010; Yuste et al., 2005), took root in earlier studies demonstrating that the mechanisms of learning cannot fully be described in terms of an association of unconditioned and conditioned stimuli and that "mental constructs" predict future events on the basis of past experiences (Clayton et al., 2003; Dickinson and Mackintosh, 1978; Domjan, 2000, 2005; Fanselow and Wassum, 2015; Timberlake, 1993, 1994). The notion that the brain works as a prediction system has since expanded to encompass interoception - the subjective cognitive assessment (i.e., perception) of physiological processes within the body (i.e., sensations from inside the body) (Barrett and Simmons, 2015; Chen et al., 2021).

One of the earliest original concepts of the predictive activity of the brain was developed in the school of Ivan P. Pavlov. Although I. P. Pavlov and his studies are widely known to Western scholars, the works of his students have received much less attention. For example, few publications of Pavlov's student Peter K. Anokhin, who arguably made the greatest contribution to systems and cognitive neuroscience in Russia, were translated into English (Anokhin, 1958, 1968, 1984; Anokhin and Shuleikina, 1977). Anokhin's theory of the functional system and his concept of the integrative activity of the neuron provide some historical background for the development of our hypothesis that predictive features of neuronal metabolism play a role in learning and memory (Aleksandrov, 2006; Shvyrkov, 1990).

3.2. P. K. Anokhin's theory of the functional system

P. K. Anokhin (1898)–(1974), one of Pavlov's most brilliant students, made across-the-board contributions to an integrative theory of behavior. In 1933–35, he proposed the theory of the functional system to explain the mechanisms of goal-directed behaviors (Anokhin, 1968, 1974, pp. 190–254) (Fig. 2). His early experiments revealed that the concept of the reflex arc does not fully explain compensatory adaptations. The reflex is a linear process and has no "goal" that would precede the reflex response itself. By contrast, the goal of compensation is to achieve a specific adaptive result. The realization of the adaptive result was considered a "function", leading to the name, i.e., a functional system. To overcome the limitations of the "stimulus-response" concept, Anokhin thus proposed the theory of the functional system, which describes a dynamic organization of central (i.e., the brain) and peripheral (i.e., peripheral organs and tissues) components that enable an organism to achieve an adaptive result (Fig. 1C). This idea of central-peripheral integration precedes the proposed concepts of embodied cognition (Barsalou et al., 2003; Critchley and Harrison, 2013; Kolbeneva and Alexandrov, 2016; Niedenthal, 2007) and allostasis. Indeed, similar to Anokhin's ideas, allostasis is considered "a core principle of organismal design" to detect and evaluate the "needs" of the body and recall from memory what previously worked to determine the actions to attain the adaptive results (Schulkin, 2003; Schulkin and Sterling, 2019; Sterling, 2012).

To the best of our knowledge, Anokhin was the first to propose the idea of self-regulation (also known as feedback) as a key physiological mechanism that informs the brain about the success or failure of the behavior being executed (Fig. 2). Success consolidates the behavior, whereas failure initiates the formation of a new functional system, enabling a new behavior. As a central mechanism for evaluating the success or failure of the behavior, Anokhin proposed *an acceptor of the results of an action* that includes the specific parameters of the future result and compares the parameters of the actual result with those anticipated by the organism. Anokhin's view was later reintroduced in cognitive neuroscience, including the concept of prediction error (Fig. 2) (Anokhin, 1968, 1974). We refer interested readers to several recent reviews of the modern status of the theory of the functional system (Alexandrov, 2018, 2022; Alexandrov et al., 2018).

As a logical extension of his theory of the functional system, Anokhin also advanced the concept of the integrative activity of the neuron

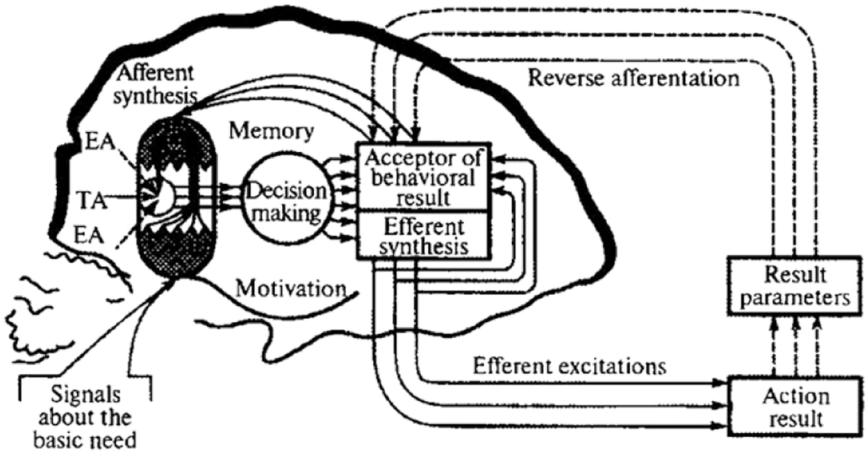

Fig. 2. General architecture of a functional system. A functional system includes afferent synthesis, which is an integration of contextual or environmental afferentation (EA), memory and metabolic needs (e.g., drive), and triggering afferentation (TA) that initiates a process of decision making. Decision making leads to the establishment of efferent synthesis (i.e., the plan of action) and an acceptor of the future results (i.e., anticipation) of a behavior to be performed. The results of the behavior are evaluated by the acceptor via regulatory feedback mechanisms originally coined "reverse afferentation" by Anokhin. If the parameters of the results do not match the acceptor's expectation (i.e., prediction error), the formation of a new functional system is initiated.
Reproduced with permission. © Springer International Publishing Switzerland. "Cognitive Systems Monographs", Volume 25, "Anticipation: Learning from the Past. The Russian/Soviet Contributions to the Science of Anticipation.", Ed. Mihai Nadin, p.159 (the original Fig. 3), 2015.

(Anokhin, 1984). When this concept was first introduced in the 1960th and was published in its final form in 1974, the neuron was mainly viewed as an element of the reflex arc, and accordingly, its main function was to conduct excitation along the reflex arc (e.g., Brink, 1951). In the context of the "reactivity paradigm", similar to the whole organism level (Fig. 1A), synaptic inputs represented a stimulus, whereas the spiking activity of the neuron was a response to that stimulus (Fig. 1B). Anokhin proposed that incoming stimuli are integrated not on the neuronal membrane as a summation of excitatory and inhibitory potentials but inside the neuron through interacting signaling pathways and metabolic processes triggered by the activation of the receptors on the membrane. Given the limited knowledge at the time of molecular processes taking place in the neuron, Anokhin could not propose a specific mechanism that increases the excitability at the hillock of the neuron to generate spiking activity. While even now the exact mechanisms are still being investigated, it has been established that the axon initial segment (AIS) has a complex protein composition, including voltage-gated channels, cell adhesion molecules, cytoskeletal proteins (e.g., microtubules), and protein kinases (Leterrier et al., 2014; Quistgaard et al., 2021; Fujitani et al., 2021). It is not inconceivable that such a sophisticated protein architecture found to modulate firing properties of AIS is under fine-tuned regulation by gene expression and/or various post-translational protein modifications. It is thus possible that AIS firing patterns could be modulated by intraneuronal pathways as was proposed by Anokhin more than 50 years ago.

