Review Article

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The Origins of Behavioral Neuroscience from a Learning and Memory Perspective

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Abstract

The discipline of behavioral neuroscience grew out of earlier incarnations such as biological psychology, physiological psychology, and psychobiology. All of these labels essentially refer to the idea that the principles of biology could be productively applied to the study of topics that had been studied before, but only from a more psychological perspective. These topics would include, but are not limited to, motivation, sensation, perception, sleep, emotion, and learning and memory. In this brief review, I focus on the topic of learning and memory and provide a history of the important milestones in the development of ideas about how the brain biologically accomplishes the task of learning and memory. Included are the early ideas of Plato, René Descartes, Théodule Ribot, et al. The review continues to the modern era of learning and memory research that begins with the description of H.M. by Brenda Milner, as well as the gradual discovery that the brain contains multiple learning and memory systems that operate in fundamentally different ways and that are supported by anatomically discrete brain structures. I conclude with a brief description of the work that lead to 2000 Nobel Prize being awarded to Eric Kandel and the 2014 Nobel Prize being awarded to John O'Keefe, Edvard Moser, and May-Britt Moser.

Keywords: Behavioral neuroscience, Learning and memory, Review, Origins, History

Introduction

The only impressions that can be made upon [the brain] are...through the sensory nerve-roots... The currents, once in, must find a way out. In getting out they leave their traces in the paths which they take. The only thing they can do, in short, is to deepen old paths or to make new ones; and the whole plasticity of the brain sums itself up in two words when we call it an organ in which currents pouring in from the sense-organs make with extreme facility paths which do not easily disappear. For, of course, a simple habit, like every other nervous event--the habit of snuffling, for example, or of putting one's hands into one's pockets, or of biting one's nails--is, mechanically, nothing but a reflex discharge; and its anatomical substratum must be the ...a path in the

system. William James (1890, p. 112).

The great questions of philosophy, the mind-body problem and the nature of knowledge, were the same questions that laid the foundations for modern psychology and then ultimately for the behavioral neuroscience of learning and memory. William James (Figure 1C; 1842-1910), a major figure in the development of modern psychology, devoted a full third of his seminal treatise *Principles of Psychology* (1890) to the brain and nervous system. Both James and Wilhelm Wundt, who founded experimental psychology, studied medicine and philosophy, and both considered themselves physiologists. Their objectives were not to reduce psychology to physiology, but rather to apply the scientific methods of physiology to the study of the mind

and then the brain and nervous system. Thus, philosophy gave rise to psychology and a branch of psychology gave rise to biological or physiological psychology, which then grew into behavioral neuroscience. The major topics in the behavioral neurosciences are sensory and motor processes, motivation, emotion, cognition and, as this review describes, learning and memory.

Figure 1: Headshots of Descartes (A), Ribot (B), James (C), Pavlov (D), Lashley (E), and Milner (F).

In the epigraph, William James was writing specifically of learned “habits.” James considered these habits to be learned forms of complex reflexive behaviors. The passage is interesting because it clearly identifies and addresses several important issues with respect to the neuroscience of learning and memory. First, in order to analyze learning and memory, it must be verifiable that it has indeed occurred. This has traditionally been accomplished by observing some change in behavior that indexes the learning. This requires that the memory has some neural “pathway” by which it can influence an output (i.e. “find a way out”) that can be measured, usually as an observable behavior. Secondly, in order for learning to take place, external stimuli capable of inducing the learning and memory must have access to a “pathway” into the nervous system. Finally, some change or modification must take place within the nervous system that serves as the neural substrate of the learning and the resulting memory.

To understand this simple scenario is to understand the nature of the physical processes that change the nervous

system and form the foundation of learning and memory. This fundamental problem has challenged and perplexed initially philosophers, more recently psychologists, and most recently neuroscientists. The philosopher Plato stated in his *Theaetetus* on the nature of knowledge that “there exists in the mind of man a block of wax, which is of different sizes in different men; harder, moister, and having more or less purity in one than another. Let us say that this tablet is a gift of Memory”. (Plato, circa 396 B.C. reviewed in Campbell, 1883) [1,2]. Plato believed that in the minds of men there existed some substance that was modifiable or pliant which served as the substrate for memory.

