About learning, memory, and neural circuits: an approaching to the cognitive processes in living systems.

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Abstract:

Learning can be considered a fundamental evolutionary advance to those living systems that acquired this capacity during the early evolution of life. Perception of an environment that has past and present, permitted primitive animals to acquire a more complete vision of the surrounding world. The cognitive use of information that is permanently available to the living system is now recognized as “learning”. Although many years have passed, and many researchers are deeply involved in the study of learning and memory, still its intricate nature is not completely understood. A review of common terms used in memory research such as, memory, learning, and trial are discussed and redefined in a more restricted form with the intention of reaching a common consensus. The most accepted model of learning is presented in a diagram of a “learning unit”, and a unifying concept of a “vector memory engram unit” for learning and storing of memory is also discussed. Finally, implications of the model are considered in the context of diseases that produce memory deficits in order to compare the predictions of the model with the behavioural evidence from patients with lesions in restricted brain zones.

1. Introduction:

One of the most fascinating problems in biology is the mechanisms and processes that living systems have developed in order to adapt to a changing and hostile environment enduring to achieve reproduction, and thus persisting in time as a species. The faculty to retain information about aspects of the environment turned out to be a very successful strategy as those systems having this capacity acquired a significant advantage with respect to any other simple living system that does not. Learning is the property that confers on the organisms the capacity to adapt to a changing environment by responding with appropriate behaviours based on previous experience. With this acquisition, complex organisms could access events that depend on time and, consequently, perceive the world with knowledge of the “past” and the “present”. This achievement was made possible by the development of analyzing neuronal units which coherently integrated environmental information on a time scale. Learning is a very complex process, and in spite of all the efforts that have been expended by many workers during the past years, its intrinsic mechanism is still not completely understood. Part of the difficulty lies on the molecular and cellular mechanisms whereby neuron codifies information remain unknown. Furthermore, the biochemical, behavioural and physiological approaches performed by independent researchers seldom interact to produce a complementary merged view. The purpose of the present review is to examine and revise concepts about learning, with the hope of reaching some consensus, to propose an alternative unifying idea of memory, and to speculate how encoded information may last in the neural circuits of neurons.

2. Concepts of learning and memory.

2.1 Memory.

In neuroscience, “memory” is a rather imprecise term. This is because this word is amply familiar and used in many different ways. This is not really very surprising, considering that even in scientific domains *memory* has been defined in a somewhat confusing manner, implying different notions, some of them contradictory. Many workers consider that *memory* is a process (Pontecorvo et al., 1996, Shen et al., 1994, Brunelli et al., 1997), many others view *memory* as information stored in the brain (Murray and Gaffan, 1994, McGaugh et al., 1993, Eichenbaum and Otto, 1992, Izquierdo et al., 1999, Holdstock et al., 2002, Squire and Bayley, 2007, Alvarez and Banzan, 1999, Alvarez and Ruarte, 2002), sometimes the term is applied at the same time with both connotations (Shen et al., 1994,), and frequently researchers do not define what memory is, assuming that the concept is clear enough and that its understanding may be taken for granted (Sutherland and McDonald, 1990, Schmajuk and DiCarlo, 1992, Volpe et al., 1992, Squire, 1992, Horel,1994, Ridley et al., 1996, Izquierdo et al., 1999, Squire and Bayley, 2007, Eisenstein, 1997, Chun and Turk-Browne, 2007, Jager et al., 2007, Diehl et al., 2007, Hartley et al., 2007). As one might expect, conclusions from possible projections of the experimental work appear confused or subject to a long-sustained debate. Thus, in this review some basic concepts implicit in memory research are revised, presenting and clarifying the author’s points of view and proposing a consensus for the many terms frequently used in memory and learning literature.