The replacement of the "conductance through summation" concept with one that emphasizes intracellular processes set the stage for viewing neuronal metabolism as a key determinant of the intrinsic and predictive activity of neurons (Aleksandrov, 2006; Shvyrkov, 1990). Notably, the idea of anticipatory activity of cell metabolism was already emphasized by Anokhin. Considering the predictive activity of an individual cell or a primitive organism in the context of evolution, he pointed to the development of its ability to actively anticipate through a sequence of metabolic reactions a sequence of recurring external events (Anokhin, 1974, p12–13).

3.3. Neuronal metabolism in learning and memory

Molecular and cellular neuroscientists have still widely used the reactivity paradigm in their views of neuronal activity. However, there is growing recognition that the predictive activity of the brain can be attributed to neurons (Bar, 2007; Luczak et al., 2022; Sandler, 2008; Watts, 2017). For example, Luczak et al. argue that a neuron is endowed with the cellular mechanisms that function on small timescales (e.g., ~10–100 ms) to enable the neuron to predict future activity (Luczak et al., 2022). Predictive activity is now being reported in non-neuronal cells as well. For example, Cheng et al. describe a new role for NF-κB, a transcriptional factor, in controlling gene expression in anticipating future events (Cheng et al., 2021). Further, predictive activity may also exist in single-cell organisms as networks of proteins that empower a cell to anticipate the future (Bray, 2009).

The anticipatory activity of an individual neuron may be determined by the metabolic processes that occur during a learning event (Alexandrov and Jarvilehto, 1993; Aleksandrov, 2006; Alexandrov, 1999; Shvyrkov, 1986, 1990). We argue that involvement of neurons in a new learning event or formation of a new functional system (i.e., a new learning event) is initiated by an alteration in their metabolic states, i.e., a mismatch between the basal metabolic "needs" in those neurons and the new learning-produced metabolic requirements that cannot be met without acquiring a new skill/behavior. Such a mismatch might occur when existing memories and past experiences are insufficient to achieve adaptive results. If the mismatch cannot be resolved or reduced by reactivating the existing memories, then new neurons become active and form a new co-active network of neurons to help the organism achieve an adaptive result that, in turn, will lead to elimination of metabolic mismatch in these neurons (Fig. 1D).

Successful completion of a behavior also leads to cessation of the activity of the neurons built-in the functional system of a given behavior. Our prior findings demonstrate how activity of neurons change after achieving the results of the newly established behaviors to get food by pulling a ring (Fig. 3A-B) or pressing a lever (Fig. 3C-D). We found that neuronal activity takes place before obtaining the result and ceases as soon as the result has been achieved. Such a pre-result (i.e., anticipatory) activity of individual neurons is determined by the metabolic processes inside the neurons. The formation of a new functional system during learning is called "systemogenesis" and the neurons that are involved in the new functional system become specialized for it (Anokhin, 1974; Shvyrkov, 1986, 1990; Aleksandrov, 2006; Egorova and Anokhin, 2003).

3.4. Neuronal metabolism and memory engram

The concept that learning involves the formation of new neuron ensembles is compatible with the hypothesis that a memory engram comprises neurons that have outcompeted others (Han et al., 2007; Park et al., 2016; Rao-Ruiz et al., 2019; Yiu et al., 2014). Elegant studies have demonstrated that intrinsic excitability increases the probability that a neuron will win this competition (Josselyn and Frankland, 2018; Josselyn et al., 2015; Tonegawa, Liu et al., 2015; Tonegawa, Pignatelli et al., 2015). This intrinsic excitability-based allocation is also observed in invertebrates, suggesting that the intrinsic activity of neurons (and neuronal metabolism, we would add) is evolutionarily conserved and critical for learning and memory (Josselyn and Tonegawa, 2020).

A small proportion of neurons might be "primed" for recruitment to an engram (Josselyn and Tonegawa, 2020). We propose that this priming is determined by the metabolic state of the neuron, which is also reflected in the electrophysiological properties of neurons. Furthermore, we argue that primed neurons are not simply recruited by external stimuli but rather actively compete to join an engram in a new functional system ensuring that the result is adaptive for the neuron and the organism. We agree with Josselyn and Tonegawa (2020) that the allocation and selection of neurons "resonate with…Darwinian competition, " which further supports our main idea that neurons maintain their metabolism by proactively initiating new functional systems during learning. Josselyn and Tonegawa (2020) also proposed that neuronal activity and metabolism have an ancient and highly conserved relationship. This is consistent with our previously expressed view of a neuron as an evolutionary goal-directed organism developed to survive (Aleksandrov, 2006; Aleksandrov and Korpusova, 1987; Alexandrov et al., 2000, 2018) and early views of a single cell as an individual organism posited by Virchow (1860), Verworn and Lee (1899), and Sir Sherrington (1951). This view is also in line with Dennett's idea about cells as "takers" (Dennett, 1996) and Edelman and Finkel's idea that a neuron is a metabolic feedback-regulated cell (Edelman, 1984, pp. 686–687).

The idea of predictive neuronal metabolism can also explain the foundational mechanism of learning, namely, long-term potentiation (LTP) of synaptic transmission (Baltaci et al., 2019; Nicoll, 2017). The current interpretation of LTP is in line with the synaptic efficiency theory of learning and memory and the view of neurons as brain cells that react to incoming stimuli, i.e., action potentials. According to our hypothesis and from the neuronal metabolism perspective, LTP can be regarded as an electrophysiological reflection of the metabolic state that has been altered to resolve the increased energy demand (Drdla et al., 2009; McEachern and Shaw, 1996; Vikman et al., 2003). In LTP induction protocols, tetanic stimulation is not applied with the intention of altering neuronal metabolism, but it does.

3.5. Synchronous activity and metabolic cooperation

Modern views on spontaneous brain activity (Raichle and Mintun, 2006) are still described in the context of the reactivity paradigm, with