Antecedents for the behavioral neuroscience of learning and memory

René Descartes (Figure 1A; 1596-1650) is primarily remembered as a philosopher and mathematician, but he was also substantially interested in anatomy and physiology and could be considered a founding father of objective animal psychology. He viewed and explicitly defined animals as a collection of reflexive automatons. He suggested that memory was representations subserved by physical traces in the brain. Descartes suggested that memory was an activity-dependent facilitation between these traces:

Thus, when the soul wants to remember something... volition makes the gland lean first to one side and then to another, thus driving the spirits towards different regions of the brain until they come upon the one containing traces left by the object we want to remember. These traces consist simply of the fact that the pores of the brain through which the spirits previously made their way, owing to the presence of this object, have thereby become more apt than the others to be opened in the same way when the spirits again flow towards them. And so the spirits enter into these pores more easily when they come upon them, thereby producing in the gland that special movement which represents the same object to the soul, and makes it recognize the object as the one it wishes to remember [3].

This quote could be considered a prescient description of what was later formalized by Donald Hebb (1904-1985) in his book *The Organization of Behavior* (1949). Hebb postulated that “When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased [4]. This postulate

became known as *Hebb's Law* and is often colloquially described as "Neurons that fire together wire together." Accordingly, with Descartes's activity-dependent plasticity as a historical antecedent, Hebb predicted the now well-understood physiological phenomenon of activity-dependent, associative long-term potentiation (LTP), whereby prior activity patterns can result in a persistent strengthening/potentiation of an individual synapse, such that the activation of one neuron produces a larger response in another neuron than before the prior activity [5]. Today, LTP (and long-term depression) are widely accepted as primary physiological mechanisms for learning and memory.

William James labeled the neural changes described by Descartes and Hebbas plasticity. "Plasticity, then, in the wide sense of the word, means the possession of a structure weak enough to yield to an influence, but strong enough not to yield all at once" [6]. In 1825, as part of his theory of phrenology, Franz Joseph Gall proposed that specific memories were located in specific places in the brain [7]. These thoughts were echoed by James when he described this localized region as an area in the brain "more liable to be abraded than neighboring parts; a *locus minoris resistentiae*." (p. 222). We now know that the *locus minoris resistentiae* are the brain's "synapses," a term coined by the 1932 Noble Prize for Medicine winner Charles Sherrington (1857-1952).

According to Azmitia (2007) [8], the great neuroanatomist and the 1906 Nobel Prize in Physiology or Medicine winner, Santiago Ramón y Cajal (1852-1934) [9], suggested that learning and memory could cause cortical neurons to expand and contract. Cajal presented these ideas in his Croonian Lecture read on March 8th, 1894 to the Royal Society of Science in England:

One can admit as very likely that mental activity provokes a greater development of the protoplasmic apparatus and of the nerve collaterals in the part of the brain most utilized. In this way, preexisting connections between groups of cells could be notably reinforced by multiplication of the terminal branches of protoplasmic appendices and nerve collaterals; and, in addition, novel intercellular connections could be established thanks to the new formation of collaterals and protoplasmic expansions [9].

It has been understood for more than 125 years that memory changes over time. The French psychologist Théodule Armand Ribot (Figure 1B; 1839-1916) was

the first to suggest that memories are not immediately acquired in a form that will persist unchanged, but rather are slowly reorganized. Ribot was also the first to provide a general theory of memory based on the observation of pathological conditions. This theory was described in his monograph, *Diseases of Memory*, published first in French in 1881 [10] and translated into English in 1882 [11]. Ribot noted, "The destructive process is a regression from the new to the old, from the complex to the simple, from the voluntary to the automatic, from the least organized to the best organized" [11]. The final sentence of his book reads, "Finally, our pathological study has led us to this general conclusion: Memory consists of a process of organization of variable stages between two extreme limits-the new state, [and] the organic registration." Concerning "organic registration" Ribot wrote: "Modifications established for years in the nervous elements until they have become organic-dynamical associations and groups of associations called into activity hundreds and thousands of times-these remain; they have a great power of resisting destructive agencies. In this manner we explain a paradox of the memory: the new perishes and the old endures." (page 119). He described this phenomenon as "The Law of Regression, or Reversion." This law now is often referred to as *Ribot's Law* and can be used to describe the phenomenon of temporally graded retrograde amnesia.

In 1904 Ivan Petrovich Pavlov (Figure 1D; 1849-1936) was awarded the Nobel Prize in medicine for research in which he used dogs to study the physiology of digestion. This research on digestion set the stage for observing the phenomenon of classical conditioning. As early as 1880, Pavlov and his associates noticed that sham feedings, in which food was eaten but failed to reach the stomach (being lost through a surgically implanted esophageal fistula), produced gastric secretions, just like real food (Clark, 2004). Pavlov and his associates not only discovered the learning process of classical conditioning, they then went on to identify almost all of the major components of classical conditioning (i.e. conditioned and unconditioned stimuli and responses). His laboratory also developed the primary paradigms of delay, trace, simultaneous and backward conditioning, and identified and described many of the parameters that influence the process of classical conditioning.