From a general point of view, the brain of complex living systems is mainly concerned with information, changes or steady state situations analysis of the environment. The well known fact that in man the relationship of afferent to efferent nervous fibers is about 20:1 (Livingston, 1991), conspicuously suggests that the brain is more interested in analyzing input data than generating effector actions on the environment. It can be speculated that the capacity to retain fragments of the environmental reality was a considerable and important evolutionary gain to animals. Thus, *memory* can be regarded as environmental information stored codified somewhere in the central nervous system. It then follows that having a *permanent* register or *long-term* memory of environmental data would be of benefit to an organism. It would be very difficult to visualize a living system *recognizing* a mate if memory of its congeners is not a constant register in its brain. Similar natural situations in daily environment-organism interactions would be disastrous if food, shelter, geographical regions, predators, threatening situations or sexual partners, to mention just a few, are not distinguished appropriately by the individual. This is evidently the main biological sense for possessing a *long-term memory* (Glenberg, 1997, Brunelli et al., 1997). In addition, this characteristic of long persistence of information in time has been the rationale for defining this memory as long-term memory (Cherkin, 1997, McGaugh, 1966, 1968, Funahashi and Kubota, 1994). Most of the time, the formation of a permanent register (memory) in the brain circuits is not a simple or straightforward process. Several steps appear necessary in order to generate a memory. The biological reason for this investment in time and energy is not clear, but from a practical point of view not all the possible information available from the environment needs to be stored as memory. Some critical mechanism filtering useful information from all the irrelevant data should be necessary, and this "filtering" action might require some time.

The process or processes occurring in brain neuronal circuits that permit environmental information to be stored as memory, and later used to cope the environment challenges, is defined as *learning* (Brunelli et al., 1997). Then, *learning* can be viewed as a *proprerty* of living systems that is sustained by a set of neuronal processes. According to this definition, *learning* is possible when one or many neural circuits are activated changing or generating inter- and intracellular changes during the processing of input signal information that eventually ends in a memory register (Woolf, 1998, Martinez and Derrick, 1996, Eichenbaum, 2003).

2.2 Learning as the result of different interacting processes.

Evidence has accumulated showing that learning occurs in three phases: acquisition, consolidation and evocation (Shen et al., 1994). During acquisition it is thought that the neural circuits establish a "trace" memory. Notwithstanding that after this stage a "memory" record is produced, it has been observed that this trace is not permanent. It is necessary that a *consolidation* of the labile trace memory must occur (Shen et al., 1994, Ridley et al., 1996, Steckler and Muir, 1996). This process for some experimental stimuli appears to last 2-3 hours after training or completion of acquisition (McGaugh, 1966, Izquierdo et al., 1999). Although some debate exists regarding whether acquisition and consolidation need to be sequential in order to a memory be generated, experimental data show that acquisition is a prerequisite for consolidation, and a memory is established only after the latter process is completed, (Gold and McGaugh, 1975, Alvarez and Banzan, 1996, Eichenbaum, 2003). A useful way to look at how memory can be generated in the brain is to define a *learning loop* such as is shown in

Figure 1.This loop is based on an analogy between computer digital software programs and the intrinsic biological function of learning in a living brain. The basic and key concept in this loop is the *task*. *Task* is all the instructions, steps or sensorial information from the environment that the system must follow in order to generate a memory. In general physiology the task represents a stimulus, and can be very simple or very complex. For example, to learn that the sign "♀" means "feminine" or "woman" can be considered a simple task. Meanwhile, to associate a particular sound with an imminent danger or with some particular threatening situation, or to look for an escape from a labyrinth guided by external clues are more complex tasks. Of course, tasks can be highly complex, and we may assert in general that while the more relationships or associations that must be made in the brain in order to acquire a given task, the more complex is the learning of that task. Tasks always imply some target or some objective to be accomplished. The task is the basic experimental instrument of researchers in the study of learning and memory. It has been used in a great variety of experimental models giving much useful information about learning processes (McGaugh et al., 1993, Dere et al., 2007, Alvarez and Banzan, 1996, 1999, Alvarez et al., 2001, Squire, 1992, Izquierdo et al., 1999, Meneses, 2007, Wood et al., 1999, Davis, 1992, Maxwell et al., 2003, Tavares and Tomaz, 2002, Barnes 1988). It is very instructive to view a "task" as being composed of discrete units of information that can be identified as steps or "items". In many cases, the steps or items are very easy to identify, as in the case of some passive conditioned avoidance responses (McGaugh et al., 1993, Izquierdo et al., 1999); however in some other cases distinguishing items can be more difficult (Barnes, 1988, Davis, 1992). Nevertheless, the artificial division of the task into steps has been very fruitful in understanding many characteristics of the learning process. Interestingly,

tasks are always associated with some particular behavioural response in subjects which usually indicate to the observer that a memory has been stored.