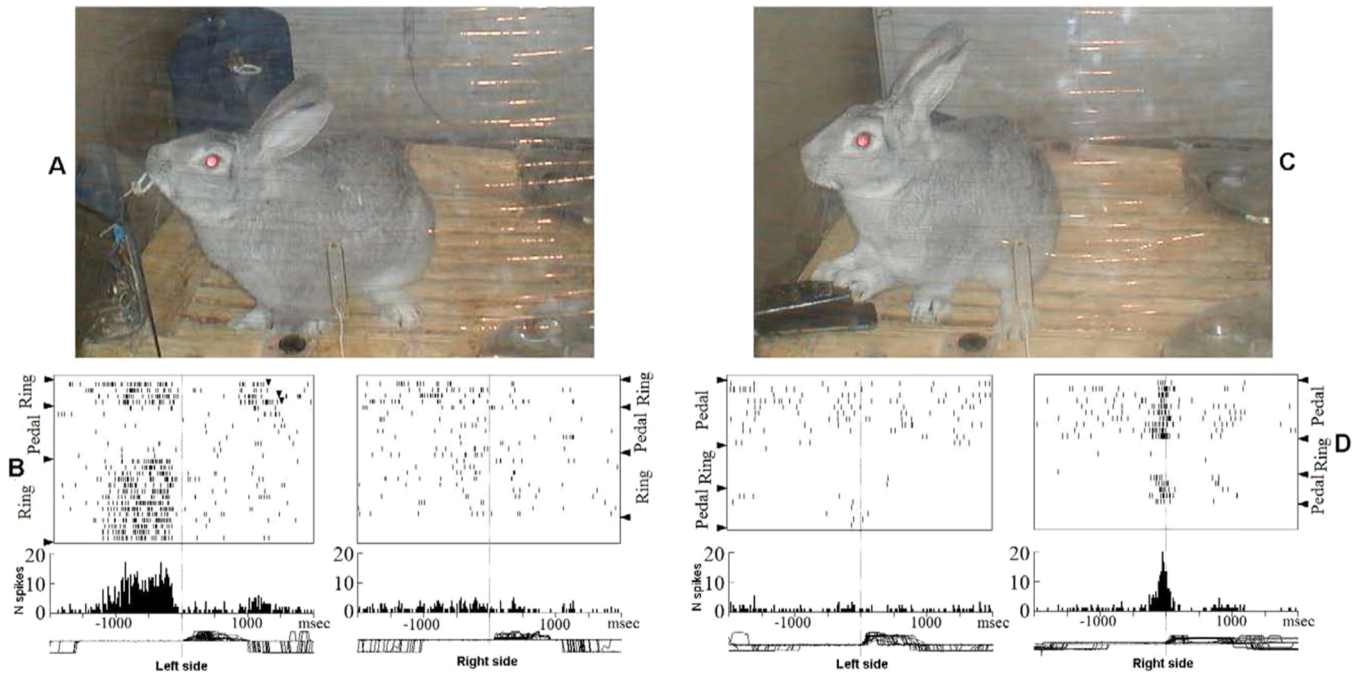

Fig. 3. Anticipatory activity of neurons. Activation of neurons in the rabbit cingulate and anterolateral motor cortex that are specialized for behavioral acts established during the learning of a food-reinforced behavior. The rabbits in the experimental cage pull on the ring (A) or press the pedal (B) to receive a food reinforcer. Raster plots of spiking activity and the histograms of neuronal activity in the cingulate (C) or anterolateral (D) areas of the cortex and the actograms. A neuron of the cingulate cortex is activated while the left but not the right ring is being pulled; notably, there is no activation while approaching or pressing the pedals (C). A neuron of the anterolateral cortex is activated while the right but not the left pedal is being pressed; there is no activation approaching or pulling the ring (D). The raster plots and histograms correspond to the start of the reinforced behavior. The vertical lines depict the time points at which the raster plots and histograms were made. The vertical bars on the raster plots show individual neuron spikes, and the horizontal bars show the sequences of spikes in an individual cycle of the food acquisition behavior. The cumulative histograms with a channel width of 20 ms are shown beneath the raster plots. The bottom plots are the behavior actograms for all cycles of the food acquisition behavior performed by the animals. The curved lines above the line show pulling the ring or pressing the pedal; the curved lines beneath the straight line depict the positioning of the animal's snout at the feeder. The diamonds depict repeat pulls.

the brain as a "sensory-motor analyzer" (reviewed by Pezzulo et al., 2021). However, there is the notion that simultaneous spontaneous activity of different brain areas may reflect "the history of task activation" to help execute "behaviorally relevant tasks" (Pezzulo et al., 2021).

We previously reported that synchronous extracellular unit activity in the visual and sensorimotor cortices in rabbits appears strongest right before the presentation of a negative reinforcement, i.e., a foot shock (Aleksandrov and Shvirkov, 1974). We proposed that this synchronous activity is a key feature of the integration of brain-wide systems to ensure the success of a goal-directed defensive behavior. Later, Engel and associates also observed synchronization between sensory and motor areas during the time when a cat anticipated the appearance of a behaviorally relevant stimulus (Engel et al., 2001, 2013). In addition to several indications of the functional importance of spontaneous brain activity (Buzsáki, 2019; Pezzulo et al., 2021; Raichle, 2015; Raichle and Mintun, 2006), we would like to add that the neuronal metabolism that determines spontaneous activity reflects "*a metabolic state for anticipatory activity*" (Shvyrkov, 1986; Alexandrov, 2015) and simultaneous activities of neurons reflect their metabolic co-operation.

The strong relationship between the metabolism and electrical activity of neurons suggests that the synchronous activity of neurons across different brain regions may be an indication of the metabolic integration required for a behavior to attain adaptive results and eliminate metabolic mismatches in synchronically active neurons. Systemogenesis may thus reflect a new metabolic cooperation, in which neurons "learn" to metabolically cooperate with one another during memory formation. One could propose that metabolic cooperation involves a broad spectrum of neuromodulators and classical neurotransmitters that influence (i.e., synchronize) metabolic processes in co-active neurons. From the metabolic perspective, a new learning might recruit neurons experiencing similar metabolic mismatches to establish a new neuronal ensemble. In this network, neurons acquire new metabolic "features" needed for the new functional system (Cedernaes et al., 2019; Llinas et al., 2002; Mann et al., 2021; Tingley et al., 2021).

We believe that this metabolic cooperation has evolutionary roots and is consistent with our knowledge about the evolution of multicellular organisms. There are examples coactivation, cooperation, and complex cell-cell communication in "societies" of unicellular organisms, in which these interactions are essential for attaining adaptive results shared by all unicellular organisms in the network (Ben Jacob et al., 2004; Benomar et al., 2015; Pande et al., 2015; Pfeiffer and Bonhoeffer, 2004). One example involves oscillatory metabolic processes for glycolysis in yeast (Olsen et al., 2009). The oscillations are synchronized by the diffusion of metabolites and other signaling molecules, which establishes an extracellular concentration gradient of critical metabolites (Weber et al., 2012). Such cell-cell interactions may have been one of the major driving forces for the evolution of multicellular organisms (Brodsky, 2006). Curiously, a single isolated yeast cell displays no oscillations (Olsen et al., 2009), whereas isolated neurons exhibit rhythmic activity (Chen et al., 1973).

4. Future studies of learning and memory

Future studies will determine whether the metabolism within a neuron differs before and after a new learning event. It would be critical

to determine metabolic changes in neurons that were activated during learning but not selected for a memory engram (i.e., the ones that lost the competition with other neurons) with those in neurons that were activated during the learning process but *were selected*. However, to fully address the hypotheses we presented in this review, significant technological advances are needed, such as in vivo monitoring of cellular metabolism before and during the acquisition of a new skill, subsequent memory consolidation, and memory retrieval.

We also believe that the intrinsic activity and intracellular metabolism of non-neuronal brain cells influence learning and memory. For example, glial cells contribute to information encoding and memory storage (Zorec et al., 2015). Astrocytes and microglia modulate synaptic function by releasing gliotransmitters, neurotropic and synaptogenic factors, chemokines, and cytokines (Ben Achour and Pascual, 2010). Oligodendrocytes and the myelin sheaths they generate are also crucial for certain types of learning (Xin and Chan, 2020). Thus, studies that explore these so-called supportive neural cells will provide a more complete picture of the mechanisms underlying learning and memory. Of particular interest is the comparison of the "metabolic profile" between glial cells and neurons during different stages of learning and memory formation.