It is under appreciated that the phenomenon of classical conditioning was also independently discovered in the United States by Edwin B. Twitmyer (1873-1943) while finishing his dissertation work on the "knee-jerk" reflex. Twitmyer observed, "during the adjustment of

the apparatus for an earlier group of experiments with one subject...a decided kick of both legs was observed to follow a tap of the signal bell occurring without the usual blow of the hammers on the tendons." Twitmyer conducted a number of follow-up studies that convinced him his initial observations were not an artifact. He was able to demonstrate the phenomenon with every subject he tested and determined that the new type of response required between 150 and 238 previous pairings of the bell and patellar tap. Subsequent interviewing indicated that the subjects insisted that the responses were not voluntary and in some cases could not be voluntarily inhibited by the subject. Twitmyer reported these findings in a paper entitled "Knee-jerks without stimulation of the patellar tendon" [12] at the 13th Annual Meeting of the American Psychological Association held in Philadelphia in 1904. In attendance were America's most distinguished psychologists and the meeting was presided over by none other than William James.

It is notable that although Twitmyer remained in relative obscurity, his single attempt to cast his newly discovered phenomenon in terms of neurophysiology, was in retrospect, far closer to modern-day concepts than any of Pavlov's theories, which were based on at least 532 papers published on the cerebral involvement in conditioning. It is now clear that Pavlov grossly underestimated the contribution subcortical structures make to classical conditioning. In contrast, and though brief in description, Twitmyer's theory regarding the neurophysiology of the conditioned patellar tendon reflex was not only prescient, but also entirely consistent with current work. According to Twitmyer:

"After a certain number of such trials [bell-tap-kick], the number varying for different subjects, the association of the sound of the bell and the kick becomes so fixed that the bell itself is capable of serving as a stimulus to the movement. Physiologically the repeated association of the functioning of the motor cells in the lumbar segment of the cord, upon which the kick immediately depends, with the excitation of centers in the nuclei of the medulla connected with the auditory conduction path, has resulted in developing a fixed relationship between them. The impulse entering the latter therefore finds an accustomed channel to the former [Thus], the sound of the bell alone is an adequate stimulus to the movement" (for review see Clark, 2004).

Pavlov's work on classical conditioning was essentially unknown in the United States until 1906 when his lecture

"The scientific investigation of the psychical faculties or processes in the higher animals" was published in the journal *Science* [13]. Pavlov's book *Conditioned Reflexes* was translated into English by a former student, G.V. Anrep, and published in 1927 [14]. This made all of Pavlov's conditioning work available in English for the first time. The availability of 25 years' worth of Pavlov's research, in vivid detail, led to increased interest in the experimental examination of classical conditioning as a phenomenon and as an enormously important paradigm for the behavioral neuroscience of learning and memory.

The search for the engram

Karl Lashley (Figure 1E; 1890-1958) was the most important early figure in the development of the behavioral neuroscience of learning and memory in the United States. Lashley earned his Ph.D. while working with John B. Watson (1878-1958) and was greatly influenced by Watson's developing concepts of "Behaviorism". Behaviorism was the purely objective experimental branch of psychology with a theoretical goal of predicting and controlling behavior [15,16]. The physical processes that underlie learning and the storage of memory was termed the "engram" by Richard Semon in 1904 [17] and given widespread attention by Lashley who was perhaps the first person to clearly conceptualize the issue in a framework that would lend itself to experimental analysis. Lashley focused on analyzing the brain mechanisms of learning and memory for the better part of the 1920s. During this period, Lashley's theoretical views of learning and memory were influenced by two synergistic paradigms: First, the localization of function in neurology and second, behaviorism in psychology.

At this point, localization of function in the cerebrum was the dominant view of brain organization. Consequently, Lashley believed it should be possible to localize the place in the cerebral cortex where learning changed the brain's organization to store the memory (i.e. localize the engram). Thus, localization of function and behaviorism were ideally suited schools of thought for merging. Lashley set about to systematically identify these learning locations-the engrams-in a series of studies culminating in his seminal monograph, *Brain Mechanisms of Intelligence* (1929) [18]. In this long series of experiments, he made lesions of varying sizes and locations in the rat cerebral cortex and tested the rats on mazes differing in difficulty. The conclusions of this series of experiments profoundly changed Lashley's view of the organization of learning and memory and had a remarkable impact on the young field-a field that was then termed "physiological