It would appear that the concept of "task" is meaningful only in the field of scientific research. However, it can be extended easily to daily activities in our own lives. To sit down and learn how to use a computer program, to read and understand some topic in a chapter from a textbook, and to learn how to drive a car, can all be divided into a series of steps or items composing the "task" to be learned. Many times after the task has been learned, it can be explained in detail, specifying each of the items from which it is composed. At other times, it can be executed in an automatic form, without a clear conscious notion of the individual items. Whether we consciously can explain the task or not, the information *is* recorded in a coded form as memory in the brain, thus permitting us to execute it correctly as many times as necessary, i.e. there is a *memory* register.

2.3 The concept of Trial.

The opportunity that a living system has to perform a task in order to retain it as a memory is called a *trial*. It is very useful to define the *trial* in terms of time and space, since the concept is valid not only in experimental work, where an investigator sets the conditions by which the animal can learn the task, but is also valid in everyday life where the environment and social life *impose* the need to learn information. Thus, when we are given a telephone number to remember or when we sit in front of a computer trying to learn to use some particular software, the number of times we actually perform the task are *trials*. The generality of this definition is that it can be applied to humans and also to animals, implying a similarity in the cognitive processes between species.

In some experimental models, many trials are necessary in order for some specific task to be retained (Barnes, 1988, Tavares and Tomaz, 2002, Wood et al., 1999, Alvarez and

Banzan, 1996). In others just only one single trial is enough (Izquierdo et al., 1999, Dere et al., 2007, McGaugh, 1966). When motivation or emotionality are present in the subject during acquisition, memory consolidation is facilitated (McGaugh et al., 1993), and the number of trials tends to diminish. However, if in an emotional situation the task is complex, such as the association of many clues to learn an avoidance response, trials do not necessarily tend to a minimum (Alvarez and Banzan, 1996, 1999). It appears then that the "quality" or complexity of the task demands reinforcement or repetitions in order for the neural circuit to consolidate it as memory (Tavares and Tomaz, 2002, Squire, 1992, Wood et al, 1999, Alvarez and Banzan, 1996, 1999).

Sometimes, the meaning of trials may be ambiguous, such as when a subject is *learning* some particular new task, and the trials can then be viewed as *training* opportunities for acquisition of the task. However, when the training period is over and sufficient time has elapsed to allow the consolidation phase to be completed, repetition of the trials now represents the *testing* of the recently consolidated memory. Thus, trials can have different connotations at the same time (Alvarez et al., 2001, Dere et al., 2007, Wolfman et al., 1994). From the experimental point of view, there is always a *delay* between acquisition and testing. It is this delay that is used to measure "memory efficiency" in many experimental models (Tavares and Tomaz, 2002, Squire, 1992, Eichenbaum, 2003).