Placing our hypothesis in a broader context of cell metabolism and considering the significance of central-peripheral integration in learning and memory, one could also suggest that the metabolic properties of cells in peripheral tissues influence their integration into a new functional system during learning (Hiramoto et al., 1997). We would need to identify how the metabolic changes in peripheral tissues during learning correspond to those in the brain and how long lasting the metabolic changes are. Notably, greater attention has been paid in the last decade to the role of peripheral organs and tissues in learning and memory. For example, the enteric nervous system and gut microbiota communicate with the brain via immune, endocrine, and neural pathways (Collins and Bercik, 2009; Cryan and Dinan, 2012; Marin and Kipnis, 2013) and can affect learning and memory, as demonstrated in adult bumble bees (Gareau et al., 2011; Hsiao et al., 2013). Tingley and associates (2021) presented data suggesting that activity in the hippocampus coordinates mnemonic and cognitive processes with whole-body metabolism. In addition, skeletal muscles secrete an amylase enzyme (amyrel) into circulation, which can induce responses in the brain to mediate anticipatory changes in distant organs (Rai et al., 2021). To evaluate central-peripheral integration in learning and memory, we can leverage approaches and techniques used to examine tissue-specific metabolic adaptation of immune cells in a cancer microenvironment (Elia and Haigis, 2021; Varanasi et al., 2020; Venerin et al., 2020) and NF-κB-regulated gene expression in microphages (Cheng et al., 2021; Nandagopal et al., 2021). Furthermore, multitissue multiomics analyses have been developed to dissect the central-peripheral complexities of behavior (Yang, 2020). We believe that systematic evaluation of metabolic activity throughout the body will reveal peripheral components of memory engrams and provide new insights into how peripheral tissues and metabolic networks are involved in new learning events.

5. Conclusion

We provided a brief history of the development of ideas about the intrinsic activity of the brain in the context of learning and memory, with a focus on the theory of the functional system developed in the scientific school of P. K. Anokhin. The ideas of P. K. Anokhin and V. B. Shvyrkov preceded the concepts emerging in cognitive neuroscience in which the intrinsic activity of the brain determines our perception, cognitive function, and goal-directed behavior. Moreover, their ideas led us to propose that neuronal metabolism is a determinant of predictive neuronal activity and crucial for the formation of a new functional system that leads to adaptive results.

We also hypothesize, as a mechanism underlying learning and memory, that neurons are recruited into a new functional system to resolve a metabolic mismatch. Successful learning leads to the elimination of this metabolic mismatch and the formation of a new network of neurons and non-neruonal cells (i.e., the new functional system), thereby achieving an adaptive result at the level of individual cells and the whole organism. Thus, learning cannot solely be attributed to increased synaptic connectivity but rather to the formation of a new metabolic state within the neurons and likely non-neruonal cells selected and recruited to a memory engram.

Data availability

Data will be made available on request.

Acknowledgments

We thank Dr. Karen Dietz for her expert help with scientific and language review of the manuscript.

Funding Information

This work was in part supported by the National Institutes of Health (MH-083728, R01DA041208, and MH-094268) to MVP, and the assignment # 0138–2022-0002 to YIA.

Conflict of interest

The authors declare no biomedical financial interests or potential conflicts of interest.

Authors' Contributions

YIA and MVP contributed equally to this work.

References

Alexandrov, Y., Jarvilehto, T., 1993. Activity versus reactivity in psychology and neurophysiology. Ecol. Psychol. 5 (1), 85–103. https://doi.org/10.1207/s15326969eco0501_4.

Abraham, W.C., Jones, O.D., Glanzman, D.L., 2019. Is plasticity of synapses the mechanism of long-term memory storage? NPJ Sci. Learn 4, 9. https://doi.org/10.1038/s41539-019-0048-y.

Aleksandrov, Y.I., 2006. Learning and memory: Traditional and systems approaches. Neurosci. Behav. Physiol. 36 (9), 969–985. https://doi.org/10.1007/s11055-006-0133-6.

Aleksandrov, Y.I., Korpusova, A.V., 1987. Role of goal in determination of neuronal activity of the rabbit motor and visual cortical areas. Neurosci. Behav. Physiol. 17 (6), 473–479. https://doi.org/10.1007/bf01186344.

Aleksandrov, Y.I., Shvirkov, V.B., 1974. Latent periods and synchronization of unit discharges of the visual and somatosensory cortex in response to conditioning flashes. Neurophysiology 6 (5), 437–439. https://doi.org/10.1007/BF01062619.

Alexandrov, Y.I., 1999. Psychophysiological regularities of the dynamics of individual experience and the "stream of consciousness". In: Taddei-Ferretti, C, C.M. (Ed.), Neuronal bases and psychological aspects of consciousness, Vol. 8. World Scientific, pp. 201–219. https://doi.org/10.1142/9789814313254_0017.

Alexandrov, Y.I., 2018. The subject of behavior and dynamics of its states. Russ. Psychol. J. 15 (2/1), 131–150. https://doi.org/10.21702/rpj.2018.2.1.8.

Alexandrov, Y.I., 2022. Systemic pscyhophysiology. In: Forsythe, C., Zotov, M.V., Radvansky, G.A., Ťsvetkova, L.A. (Eds.), Russian Cognitive Neuroscience: Historical And Cultural Context. Brill, pp. 56–86. https://doi.org/10.1163/9789004505667_004.

Alexandrov, Y.I., Grechenko, T.N., Gavrilov, V.V., Gorkin, A.G., Shevchenko, D.G., Grinchenko, Y.V., Aleksandrov, I.O., Maksimova, N.E., Bezdenezhnych, B.N., Bodunov, M.V., 2000. Formation and realization of individual experience: a psychophysiological approach. In: Miller, I.A.M., Balaban P. V, R. (Eds.), Complex Brain Functions. Conceptual Advances in Russian neuroscience, Vol. 2. Harwood Academic Publishers, pp. 181–200.

Alexandrov, Y.I., Sozinov, A.A., Svarnik, O.E., Gorkin, A.G., Kuzina, E.A., Gavrilov, V.V., 2018. Neuronal bases of systemic organization of behavior. In: Cheung-Hoi Yu A, L. L. (Ed.), Systems Neuroscience. Advances in Neurobiology, Vol. 21. Springer, pp. 1–33. https://doi.org/10.1007/978-3-319-94593-4_1.

Anokhin, P.K., 1958. Significance of the reticular formation for conditioned reflex. Acta Physiol. Pol. 9 (2), 131–141. ⟨https://www.ncbi.nlm.nih.gov/pubmed/13594558⟩.

Anokhin, P.K., 1968. Nodular mechanism of functional systems as a self-regulating apparatus. Prog. Brain Res 22, 230–251. https://doi.org/10.1016/s0079-6123(08)63509-8.