psychology", but would now be referred to as "behavioral neuroscience". Lashley concluded that the locus of the lesions was unimportant; the size however, was the critical variable, especially for the more difficult mazes. These findings led to the theoretical concepts of "mass action" and "equipotentiality". Mass action stated that what was critical to disrupting memory was the amount of cerebral tissue removed (larger lesion = larger impairment) and equipotentiality stated that all areas of the cerebral cortex were equally important (at least insofar as maze learning was concerned). These concepts of mass action and equipotentiality created vigorous debates in the field. An influential alternative perspective argued that rats were using a variety of sensory cues to solve the mazes; as more of the sensory regions of the cortex were destroyed, fewer and fewer cues remained available to guide performance. Lashley and his associates however countered by demonstrating that removing the eyes produced less effect on maze learning than removing the visual area of the cortex. Out of this debate came a long series of lesion-behavior experiments in the 1940s analyzing behavioral "functions" of the cerebral cortex. This work essentially failed to settle the matter. This led to Lashley's often quoted and particularly pessimistic observation: "This series of experiments has yielded a good bit of information about what and where the memory trace is not. It has discovered nothing directly of the real nature of the memory trace. I sometimes feel, in reviewing the evidence of the localization of the memory trace, that the necessary conclusion is that learning is just not possible. It is difficult to conceive of a mechanism that can satisfy the conditions set for it. Nevertheless, in spite of such evidence against it, learning sometimes does occur" [19]. It is interesting to consider that like Pavlov, Lashley grossly underestimated the contributions non-neocortical structures make to learning and memory. Clearer insights into the organization of learning and memory would have to await the dawning of the modern era of the behavioral neuroscience of learning and memory, which began a mere seven years later with the description of patient H.M. [20] by Brenda Milner (Figure 1F; 1918).

Neurologic patient Henry Molaison (H.M.)

H. M. had a history of minor and major seizures that were unresponsive to antiepileptic medications that were reaching toxic levels. In an effort to control the seizures, a decision was made to utilize an experimental surgical procedure. On September 1, 1953, William Scoville removed H.M.'s medial temporal lobes (MTL) bilaterally. The surgery succeeded in that it reduced the frequency

and severity of the seizures. However, H.M. was left with profound amnesia that was readily apparent immediately after surgery [21]. In the decades that followed, the evaluation of H.M. and others with similar brain damage revealed several fundamental properties concerning the biological organization of learning and memory.

Importantly, this work revealed that memory was indeed dependent upon the cerebrum and was distinct from other abilities and dispositions like personality, motivation, perception and intelligence. Damage to the MTL only impaired long-term memory and did not impair working memory. That is, a limited amount of information could still be held for a brief period. This allows, for example, a posed question to be remembered long enough to provide an appropriate answer. It was also discovered that there were other forms of memory not disrupted by MTL damage such as habits and perceptual learning (see below; Multiple Memory Systems). In fact, the MTL only supports one form of memory termed declarative memory. This is memory in the ordinary or colloquial use of the term. It is the type of memory that we are consciously aware of the content, which can be brought to mind and declared. Finally, the MTL is not the ultimate repository of long-term memory. Memories learned shortly before MTL damage is lost whereas more remote memories are spared and independent of the MTL.

It is notable that these observations were met initially with great skepticism. This was primarily due to the early failures to develop an animal model of H.M.'s memory impairments. These attempts began almost immediately when the surgeon who performed the resection on H.M., William Scoville, made similar lesions in monkeys [22]. The problem was, it was not yet understood that humans and experimental animals often approach ostensibly similar tasks using different strategies-strategies that are often independent of the MTL. This situation was true for work in the monkey and in the rodent. Experimental work during the 1960s made it clear that the observed impairments in rats with, for example, hippocampal lesions, did not adequately model the human condition [23]. Thus, researchers were more likely to interpret their findings within the framework of response inhibition as first outlined by Ivan Pavlov [14], and less likely to relate their work to human studies of memory-impaired patients. Tellingly, in a review of the literature on the hippocampus and behavior, published a decade after the initial description of H.M., Robert Douglas lamented:

"Hippocampal lesions obviously do not impair learning in general, even when the learning involves retention for long periods of time. Thus, the animal and human data would appear to be in contradiction. This contradiction could be 'resolved' by postulating that the hippocampus has a different basic function in man and beast. Such a solution to this problem is generally unacceptable to physiological psychologists, however. Another possible resolution of this paradox is that the recent memory loss in man is a secondary effect of a different type of primary disorder. The author has chosen the latter course, and suggests that the recent memory loss in man is a genuine phenomenon, but that it is a byproduct of interference during storage and not due to a lack of ability to store, per se" [24].