2.4 The Learning Loop.

In the *learning loop* (Fig 1), the acquisition, consolidation and memory retrieval processes are assumed to be executed by separate functional modules (I-IV, Fig 1). Selective interference with these processes or lesions restricted to specific brain areas suggest that they are under separate control (Alvarez & Banzan, 1995, 1996a,b, McGaugh, 1966, Scoville and Milner, 1957, Milner 1966). However, it is not clear if these modules need to a single anatomical unit, or whether they can be in separate but connected brain regions. It is assumed that this functional unit works following an operational cycle. When a subject faces a task for the first time, a brain circuit evaluates whether the incoming task is “known” or not. Thus, an internal comparison is made by the relevant brain circuits. It is not known how this process is performed, but one of the simplest solution would be a logic comparison (is $S_{\text{input}} = S_{\text{stored}}$?). Input coded information (S_{input}) is compared with stored coded information (S_{stored}). This logic process is possible if a “search” is executed in the memory registers. If a match is found, *recognition* is produced. If not, the stimulus (S_{input}) is internally classified as unknown or new. If a second trial occurs, or if some environmental constrictions are present (a very high emotional situation, for example), task information pass into the acquisition phase (module II), and a labile or short term memory is generated. This memory endures for some finite short time (Fig. 1). Sometimes it is necessary to perform internal operational procedures which facilitate task acquisition due to the particular task characteristics, and in order to generate a memory. Some authors think that these processes are different from and useful to the task to be memorized. Since these procedural steps also *need* to be remembered, they have been called *working memory* (Atkinson and Shiffrin, 1968, Baddeley and Hitch, 1974). Although some researchers see the *working memory* as one particular “type” of memory, the procedural steps the neural circuits generate in order to learn the task can be viewed as learning of an operational algorithm, composed of many sequential steps, similar to the strategy followed by some animals to cope a specific problem. Under this view, *working memory* should be stable and persistent in order to be available when the primary stimulus is presented once more to the animal. This is the reason why some researchers think that *working memory* is a long-term memory (Ericsson & Kintsch, 1995). However, other authors believe that *working memory* is the opposite, i.e. of short duration (Atkinson & Shiffrin, 1968, Funahashi & Kubota, 1994, Pontecorvo et al., 1996, Wagar & Dixon, 2005). Furthermore, some authors view *working memory* as a sophisticated function with intrinsic operational sub-modules of high complexity (Baddeley & Hitch, 1974, Baddeley, 2000, Zimmer, 2008). Thinking in the parallelism between the natural biological phenomena and the operation of a computer, *working memory* is like the transitory memory in the buffer of the computer performing intrinsic operations during the running of a program. Once the operations are over, the transitory memory disappears. However, if some *strategic* operations are necessary in order to operate a given program, it is necessary that the algorithm have the potential to be memorized. In this case, the *working* procedure is stored as a permanent part of the program. Part of these conflicting interpretations regarding *working memory* arises from the ambiguity of the description and the belief that memories are of different kinds. As will be discussed later, this conflict would not be apparent if it is accepted that the molecular and cell mechanisms storing a memory are the same for all tasks, independent of the content or the "text" of the task to be memorized. *Working memory* is just a useful descriptive term, such as *visual memory*, *somato-sensory memory* and so on, but this is not meant to be a particular *kind* of memory. From this perspective, generation of a *working memory* is possible at the level of the acquisition of the information (module II), because once the strategy comprising the *working memory* has been acquired, retrieval rescues an already present functional paradigm to be executed like any other memory stored in the system. After acquisition is over the data are consolidated, and when this happens a memory has been generated and stored in the brain.

Some generalizations can be made with the Learning Loop concept. The following situations can generate failure to learn or amnesia:

1) Impairment in the task acquisition, the subject does not learn.

2) Impairment in the task consolidation, the subject forgets or presents amnesia.

3) Impairment in the task evocation, the subject presents amnesia.

3. The complexity of memory.

After the pioneering studies on patient H.M., who was amnesic after a bilateral surgical removal of the temporal lobe (Scoville and Milner, 1957, Milner 1966), two important features of learning and memory were established in neuroscience: the central role of hippocampus in cognitive processes, and the apparent multifactorial feature of memory (Squire, 1992, Shen et al., 1994, Zola Morgan and Squire, 1993). Subsequent research over the last 17 years has strongly confirmed the role of the hippocampus in memory mechanisms (Sutherland and McDonald, 1990, Volpe et al., 1992, Squire, 1992, Shen et al., 1994, Horel, 1994, Ridley et al., 1996, Dusek and Eichenbaum, 1997, Henke et al., 1997, Holdstock et al., 2002, Squire et al., 2007, Alvarez and Banzan, 1996, 1999); with regards to the second feature, interesting proposals were advanced generating much attention in the scientific community due to their scientific and philosophical implications. The studies performed on H.M. and several other human subjects (Scoville and Milner, 1957, Milner, 1966, Cohen, 1984, Squire, 1982, Zola-Morgan et al., 1986, Hanley et al., 2001, Holdstock et al., 2002, Squire and Bayley, 2007, Maxwell et al., 2003) suggested that two "types" of memories might be possible: contextual memory that can be declared (*declarative* memory), and contextual memory that is not declarative (*procedural or non-declarative* memory, Squire, 1992, Eichenbaum, 2003). Although the choice of the term *declarative* was not precisely fortunate, since its definition is based on the capacity of humans to consciously narrate the context of the coded information, thus excluding the general characteristics of this form of memory in animals (Squire, 1992), this *type* of learning was severely affected in the famous patient