Anokhin, P.K., 1974. Biology and Neurophysiology of the Conditioned Reflex and Its Role in Adaptive Behavior. Pergamon Press first ed.
Anokhin, P.K., 1984. Systems analysis of the integrative activity of the neuron (1974). Pavlov J. Biol. Sci. 19 (2), 43–101. https://doi.org/10.1007/BF03003132.
Anokhin, P.K., Shuleikina, K.V., 1977. System organization of alimentary behavior in the newborn and the developing cat. Dev. Psychobiol. 10 (5), 385–419. https://doi.org/10.1002/dev.420100502.
Arshavsky, Y.I., 2006. "The seven sins" of the Hebbian synapse: Can the hypothesis of synaptic plasticity explain long-term memory consolidation? Prog. Neurobiol. 80 (3), 99–113. https://doi.org/10.1016/j.pneurobio.2006.09.004.
Arshavsky, Y.I., 2017. Neurons versus networks: The Interplay between individual neurons and neural networks in cognitive functions. Neuroscientist 23 (4), 341–355. https://doi.org/10.1177/1073858416670124.
Attwell, D., Laughlin, S.B., 2001. An energy budget for signaling in the grey matter of the brain. J. Cereb. Blood Flow. Metab. 21 (10), 1133–1145. https://doi.org/10.1097/00004647-200110000-00001.
Baltaci, S.B., Mogulkoc, R., Baltaci, A.K., 2019. Molecular mechanisms of early and late LTP. Neurochem Res 44 (2), 281–296. https://doi.org/10.1007/s11064-018-2695-4.
Bar, M., 2007. The proactive brain: using analogies and associations to generate predictions. Trends Cogn. Sci. 11 (7), 280–289. https://doi.org/10.1016/j.tics.2007.05.005.
Barrett, L.F., Simmons, W.K., 2015. Interoceptive predictions in the brain. Nat. Rev. Neurosci. 16 (7), 419–429. https://doi.org/10.1038/nrn3950.
Barsalou, L.W., Kyle Simmons, W., Barbey, A.K., Wilson, C.D., 2003. Grounding conceptual knowledge in modality-specific systems. Trends Cogn. Sci. 7 (2), 84–91. https://doi.org/10.1016/s1364-6613(02)00029-3.
Bauernfeind, A.L., Barks, S.K., Duka, T., Grossman, L.I., Hof, P.R., Sherwood, C.C., 2014. Aerobic glycolysis in the primate brain: Reconsidering the implications for growth and maintenance. Brain Struct. Funct. 219 (4), 1149–1167. https://doi.org/10.1007/s00429-013-0662-z.
Ben Achour, S., Pascual, O., 2010. Glia: The many ways to modulate synaptic plasticity. Neurochem Int. 57 (4), 440–445. https://doi.org/10.1016/j.neuint.2010.02.013.
Ben Jacob, E., Becker, I., Shapira, Y., Levine, H., 2004. Bacterial linguistic communication and social intelligence. Trends Microbiol. 12 (8), 366–372. https://doi.org/10.1016/j.tim.2004.06.006.
Benomar, S., Ranava, D., Cárdenas, M.L., Trably, E., Rafrafi, Y., Ducret, A., Hamelin, J., Lojou, E., Steyer, J.P., Giudici-Orticoni, M.T., 2015. Nutritional stress induces exchange of cell material and energetic coupling between bacterial species. Nat. Commun. 6, 6283. https://doi.org/10.1038/ncomms7283.
Blair, H.T., Schafe, G.E., Bauer, E.P., Rodrigues, S.M., LeDoux, J.E., 2001. Synaptic plasticity in the lateral amygdala: A cellular hypothesis of fear conditioning. Learn Mem. 8 (5), 229–242. https://doi.org/10.1101/lm.30901.
Bordone, M.P., Salman, M.M., Titus, H.E., Amini, E., Andersen, J.V., Chakraborti, B., Diuba, A.V., Dubouskaya, T.G., Ehrke, E., Espindola de Freitas, A., Braga de Freitas, G., Goncalves, R.A., Gupta, D., Gupta, R., Ha, S.R., Hemming, I.A., Jaggar, M., Jakobsen, E., Kumari, P., Seidenbecher, C.I., 2019. The energetic brain - A review from students to students. J. Neurochem. 151 (2), 139–165. https://doi.org/10.1111/jnc.14829.
Bray, D., 2009. Wetware: A Computer in Every Living Cell. Yale University Press.
Brink, F., 1951. Excitation and conduction in the neuron. In: Stevens, S.S. (Ed.), Handbook of Experimental Psychology. Wiley, pp. 50–93.
Brodsky, V.Y., 2006. Direct cell-cell communication: a new approach derived from recent data on the nature and self-organisation of ultradian (circahoralian) intracellular rhythms. Biol. Rev. Camb. Philos. Soc. 81 (1), 143–162. https://doi.org/10.1017/S1464793105006937.
Buzsáki, G., 2019. The Brain from inside Out. Oxford University Press.
Cedernaes, J., Waldeck, N., Bass, J., 2019. Neurogenetic basis for circadian regulation of metabolism by the hypothalamus. Genes Dev. 33 (17–18), 1136–1158. https://doi.org/10.1101/gad.328633.119.
Chen, C.F., von Baumgarten, R., Harth, O., 1973. Metabolic aspects of the rhythmogenesis in Aplysia pacemaker neurons. Pflug. Arch. 345 (3), 179–193. https://doi.org/10.1007/bf00586333.
Chen, W.G., Schloesser, D., Arensdorf, A.M., Simmons, J.M., Cui, C., Valentino, R., Gnadt, J.W., Nielsen, L., Hillaire-Clarke, C.S., Spruance, V., Horowitz, T.S., Vallejo, Y.F., Langevin, H.M., 2021. The emerging science of interoception: sensing, integrating, interpreting, and regulating signals within the self. Trends Neurosci. 44 (1), 3–16. https://doi.org/10.1016/j.tins.2020.10.007.
Cheng, Q.J., Ohta, S., Sheu, K.M., Spreafico, R., Adelaja, A., Taylor, B., Hoffmann, A., 2021. NF-κB dynamics determine the stimulus specificity of epigenomic reprogramming in macrophages. Science 372 (6548), 1349–1353. https://doi.org/10.1126/science.abc0269.
Clayton, N.S., Bussey, T.J., Dickinson, A., 2003. Can animals recall the past and plan for the future? Nat. Rev. Neurosci. 4 (8), 685–691. https://doi.org/10.1038/nrn1180.
Collins, S.M., Bercik, P., 2009. The relationship between intestinal microbiota and the central nervous system in normal gastrointestinal function and disease. Gastroenterology 136 (6), 2003–2014. https://doi.org/10.1053/j.gastro.2009.01.075.
Corson, S.A., Corson, E.O., 1985. From Descartes to Pavlov to Anokhin: the Evolution of General Systems Concepts in Biomedical Sciences in Eastern Europe. In: Pichot, P.B., Wolf, P., Thau, K, R. (Eds.), Biological psychiatry, higher nervous activity. Plenum Press, pp. 679–683. https://doi.org/10.1007/978-1-4684-8329-1_101.
Critchley, H.D., Harrison, N.A., 2013. Visceral influences on brain and behavior. Neuron 77 (4), 624–638. https://doi.org/10.1016/j.neuron.2013.02.008.