Multiple learning and memory systems

It is now clear that the tasks given to animals with hippocampal lesions were tasks that animals would learn as a skill even if humans tended to learn the task by consciously memorizing the material. It was suggested that establishing an animal model would require developing tasks that assess the type of memory impaired in human amnesia and not just whatever task was convenient to use [25]. In 1978 Mortimer Mishkin [26], trained monkeys with lesions designed to mimic those of H.M. and tested them on the delayed no matching to sample (DNMS) task. This is a one-trial test of recognition memory. The monkeys displayed an impairment profile that was strikingly similar to H.M.'s profile in that working memory appeared to be spared, while long-term memory was robustly impaired. This groundbreaking study, along with others that followed, finally established an animal model for human MTL amnesia in the monkey (e.g. Squire and Zola-Morgan, 1983; Zola-Morgan and Squire, 1993) [27].

It is now understood that the MTL lobe exclusively supports declarative memory for facts (termed semantic memory) and events (termed episodic memory). Declarative memory can be contrasted with non declarative memory, which is a collection of different memory abilities that depend on different and discrete brain structures. We do not have conscious access to the content of non declarative memory. Rather these forms of memory are expressed through experience-based changes in performance.

Work in humans identified the phenomenon of priming, which is the improved ability to classify, detect, or produce an item because of a recent experience with the same or related item [28]. The striatum was

discovered to be important for gradual, feedback-guided learning that forms the basis of habit memory [29,30]. Simple forms of classical conditioning, like delay eye blink classical conditioning were found to be dependent on the cerebellum and associated brainstem circuitry [31,32]. Classical conditioning of fear responses is critically dependent on the amygdala, which is thought to be the structure that permanently encodes and stores the hedonic value of the aversive stimulus, used to classically condition the fear response [33]. Finally, phylogenetically early forms of non associative learning like habituation (a decrease or cessation of a response to a stimulus after repeated presentations) and sensitization (a learning process in which repeated administration of a stimulus results in the progressive amplification of a response) are also forms of non declarative memory. Figure 2 shows the categorical organization of the mammalian long-term memory systems and the brain structures that support these systems. It is important to note that other abilities that are related to learning and memory are the province of the neocortex, such as working memory, consolidation of memory, memory guided decision-making, and neocortical associative memory; and all of these forms of learning and memory can be modulated by transmitter systems.

The description of H.M. provided perhaps the most fundamental insight concerning the behavioral neuroscience of learning memory. Namely, that memory is a distinct ability that is completely dissociable from other cognitive abilities like intelligence, perception, and personality. This description also provided the first clear insights, which were gradually brought into sharper focus with animal studies that memory is a collection of different abilities that operate in fundamentally different ways and depend on discrete brain structures and systems.

Finally, it is important to note that Eric Kandel was awarded The Nobel Prize in Physiology or Medicine in 2000, primarily for his work with the large sea slug *Aplysia*. Kandel and his laboratory showed how memory is represented in neural circuits by changes in the efficiency of synapses and by identifying the molecular cascades that are responsible for those synaptic changes. His group demonstrated that phosphorylation in synapses is critical for establishing a form of short-term memory and that long-term memory requires protein synthesis that can lead to alterations in the function and shape of synapses [35]. Finally, to the extent that forming spatial maps and successful navigation requires learning and memory, the 2014 Nobel Prize in Physiology or

Medicine presented to John O'Keefe, Edvard Moser, and May-Britt Moser should be mentioned. In 1971, O'Keefe discovered hippocampal "place cells." These cells are always activated whenever a rat moved to a particular location in a room. Different cells were active in different locations. Thirty-three years later the Edvard and May-Britt Moser laboratories discovered entorhinal cortical "grid cells." Grid cells are place-modulated neurons that exhibit multiple firing fields that produce a periodic triangular array that covers the entire area of an open two-dimensional environment. These discoveries provide an electrophysiological explanation for how the brain forms a cognitive map and facilitates spatial navigation.

Figure 2: Memory taxonomy. Long-term memory (purple box) is made up of declarative memory (red boxes), which includes memory for facts (semantic memory) and events (episodic memory) and depends on the function of medial temporal lobe (MTL) regions. Non-declarative memory (blue boxes) is an umbrella term encompassing a collection of learning and memory abilities that are independent of the MTL and are principally supported by anatomically distinct and functionally independent brain regions. The critical brain region for each memory system (coronal sections through the human brain) is highlighted in red [34].

The basic insights described in this review provide many of the fundamental components that served as the foundation for the modern understanding of the behavioral neuroscience of learning and memory.

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Ethics approval and consent to participate

n/a

Consent for publication

I consent for this article to be published.

Availability of data and material

n/a

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I have no competing interests.

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Authors' contributions

I conceived of, researched, and wrote the paper.

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