H.M. (Scoville and Milner, 1957, Milner, 1966, Eichenbaum, 2003). The supporting evidence for these ideas was the observation that H.M. was able to learn motor skills at a normal rate, for example drawing the outlines of a star while looking at his hand and the star in a mirror (Blakemore, 1977). In addition, good learning in amnesic patients on tasks not requiring motor skills, such as those where the acquisition trials were enriched with provided partial information (*priming*) was also found (Squire, 1992, Warrington and Weiskrantz, 1968, 1970, 1974, 1978). Furthermore, several types of *procedural* or *non-declarative* learning were selectively impaired after brain lesions affecting different brain regions (Squire, 1992). These observations were interpreted as that learning processes can generate several "different memory types" that do not have the same anatomical localization (Squire, 1992); thus, *semantic*, *episodic*, and *recognition* memory were proposed as distinct entities (Squire, 1992, Squire et al., 2007, Squire and Bayley, 2007, Patterson et al., 2007). It is interesting to note that the main argument in favor of distinct memories is the different brain regions which appear to be involved in their processing (Patterson et al., 2007, Hanley et al., 2001, Squire and Bayley, 2007, Squire et al., 2007, Squire 1992). Although this is an interesting argument, it is hardly conclusive support for distinctive memory types. For example, the complex brain processing of vision is known to occur in the retina, the lateral geniculate nuclei, and the occipital striate cortex, at the least (Horton, 1992). However, it is not said that we possess three "types" of vision in the same sense that multiple types of memories are proposed. A similar argument may be made for auditory processes. Another conflicting aspect is the ambiguity of definition and functional superposition of the different memory types. For example, let's consider the difference between *semantic* and *episodic* memory. Semantic memory has been defined as "*the aspect of human memory that corresponds to general knowledge of objects, word meanings, facts and people,* *without connection to any particular time or place…*” (Patterson et al., 2007, Tulving, 1972). Meanwhile, episodic memory “*...has been used to refer to memories for personally experienced episodes or events…*” (Tulving, 1972, Holdstock et al., 2002). In the following situation the difference between *semantic* and *episodic* memory is not a straightforward matter but a rather ambiguous and unclear concept. Consider a subject “A”, living in London and never traveling abroad. He may have learned from a book that in Black Island, a small coastal town in the central region of Chile, a country in South America, there are many restaurants offering seafood; that the average temperature during the day in summer is around 20ºC, and that there are many forests and rocky beaches. It can be said that displaying this knowledge is a retrieval of a “semantic” or a conceptual memory (Anderson et al., 2007). Let’s represent this body of knowledge as {S}. However, if subject “A” during summer actually visits Black Island, he will very likely find that his “conceptual knowledge” will be supported by his vivid personal experience directly acquired in his visit. Let’s represent this “other” but familiar body of knowledge as {E}. It is easily to verify that {S} = {E}. Thus, the same data previously stored as “semantic” information now represents “episodic memory”. Does it mean that the semantically coded information has transformed into episodically coded information? Or that wherever the semantic data was stored initially in the brain it has now “moved” into another part of the brain only because this is now “episodic memory”? It is apparent that the principal difference between *semantic* and *episodic* knowledge is based on psychological descriptions emphasizing the *source* of the input data to the brain. It appears that discerning whether knowledge has been acquired by direct personal experience or by indirect reading from books depends more on the conscious analyzing capacity of the brain than on a recall of some “specific memories”. It is clear that in order to analyze some problem in particular, the neural processing needs to recall stored information. Memories can be conceived then as working pieces within a larger comparative and integrative process.

An additional aspect of the cognitive mechanisms that need to be considered is how the brain apparently incorporates the different aspects of some task to be learned into a permanent register of memory. Tasks appear to be divided into "core" or "target" items to be remembered (T), and into complementary or "surrounding" items present at the same time during the task (S). For example, if one is reading a particular book about animal behaviour in a country house, the "target" task is represented by the content of the book; and the "surrounding" task is represented by many additional details, such as the temperature, characteristics of the day, the sound of birds, details of the house, etc. Thus, memory is a complex of $\{T + S\}$. Often the S component is not consciously perceived by the subject except in retrieval, when some item of the S component induces the recall of the complete $\{T + S\}$ memory. For example, a particular scent can evoke the recall of the complete stored memory composed of the many items that were present when the main "target" was acquired.