Cryan, J.F., Dinan, T.G., 2012. Mind-altering microorganisms: The impact of the gut microbiota on brain and behaviour. Nat. Rev. Neurosci. 13 (10), 701–712. https://doi.org/10.1038/nrn3346.
Davis, H.P., Squire, L.R., 1984. Protein synthesis and memory: A review. Psychol. Bull. 96 (3), 518–559. ⟨https://www.ncbi.nlm.nih.gov/pubmed/6096908⟩.
Dennett, D.C., 1996. Kinds of Minds: Toward an Understanding of Consciousness. Basic Books.
Dickinson, A., Mackintosh, N.J., 1978. Classical conditioning in animals. Annu Rev. Psychol. 29, 587–612. https://doi.org/10.1146/annurev.ps.29.020178.003103.
Domjan, M., 2000. General process learning theory: Challenges from response and stimulus factors. Int. J. Comp. Psychol. 13 (3–4), 101–118.
Domjan, M., 2005. Pavlovian conditioning: A functional perspective. Annu Rev. Psychol. 56, 179–206. https://doi.org/10.1146/annurev.psych.55.090902.141409.
Drdla, R., Gassner, M., Gingl, E., Sandkühler, J., 2009. Induction of synaptic long-term potentiation after opioid withdrawal. Science 325 (5937), 207–210. https://doi.org/10.1126/science.1171759.
Duran, J., Saez, I., Gruart, A., Guinovart, J.J., Delgado-Garcia, J.M., 2013. Impairment in long-term memory formation and learning-dependent synaptic plasticity in mice lacking glycogen synthase in the brain. J. Cereb. Blood Flow. Metab. 33 (4), 550–556. https://doi.org/10.1038/jcbfm.2012.200.
Edelman, G.M., Finkel, L.H., 1984. Neuronal group selection in the cerebral cortex. Dynamic Aspects of Neocortical Function. J. Wiley,, pp. 635–695.
Egorova, O.V., Anokhin, K.V., 2003. Experimental analysis of the processes of systems genesis: Expression of the c-fos gene in the chick brain during treatments inducing the development of the species-specific results-of-action acceptor. Neurosci. Behav. Physiol. 33 (3), 209–216.
Elia, I., Haigis, M.C., 2021. Metabolites and the tumour microenvironment: From cellular mechanisms to systemic metabolism. Nat. Metab. 3 (1), 21–32. https://doi.org/10.1038/s42255-020-00317-z.
Engel, A.K., Fries, P., Singer, W., 2001. Dynamic predictions: Oscillations and synchrony in top-down processing. Nat. Rev. Neurosci. 2 (10), 704–716. https://doi.org/10.1038/35094565.
Engel, A.K., Maye, A., Kurthen, M., Konig, P., 2013. Where's the action? The pragmatic turn in cognitive science. Trends Cogn. Sci. 17 (5), 202–209. https://doi.org/10.1016/j.tics.2013.03.006.
Fanselow, M.S., Wassum, K.M., 2015. The origins and organization of vertebrate pavlovian conditioning. Cold Spring Harb. Perspect. Biol. 8 (1), a021717. https://doi.org/10.1101/cshperspect.a021717.
Fujitani, M., Otani, Y., Miyajima, H., 2021. Pathophysiological roles of abnormal axon initial segments in neurodevelopmental disorders. Cells 10 (8), 2110. https://doi.org/10.3390/cells10082110.
Fünfschilling, U., Supplie, L.M., Mahad, D., Boretius, S., Saab, A.S., Edgar, J., Brinkmann, B.G., Kassmann, C.M., Tzvetanova, I.D., Möbius, W., Diaz, F., Meijer, D., Suter, U., Hamprecht, B., Sereda, M.W., Moraes, C.T., Frahm, J., Goebbels, S., Nave, K.A., 2012. Glycolytic oligodendrocytes maintain myelin and long-term axonal integrity. Nature 485 (7399), 517–521. https://doi.org/10.1038/nature11007.
Gareau, M.G., Wine, E., Rodrigues, D.M., Cho, J.H., Whary, M.T., Philpott, D.J., Macqueen, G., Sherman, P.M., 2011. Bacterial infection causes stress-induced memory dysfunction in mice. Gut 60 (3), 307–317. https://doi.org/10.1136/gut.2009.202515.
Green, D.R., Galluzzi, L., Kroemer, G., 2014. Cell biology. Metabolic control of cell death. Science 345 (6203), 1250256. https://doi.org/10.1126/science.1250256.
Han, J.H., Kushner, S.A., Yiu, A.P., Cole, C.J., Matynia, A., Brown, R.A., Neve, R.L., Guzowski, J.F., Silva, A.J., Josselyn, S.A., 2007. Neuronal competition and selection during memory formation. Science 316 (5823), 457–460. https://doi.org/10.1126/science.1139438.
Hebb, D.O., 1949. The Organization of Behavior; A Neuropsychological Theory. Wiley.
Hiramoto, R.N., Rogers, C.F., Demissie, S., Hsueh, C.M., Hiramoto, N.S., Lorden, J.F., Ghanta, V.K., 1997. Psychoneuroendocrine immunology: Site of recognition, learning and memory in the immune system and the brain. Int. J. Neurosci. 92 (3–4), 259–285. https://doi.org/10.3109/00207459708986405.
Hirase, H., Akther, S., Wang, X., Oe, Y., 2019. Glycogen distribution in mouse hippocampus. J. Neurosci. Res. 97 (8), 923–932. https://doi.org/10.1002/jnr.24386.
Hsiao, E.Y., McBride, S.W., Hsien, S., Sharon, G., Hyde, E.R., McCue, T., Codelli, J.A., Chow, J., Reisman, S.E., Petrosino, J.F., Patterson, P.H., Mazmanian, S.K., 2013. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. Cell 155 (7), 1451–1463. https://doi.org/10.1016/j.cell.2013.11.024.
Hyder, F., Rothman, D.L., Bennett, M.R., 2013. Cortical energy demands of signaling and nonsignaling components in brain are conserved across mammalian species and activity levels. Proc. Natl. Acad. Sci. USA 110 (9), 3549–3554. https://doi.org/10.1073/pnas.1214912110.
Josselyn, S.A., Frankland, P.W., 2018. Memory allocation: Mechanisms and function. Annu Rev. Neurosci. 41, 389–413. https://doi.org/10.1146/annurev-neuro-080317-061956.
Josselyn, S.A., Tonegawa, S., 2020. Memory engrams: Recalling the past and imagining the future. Science 367 (6473). https://doi.org/10.1126/science.aaw4325.
Josselyn, S.A., Kohler, S., Frankland, P.W., 2015. Finding the engram. Nat. Rev. Neurosci. 16 (9), 521–534. https://doi.org/10.1038/nrn4000.
Kandel, E.R., Dudai, Y., Mayford, M.R., 2014. The molecular and systems biology of memory. Cell 157 (1), 163–186. https://doi.org/10.1016/j.cell.2014.03.001.
Kann, O., Kovács, R., 2007. Mitochondria and neuronal activity. Am. J. Physiol. Cell Physiol. 292 (2), C641–C657. https://doi.org/10.1152/ajpcell.00222.2006.
Kolbeneva, M.G., Alexandrov, Y.I., 2016. Mental reactivation and pleasantness judgment of experience related to vision, hearing, skin sensations, taste and olfaction. PLoS One 11 (7), e0159036. https://doi.org/10.1371/journal.pone.0159036.

