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Can memory exist outside of brain and be transferred? Historical review, issues & ways forward

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ABSTRACT

Learning and memory are among the executive functions attributed to intelligent forms of life. Unfortunately, there is a lack of clear understanding regarding the underlying mechanisms governing these functions. Most of the modern day scientists attribute these functions solely to brain. However, in the latter half of last century, a number of reports suggested existence of extra-cranial memory and potential of its transfer between animals. Some have linked this phenomenon to RNA while others believed that peptides were responsible. The terms like “educated RNA” and “scotophobin” were coined. This atypical work involving flatworms, yeast RNA and scotophobin was received with deep skepticism and ultimately disregarded. However, the recent reproduction of some of this earlier work by scientists at Tufts University has reignited the debate on the mechanisms of learning and memory. Keeping this in view, we believe it is high time to summarize this historical work and discuss the possibilities to delineate these atypical claims. The objective is to incite the present day researchers to explore this opportunity under the perspective of newer advancements in science.

Introduction

Learning and memory are among the executive functions that constitute cognition. The former is the process of acquiring new information, while later is the process of storing it. Memory is actually a change in response to the experience, which helps in developing more appropriate response upon next stimuli. “What actually this change is” and “where it happens” are the questions commonly encountered by scientists working in this area. These questions have mainly remained unanswered despite the enormous data generated by modern neuroscience. The older concepts such as synaptic plasticity and long term potentiation are generally used to describe the formation and storage of memories in the brain [1,2]. The flat-lining of progress in this area can also be reflected from the failure in development of drugs used to treat the memory disorders. For instance, Alzheimer is the leading cause of dementia and forecasted to affect 1 in 85 humans by the year 2050 [3]. It progresses insidiously with an average life expectancy of about 7 years for the patients after diagnosis [4]. Various underlying mechanisms have been proposed to explain the pathogenesis of Alzheimer’s disease, including amyloidosis, Tau protein hyperphosphorylation, oxidative stress, and mitochondrial alterations [5]. However, none of the aforesaid attributes has led to the development of drug(s), which can offer permanent cure. Hence, the situation presses the need of identifying newer therapeutic targets. In this regard, the understanding of the phenomenon of learning and memory is inevitable. A search of the literature revealed that much of the present day research is focused on studying mechanisms underlying neurodegeneration, and identification of compounds offering neuroprotection. On the contrary, reports describing the physiology of learning and memory are seldom encountered. A considerable amount of work done on the basics of memory during the last century resulted in the noble prize in 2000 for Eric Kandel, Arvid Carlsson, and Paul Greengard, and for O'Keefe, May-Britt Moser and Edvard Moser in 2014. However, at the same time, the enormous work carried out on body/cellular memory and transferable potential of memory remained in grey area and forgotten.

Can memory exist outside of brain?

Learning and memory have been the topics of interest since the days of emergence of modern neuroscience. The brain became the focused organ of study and neurons were considered as the sole players. Even Ramon Cajal associated memory with neuronal growth. Decades of research and reports led to the deep rooting of these concepts in the scientific community and seldom questioned [6]. Outside these

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overwhelming beliefs exists the neglected science of memory outside brain, generally termed as body or cellular memory. According to this, the entire body and its cells are capable of storing memories. It is in line with the notion that all living beings, irrespective of presence of brain, have the ability to learn and memorize [7]. In case of living beings, the organisms which lack proper brain (Aneural) demonstrate the signs of primitive learning and memory, which is generally of cellular origin. For instance, the slime mold was shown to learn the patterns of electric pulse, predict and modify its behavior accordingly [8]. This simple creation was shown to be intelligent enough to find minimum length solution between two points [9] and shown to be smart and possess intelligence [10]. These reports showed that cells, not only neurons, are smart and endowed with the potential to perceive the signal, interpret, and modify response according to the need. Furthermore, the brainless plants are generally ignored in discussions about cognition. However, the evolutionary changes to adapt for harsh climatic conditions (temperature, salinity etc) are actually the changes in response to experience and should be taken as memory. It is worth mentioning that plants are reported to exhibit the signs of intelligence through their behavior [11]. How the plant pay attention to environmental stimuli is suggested to be the point of focus for plant intelligence studies [12]. Furthermore, the intelligent temperature detection system was reported in *Arabidopsis* seeds, which plays decisive role in terminating dormancy [13]. The root tips, also called as root brains, along with motility and sensoriomotor organization was reported to constitute the system responsible for cognition [14]. It is of note that the plants are reported to possess action potential [15], which can be blocked by anesthetics [16]. Hence, they also possess animal like features generally assumed as requirements for cognition.