Learning, like other complex and higher brain functions, appears to be an emergent process very likely compromising many brain structures simultaneously to store information as memory. Thus, in the present point of view information is visualized as stored by a unique basic mechanism independent of the contextual modality of the input data. The terms *working*, *episodic*, and *semantic* memory are highly descriptive of the nature of the material to be memorized but are simply describing the *context* of the information constituting the memory, and not an inherently different type of memory.

The *learning loop* is not necessarily located in one specific neural circuit (for example, exclusively the hippocampus). Evidence of learning from H.M. and many other patients suffering memory loss strongly suggests that there are other brain regions capable of supporting learning (Scoville and Milner, 1957, Milner, 1966, Blakemore, 1977, Squire, 1992, Warrington and Weiskrantz, 1968, 1970, 1974, 1978). It is conceivable that different brain regions each have their own learning loop units, processing the appropriate input information. This could explain why sometimes it is still possible to *learn* some tasks despite trauma to or extirpation of the hippocampus and related regions rendering them non-functional. Memory as codified information, even in its simplest form, is a highly complex entity. Experience reiteratively shows that a simple recall of limited information such as, for example, number “4”, implies many superior brain functions at the same time. If one “evokes” this number, what happens is an internal *visualization* of the sign (which itself is a curved line), perhaps drawn on paper, just as if one is looking at it on a surface. The sign is *interpreted* as a symbol and is recognized by its name “four”. Apparently, in order to form a “memory”, visual, auditive, and somatic sensory input information is codified at the same time according to the nature of the stimulus. Thus, in this sense memory is associative by definition. Although the term “associative” could be ambiguous in the context of those acquisition processes known as *non-associative*, such as *habituation* and *sensitization* (Kandel et al., 2000, Eisenstein, 1997, Byrne et al., 1991), the associative property in this context is considered to be an internal mechanism of the brain. Although in this type of process no constant relationship exists between the environmental stimulus and the behavioural response after repeated presentation of the stimulus, this non-relatedness is more apparent than real because the association is more subtle. In a typical example of *habituation*, such as the startle response for the first time to a horn announcing the ending of a work shift in a factory, and its gradual fading after repeated presentation of this stimulus (“learning”), there is an *association* linking the input stimulus to the corresponding *inhibition* of the spontaneous alarm response. After the abrupt stimulus (the horn) is found to not be harmful, the initial startle response is changed to a neutral response. An association between the stimulus and the *corrected* behaviour has been established. In terms of the present model, the task (identification of the meaning of the horn sound) ends with habituation which is expressed by displaying an appropriate alternate neutral behaviour. The associative property of learning is conserved.

4. The vector memory engram unit.

Considering the basic idea that all the sensory modalities contribute to the input information when the brain is acquiring knowledge to be stored eventually as memory, it is reasonable to speculate that information is incorporated into a *vector memory engram* (Figure 2). This engram is defined by the relative contribution of the different modalities activated by the input stimulus (shown in Figure 2 as separate columns according to modality), the intensity of the activation of each modality (height of columns), and the necessary functional union of all modalities into one emergent data unit. The vector memory engram is how the task is coded when it is acquired, and also how the memory data are recalled during evocation. However, the engram unit is not stored as such. It is assumed that the vector engram is decomposed into its component modalities and separately stored in the appropriate neural processing circuits in the brain. This is not unreasonable because the brain process the different sensory modalities separately. Most likely, the visual content of the task is stored in the secondary visual circuits of the brain, the auditory content of the task in the auditory association areas of the brain, and so on (Kandel et al., 2000). Several predictable consequences arise from this general model. While acquiring some particular task, many brain circuits are activated according to the modalities of the sensorial input. This has been observed when human subjects are exposed to a simple auditory instructed word memory task while being monitored by functional magnetic resonance imaging