Langille, J.J., Brown, R.E., 2018. The synaptic theory of memory: A historical survey and reconciliation of recent opposition. Front Syst. Neurosci. 12, 52. https://doi.org/10.3389/fnsys.2018.00052.
Leterrier, C., Dargent, B., 2014. No Pasaran! Role of the axon initial segment in the regulation of protein transport and the maintenance of axonal identity. Semin Cell Dev. Biol. 27, 44–51 (Mar).
Llinas, R., Leznik, E., Makarenko, V.I., 2002. On the amazing olivocerebellar system. Ann. N.Y Acad. Sci. 978, 258–272. https://doi.org/10.1111/j.1749-6632.2002.tb07573.x.
Llinás, R.R., 2001. I of the Vortex: from Neurons to Self, first ed. MIT Press,.
Luczak, A., McNaughton, B.L., Kubo, Y., 2022. Neurons learn by predicting future activity. Nat. Mach. Intell. 4 (1), 62–72. https://doi.org/10.1038/s42256-021-00430-y.
Magistretti, P.J., Chatton, J.Y., 2005. Relationship between L-glutamate-regulated intracellular Na+ dynamics and ATP hydrolysis in astrocytes. J. Neural Transm. (Vienna) 112 (1), 77–85. https://doi.org/10.1007/s00702-004-0171-6.
Mann, K., Deny, S., Ganguli, S., Clandinin, T.R., 2021. Coupling of activity, metabolism and behaviour across the *Drosophila* brain. Nature 593 (7858), 244–248. https://doi.org/10.1038/s41586-021-03497-0.
Marin, I., Kipnis, J., 2013. Learning and memory. And the immune system. Learn Mem. 20 (10), 601–606. https://doi.org/10.1101/lm.028357.112.
Martin, S.J., Morris, R.G., 2002. New life in an old idea: The synaptic plasticity and memory hypothesis revisited. Hippocampus 12 (5), 609–636. https://doi.org/10.1002/hipo.10107.
Mason, E.F., Rathmell, J.C., 2011. Cell metabolism: An essential link between cell growth and apoptosis. Biochim Biophys. Acta 1813 (4), 645–654. https://doi.org/10.1016/j.bbamcr.2010.08.011.
Mattson, M.P., Gleichmann, M., Cheng, A., 2008. Mitochondria in neuroplasticity and neurological disorders. Neuron 60 (5), 748–766. https://doi.org/10.1016/j.neuron.2008.10.010.
McEachern, J.C., Shaw, C.A., 1996. An alternative to the LTP orthodoxy: A plasticity-pathology continuum model. Brain Res. Rev. 22 (1), 51–92.
McNay, E.C., Fries, T.M., Gold, P.E., 2000. Decreases in rat extracellular hippocampal glucose concentration associated with cognitive demand during a spatial task. Proc. Natl. Acad. Sci. USA 97 (6), 2881–2885. https://doi.org/10.1073/pnas.050583697.
McNay, E.C., McCarty, R.C., Gold, P.E., 2001. Fluctuations in brain glucose concentration during behavioral testing: dissociations between brain areas and between brain and blood. Neurobiol. Learn Mem. 75 (3), 325–337. https://doi.org/10.1006/nlme.2000.3976.
Nandagopal, N., Jambhekar, A., Lahav, G., 2021. Preparing macrophages for the future. Science 372 (6548), 1263–1264. https://doi.org/10.1126/science.abj2040.
Newman, L.A., Korol, D.L., Gold, P.E., 2011. Lactate produced by glycogenolysis in astrocytes regulates memory processing. PLoS One 6 (12), e28427. https://doi.org/10.1371/journal.pone.0028427.
Nicoll, R.A., 2017. A brief history of long-term potentiation. Neuron 93 (2), 281–290. https://doi.org/10.1016/j.neuron.2016.12.015.
Niedenthal, P.M., 2007. Embodying emotion. Science 316 (5827), 1002–1005. https://doi.org/10.1126/science.1136930.
Olsen, L.F., Andersen, A.Z., Lunding, A., Brasen, J.C., Poulsen, A.K., 2009. Regulation of glycolytic oscillations by mitochondrial and plasma membrane H+-ATPases. Biophys. J. 96 (9), 3850–3861. https://doi.org/10.1016/j.bpj.2009.02.026.
Pande, S., Shitut, S., Freund, L., Westermann, M., Bertels, F., Colesie, C., Bischofs, I.B., Kost, C., 2015. Metabolic cross-feeding via intercellular nanotubes among bacteria. Nat. Commun. 6, 6238. https://doi.org/10.1038/ncomms7238.
Pare, D., 2002. Mechanisms of Pavlovian fear conditioning: Has the engram been located? Trends Neurosci. 25 (9), 436–437. https://doi.org/10.1016/s0166-2236(02)02243-9 discussion 437-438.
Park, S., Kramer, E.E., Mercaldo, V., Rashid, A.J., Insel, N., Frankland, P.W., Josselyn, S.A., 2016. Neuronal allocation to a hippocampal engram. Neuropsychopharmacology 41 (13), 2987–2993. https://doi.org/10.1038/npp.2016.73.
Pellerin, L., Magistretti, P.J., 1997. Glutamate uptake stimulates Na+,K+-ATPase activity in astrocytes via activation of a distinct subunit highly sensitive to ouabain. J. Neurochem 69 (5), 2132–2137. https://doi.org/10.1046/j.1471-4159.1997.69052132.x.
Pezzulo, G., Zorzi, M., Corbetta, M., 2021. The secret life of predictive brains: What's spontaneous activity for? Trends Cogn. Sci. 25 (9), 730–743. https://doi.org/10.1016/j.tics.2021.05.007.
Pfeiffer, T., Bonhoeffer, S., 2004. Evolution of cross-feeding in microbial populations. Am. Nat. 163 (6), E126–E135. https://doi.org/10.1086/383593.
Quistgaard, E.M., Nissen, J.D., Hansen, S., Nissen, P., 2021. Mind the Gap: Molecular Architecture of the Axon Initial Segment - From Fold Prediction to a Mechanistic Model of Function? Oct 1 J. Mol. Biol. 433 (20), 167176. https://doi.org/10.1016/j.jmb.2021.167176.
Raefsky, S.M., Mattson, M.P., 2017. Adaptive responses of neuronal mitochondria to bioenergetic challenges: Roles in neuroplasticity and disease resistance. Free Radic. Biol. Med 102, 203–216. https://doi.org/10.1016/j.freeradbiomed.2016.11.045.
Rai, M., Coleman, Z., Curley, M., Nityanandam, A., Platt, A., Robles-Murguia, M., Jiao, J., Finkelstein, D., Wang, Y.D., Xu, B., Fan, Y., Demontis, F., 2021. Proteasome stress in skeletal muscle mounts a long-range protective response that delays retinal and brain aging. Cell Metab. 33 (6), 1137–1154. https://doi.org/10.1016/j.cmet.2021.03.005.
Raichle, M.E., 2010. Two views of brain function. Trends Cogn. Sci. 14 (4), 180–190. https://doi.org/10.1016/j.tics.2010.01.008.
Raichle, M.E., 2015. The restless brain: how intrinsic activity organizes brain function. Philos. Trans. R. Soc. Lond. B Biol. Sci. 370 (1668) https://doi.org/10.1098/rstb.2014.0172.
Raichle, M.E., Mintun, M.A., 2006. Brain work and brain imaging. Annu Rev. Neurosci. 29, 449–476. https://doi.org/10.1146/annurev.neuro.29.051605.112819.
Rao-Ruiz, P., Yu, J., Kushner, S.A., Josselyn, S.A., 2019. Neuronal competition: Microcircuit mechanisms define the sparsity of the engram. Curr. Opin. Neurobiol. 54, 163–170. https://doi.org/10.1016/j.conb.2018.10.013.
Rich, L.R., Harris, W., Brown, A.M., 2019. The role of brain glycogen in supporting physiological function. Front Neurosci. 13, 1176. https://doi.org/10.3389/fnins.2019.01176.
Sah, P., Westbrook, R.F., Luthi, A., 2008. Fear conditioning and long-term potentiation in the amygdala: what really is the connection? Ann. N. Y Acad. Sci. 1129, 88–95. https://doi.org/10.1196/annals.1417.020.
Sandler Lev, U.T., 2008. Neural cell behavior and fuzzy logic. Springer Science+Business Media, LLC,.
Schulkin, J., 2003. Allostasis: A neural behavioral perspective. discussion 28-30 Horm. Behav. 43 (1), 21–27. https://doi.org/10.1016/s0018-506x(02)00035-1.
Schulkin, J., Sterling, P., 2019. Allostasis: A brain-centered, predictive mode of physiological regulation. Trends Neurosci. 42 (10), 740–752. https://doi.org/10.1016/j.tins.2019.07.010.
Sejnowski, T.J., 1999. The book of Hebb. Neuron 24 (4), 773–776. https://doi.org/10.1016/s0896-6273(00)81025-9.
Sherrington, C., 1951. Man on his nature, second ed. Penguin Books Ltd.
Shvyrkov, V.B., 1986. Behavioral specialization of neurons and the system-selection hypothesis of learning. In: Klix, F., H, Hagendorf (Eds.), Human memory and cognitive capabilities. Elsevier, pp. 599–611.
Shvyrkov, V.B. (1990). Neurophysiological study of systemic mechanisms of behavior. Amerind Publishing Co.
Silva, A.J., 2003. Molecular and cellular cognitive studies of the role of synaptic plasticity in memory. J. Neurobiol. 54 (1), 224–237. https://doi.org/10.1002/neu.10169.
Sterling, P., 2012. Allostasis: A model of predictive regulation. Physiol. Behav. 106 (1), 5–15. https://doi.org/10.1016/j.physbeh.2011.06.004.
Styr, B., Gonen, N., Zarhin, D., Ruggiero, A., Atsmon, R., Gazit, N., Braun, G., Frere, S., Vertkin, I., Shapira, I., Harel, M., Heim, L.R., Katsenelson, M., Rechnitz, O., Fadila, S., Derdikman, D., Rubinstein, M., Geiger, T., Ruppin, E., Slutsky, I., 2019. Mitochondrial regulation of the hippocampal firing rate set point and seizure susceptibility. Neuron 102 (5), 1009–1024. https://doi.org/10.1016/j.neuron.2019.03.045.
Suzuki, A., Stern, S.A., Bozdagi, O., Huntley, G.W., Walker, R.H., Magistretti, P.J., Alberini, C.M., 2011. Astrocyte-neuron lactate transport is required for long-term memory formation. Cell 144 (5), 810–823. https://doi.org/10.1016/j.cell.2011.02.018.
Tadi, M., Allaman, I., Lengacher, S., Grenningloh, G., Magistretti, P.J., 2015. Learning-induced gene expression in the hippocampus reveals a role of neuron-astrocyte metabolic coupling in long term memory. PLoS One 10 (10), e0141568. https://doi.org/10.1371/journal.pone.0141568.
Timberlake, W., 1993. Animal behavior: a continuing synthesis. Annu Rev. Psychol. 44, 675–708. https://doi.org/10.1146/annurev.ps.44.020193.003331.
Timberlake, W., 1994. Behavior systems, associationism, and Pavlovian conditioning. Psychon. Bull. Rev. 1 (4), 405–420. https://doi.org/10.3758/BF03210945.
Tingley, D., McClain, K., Kaya, E., Carpenter, J., Buzsaki, G., 2021. A metabolic function of the hippocampal sharp wave-ripple. Nature 597 (7874), 82–86. https://doi.org/10.1038/s41586-021-03811-w.
Tonegawa, S., Liu, X., Ramirez, S., Redondo, R., 2015. Memory engram cells have come of age. Neuron 87 (5), 918–931. https://doi.org/10.1016/j.neuron.2015.08.002.
Tonegawa, S., Pignatelli, M., Roy, D.S., Ryan, T.J., 2015. Memory engram storage and retrieval. Curr. Opin. Neurobiol. 35, 101–109. https://doi.org/10.1016/j.conb.2015.07.009.
Trettenbrein, P.C., 2016. The demise of the synapse as the locus of memory: a looming paradigm shift? Front Syst. Neurosci. 10, 88. https://doi.org/10.3389/fnsys.2016.00088.
Tully, T., Preat, T., Boynton, S.C., Del Vecchio, M., 1994. Genetic dissection of consolidated memory in *Drosophila*. Cell 79 (1), 35–47. https://doi.org/10.1016/0092-8674(94)90398-0.
Varanasi, S.K., Kumar, S.V., Rouse, B.T., 2020. Determinants of Tissue-Specific Metabolic Adaptation of T Cells. Cell Metab. 32 (6), 908–919. https://doi.org/10.1016/j.cmet.2020.10.013.
Venerin, A.A., Venerina, Y.A., Alexandrov, Y.I., 2020. Cell functioning in norm and pathology in terms of the activity paradigm: Oncogenesis. Med Hypotheses 144, 110240. https://doi.org/10.1016/j.mehy.2020.110240.
Verworn, M., & Lee, F.S. (1899). General physiology; an outline of the science of life. The Macmillan company.
Vikman, K.S., Duggan, A.W., Siddall, P.J., 2003. Increased ability to induce long-term potentiation of spinal dorsal horn neurones in monoarthritic rats. Brain Res 990 (1–2), 51–57. https://doi.org/10.1016/s0006-8993(03)03385-7.
Virchow, R., 1860. Cellular Pathology, as Based upon Physiological and Pathological Histology. Twenty Lectures Delivered in the Pathological Institute of Berlin during the Months of February. R. M. De Witt. March and April, 1858 (F. Chance, Trans.).
Watts, A.G., 2017. Great expectations: Anticipatory control of magnocellular vasopressin neurons. Neuron 93 (1), 1–2. https://doi.org/10.1016/j.neuron.2016.12.033.
Weber, A., Prokazov, Y., Zuschratter, W., Hauser, M.J., 2012. Desynchronisation of glycolytic oscillations in yeast cell populations. PLoS One 7 (9), e43276. https://doi.org/10.1371/journal.pone.0043276.
Xin, W., Chan, J.R., 2020. Myelin plasticity: Sculpting circuits in learning and memory. Nat. Rev. Neurosci. 21 (12), 682–694. https://doi.org/10.1038/s41583-020-00379-8.