Bacterial resistance, efflux pumps in cancerous cells, phantom pains and sperm running are also the examples of extra neural learning. The cells do not required brain to learn and memorize. However, taking into account the organisms with centralized brain, the involvement of peripheral cells in learning and memory is generally considered irrelevant. The pioneering work in this regard was performed by McConnell in the middle of last century. He performed his experiments on the flatworms, which possesses centralized brain and remarkable ability to regenerate when chopped into small pieces. He trained the flatworm in a behavioral task followed by decapitation. It is of note that the re-grown flatworm showed the signs of training despite of the development of entirely new brain [17]. What the tail remembered is not known till date but this evidence bolstered the idea of cellular memory in complex form of life as well. In conformity, human bone [18], muscle [19], pancrease [20] and heart [21] are also shown to exhibit traces of memory. Hence, it is proposed that the biogenic approach, in contrast to anthropogenic, should be adopted in order to grasp the science of learning and memory more efficiently [22]. In this scenario, the recent work conducted at Tufts University has revived an interest in the findings of McConnell on the existence of memory outside brain [23].

Can memory be transfered *via* RNA?

McConnell further surprised the world with the report suggesting that the cannibalism of light-shock conditioned planaria enhanced the ability to learn the situation in fewer trials as compared to naïve planaria [24]. This experiment led to the basis of “memory transfer hypothesis”. As expected, the next attempt was to find out which biomolecule carried the memory. In this regard, the transfer of extracted RNA was found to be responsible [25]. The addition of RNAase, not DNAase or trypsin hindered the retention and transfer of memory [26]. Hence, he concluded that RNA is the engram and can be transferred. His work received tremendous attention as well as skepticism. Researchers started to reproduce his work. Some found similar results such as the use of ribonucleases was shown to block the retention of conditioned response in the regenerated flatworm planarian tails [27]. RNA based memory transfer was also shown in rats [28], and the same group reported an extremely exciting finding that the transfer of memory can also happen between species [29]. Another group reported the potential role of RNA in transfer of memory in rats [30]. The RNA extracted from the brain of trained rats was again shown to enhance the learning in naïve rats in passive avoidance of dark chamber [31]. Taken together, the aforementioned studies supported possibility of both extra-neural learning and role of RNA as engram. On the other hand, several other researchers failed to reproduce the results obtained from McConnell’s experiments. This included the set of experiments which supported the role of cannibalism in memory transfer, but attributed this to nutritional, metabolism, activation and sensitization factors [32]. In other words, the cannibalism gave physical strength and mental activation to the animals thereby increasing its performance in memory related tasks. These outcomes has decreased the overall acceptability of McConnell’s deductions and slowly faded from the scientific discussions. Furthermore, the arousal factor and lack of detailed mechanistic studies has also contributed in diluting the claims [33]. More recently, the flatworm experiments were successfully reproduced by scientists at Tufts University, using more sensitive automated behavioral training apparatus [23], thereby rejuvenating the forgotten claims of McConnell.

Is RNA itself an engram or a mediator?

After McConnell’s experiments, RNA has received considerable attention as a memory molecule. The fundamental questions emerging were: a) Is RNA itself a memory molecule or just an intermediate in the formation of memory? b) Are changes in RNA contents a cause or effect of behavioral change? [34]. A search of literature revealed numerous reports exhibiting the increase in RNA contents in response to learning and memory. For instance, the RNA content of lateral vestibular nucleus of rat was shown to be increased after motor learning task [35]. Avoidance learning was correlated with increased hippocampal RNA synthesis [36]. During this era, the influence of aforementioned reports on scientific community could be gauged from timely reviews on the role of RNA in memory [37,38]. These concepts were further strengthened by reports suggesting inhibition of memory formation in the presence of inhibitors of RNA synthesis such as actinomycin D [39] and 2,6 diaminopurine [40]. In similar lines, 8-Azaguanine (purine analog) hampers the formation of new memory in maze test without affecting the ability to recall previously learned maze [41]. Azaguanine was also shown to delay the fixation of experience, while 1-1,3-tricyano-2-amino-l-propene, which increases RNA concentration in brain, expedited it [42]. These set of experiments developed great deal of interest in exploring the possibility of ‘educated RNA’ as engram. The idea was further reinforced by report from Cameron and Solyom, which showed positive effect of yeast RNA on the memory of aged patients suffering from dementia [43]. Memory is often explained as a three stage phenomenon, including acquisition, consolidation (retention) and retrieval. Malfunction of any of these could potentially cause dementia. The question as to which step of memory is affected was answered by the same group, suggesting ‘retention of memory’ as the prime target of RNA administration [44]. These reports attracted considerable attention in delineating the relationship between yeast RNA and memory. It triggered series of experiments exploring the role of yeast RNA in the various memory related paradigms. In rats, the yeast RNA administration not only enhanced the rate of pole climbing learning in order to avoid shock, but also resisted extinction learning [45]. As mentioned above, the use of ribonucleases was shown to block the retention of conditioned response in the regenerated flatworm planarian tails [27]. These reports were in conformity with the aforementioned work suggesting retention of the memory as a consequence of the introduced RNA. Ideally, these outcomes should have triggered initiation of work specifically on the retention (consolidation) part of complex memory phenomenon. Our literature search could not find a single report describing progress along this important avenue. Hence, this intriguing