(Kato et al., 1998); to a face memory recognition task (Courtney et al., 1997), and "semantic" or "episodic" memory tasks (Anderson et al., 2007). When trauma or ischemic events produce localized damage to specific neural circuits, it is possible that the vector memory engram cannot be reconstructed completely, generating partial memory recall. Thus, the subject experiences specific memory deficits as in cases of associative or apperceptive agnosia (Farah, 1990, Devinsky et al., 2008). Patients that have lesions in the posterior parietal cortex cannot name objects although they can identify them (associative visual agnosia). If lesions are present in the occipital lobes and their nearby regions, patients are unable to draw objects but they can name them if relevant clues are available to them (apperceptive visual agnosia, Farah, 1990, Devinsky et al., 2008). It is not unreasonable then to think that this is the result of an imperfect reconstruction of the memory engram, due to part of the coded information is not being available. In some cases, when destruction or lesions affect the medial temporal lobes, with significant damage to the neocortex, including the frontal, lateral temporal or occipital lobes (Squire & Bayley, 2007), dramatic impairment of autobiographic memory recall specific to time and space were observed. It might be that in those cases reconstruction of the memory engram would be impossible. Some common experiences can also be explained by the concept of the vector memory engram and, at the same time expose some of the intricacy and complexity that this functional unit might posses. Traveler might register in a hotel and being informed that their room is for example 742. After a delay of several hours they return to the hotel and ask for the key to the room 724. Numbers composing the identification are correct, but the *sequence* of numbers is incorrect. This is possible if, in the reconstruction of the engram, an interference or error is produced. This also suggests that the number "742" is not stored as a single engram and recovered as such, but is "reconstructed" into the final (i.e.

original) form. Another aspect of memory retrieval that attracts the attention of many psychologists is the typical behaviour of “the feeling of knowing” (Koriat, 1993, 2000, Koriat & Levy-Sadot, 2001) which can also be explained by the vector memory engram. This behaviour refers to the common incapacity of a subject to recall a specific piece of information, while having the conviction that *it is known*. Consequently, the situation is familiar but they consciously understand that something is missing in order to complete the recalled memory.

Although the concept of a memory vector engram appears to be as a reasonable mechanism whereby memories are stored in the brain, its reductionist simplicity raises some functional questions. For example, if the engram is decomposed into its constituents modules; who perform this activity? During the recall of stored information; who recompose the separate modules into the original engram? It appears necessary to postulate another neural circuit that performs this process (Figure 3). One important question about this hypothetical neuronal unit is whether there really is some such structure in the brain. An additional question is where this neural unit could be located. These points have not been resolved as yet but it is interesting to note that some regional localization (the anterior temporal lobe) has been postulated to function as a “hub” in the brain in the representation of “semantic” knowledge in humans (Patterson et al., 2007). Although authors see the distributed plus-hub from a different perspective than the vector memory engram proposed here (Patterson et al., 2007), the anterior temporal lobe appears highly attractive as a neural circuit to organize the memory modes as explained in the present review. Degeneration of this brain region, as has been observed in cases of semantic dementia and also in Alzheimer’s disease, are correctly associated with severe cognitive dysfunctions, as predicted by impairment of a hypothetical vector memory engram organizing circuit (Figure 3).

5. How small the “learning unit” can be?: The meaning of “size”.

When a complex brain function such as for example learning and memory is analyzed, researchers frequently consider to what extent they can deconstruct the physiological unit and still maintain functionality. This research view is classic and has been successfully applied to the study of muscle, endocrine organs and nervous tissue in the past. This approach has no direct equivalent in the neurobiology of memory as it depends on what we consider to be “learning”. If it is understood to mean the capacity to store information, then it is possible to visualize lower “learning units” made up of parts of the nervous tissue, organs or more simple preparations (Eisenstein, 1997). However, if it is understood that learning involves not only the fact of storing information, but also the capacity to link these memories, recreate situations, associate data and to generate some definite behavioural response to external stimuli, then the “lower” physiological unit can be not less complex than the interconnected neural circuits subserving each function. This is because memories are made up of many different aspects that take into account the physical characteristics, texture, colors, forms, sound and other relevant data of the task to be stored. It is very difficult to conceive how such a tremendous amount of information can be retained in one single neuron of the brain. One single neuron of the nervous tissue can be viewed as one tiny information unit, quite similar to a pixel in a computer screen that is displaying an image. The complete sense of what an observer is looking at in the monitor screen is the result of hundreds of pixels activated or not at the moment the subject is observing. The physiological meaning of recalling a memory and the subsequent behavioural response after this process is performed is equivalent to the meaningful “image” that a subject sees in the computer monitor screen. It follows that many neural circuits in the brain are responsible for the recreation of former data previously stored as memory. In spite of the evidence that memory is associated with the synthesis of biologically active compounds in cells (Cambon et al., 2004, Bekinschtein et al., 2008, Cammarota et al., 2008, Lee et al., 2004) there is still uncertainty about how this intracellular process can store information as “memory”. From a physiological point of view, whatever the necessary intracellular mechanisms might be, the neuron should generate several permanent states that correlate with determined aspects of the memory information. Thus, cooperative interaction of neurons in a determined neural network could sustain many complex memories, contributing to the memory capacity of the brain (Alvarez, 2009).