Yang, X., 2020. Multitissue multiomics systems biology to dissect complex diseases. Trends Mol. Med 26 (8), 718–728. https://doi.org/10.1016/j.molmed.2020.04.006.
Yiu, A.P., Mercaldo, V., Yan, C., Richards, B., Rashid, A.J., Hsiang, H.L., Pressey, J., Mahadevan, V., Tran, M.M., Kushner, S.A., Woodin, M.A., Frankland, P.W., Josselyn, S.A., 2014. Neurons are recruited to a memory trace based on relative neuronal excitability immediately before training. Neuron 83 (3), 722–735. https://doi.org/10.1016/j.neuron.2014.07.017.
Yuste, R., MacLean, J.N., Smith, J., Lansner, A., 2005. The cortex as a central pattern generator. Nat. Rev. Neurosci. 6 (6), 477–483. https://doi.org/10.1038/nrn1686.
Zaslona, Z., O'Neill, L.A.J., 2020. Cytokine-like Roles for Metabolites in Immunity. Mol. Cell 78 (5), 814–823. https://doi.org/10.1016/j.molcel.2020.04.002.
Zorec, R., Horvat, A., Vardjan, N., Verkhratsky, A., 2015. Memory formation shaped by astroglia. Front Integr. Neurosci. 9, 56. https://doi.org/10.3389/fnint.2015.00056.