Memory research has expanded significantly in these past 15 years. Perhaps what has most attracted the attention of the scientific community has been research on “episodic” and “semantic” memory (Dere et al., 2005, 2006, 2008, Hanley et al., 2001, Squire & Bayley, 2007). It is possible to understand such an interest considering that most of the tasks in the everyday activity of man are associated with instant-to-instant experience during daily living. Sickness or specific brain damage can strikingly impair the over-all memory efficiency of subjects, which usually results in social problems, illustrating the practical need to understand the biological basis of these processes. Although considerable knowledge has been gained about some neurotransmitters, neural circuits in specific brain regions, and intracellular molecular processes, still much research remains to be done in order to fully understand the intricacy of learning and memory in complex living systems. Some interesting questions still need to be answered. For example, little is known about the time dependency of memories. Most of the models of learning and memory visualize the “data” as fixed “pictures” stored in neural circuits, even though the brain recalls vivid situations in movement. How the stored data can be recalled as animated memories is actually unknown. A related issue is how the brain organizes memories to recreate the normal and abnormal engram reconstitutions that generate dreams. There is no doubt that learning and memory are highly complex functions and that once its intrinsic mechanisms are elucidated we will have taken a great step forward in understanding the mind.

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References.

- Alvarez EO. The role of histamine on cognition. Behav Brain Res (in press).
- Alvarez EO, Banzan AM. Effects of localized histamine microinjections into the hippocampal formation on the retrieval of a one-way active avoidance response in rats. J Neural Transm 1995; 101: 201-211.
- Alvarez EO, Banzan AM. Functional regional distribution of histamine receptors in the rat hippocampus: modulation of learning of an active avoidance response. J Neural Transm 2001; 108: 1249-1261
- Alvarez EO, Banzan AM. Hippocampal histamine receptors: possible role on the mechanisms of memory in the rat, II. J Neural Transm 1996; 103: 147-156.
- Alvarez EO, Banzan AM. Hippocampus and learning: possible role of histamine receptors. Medicina (Bs As) 1996; 56: 155-160.

- Alvarez EO, Banzan AM. Ventral hippocampus glutamate receptors in the rat: possible involvement in learning mechanisms of an active avoidance response. J Neural Transm 1999; 106: 987-1001.
- Alvarez EO, Ruarte MB, Banzan AM. Histaminergic systems of the limbic complex on learning and motivation. Behav Brain Res 2001; 124: 195-202.
- Alvarez EO, Ruarte MB. Glutamic acid and histamine-sensitive neurons in the ventral hippocampus and basolateral amygdala of the rat: functional interaction on memory and learning processes. Behav Brain Res 2004; 209-219.
- Alvarez EO, Ruarte MB. Histaminergic neurons of the ventral hippocampus and the baso-lateral amygdala of the rat: functional interaction on memory and learning mechanisms. Behav Brain Res 2002; 128: 81-90
- Alvarez EO, Banzan AM. The activation of histamine-sensitive sites of the ventral hippocampus modulates the consolidation of a learned active avoidance response in rats. Behav Brain Res 2008; 189: 92-99.
- Amano R, Hiruma H, Nishida S, Kawakami T, Shimizu K. Inhibitory effect of histamine on axonal transport in cultured mouse dorsal root ganglion neurons. Neurosci Res 2001; 41: 201-206.
- Atkinson RC, Shriffin RM. Human memory: a proposed system and its control processes. In: KW Spence and JT Spence (Editors), The Psychology of Learning and Motivation: Advances in Research and Theory, Vol 2, Academic Press, New York, 1968, pp89-195.
- Babe KS, Serafin WE. Histamine, bradykinin, and their antagonists. In Goodman and Gilman’s The Pharmacological Basis of Therapeutics. 9th Edition, Hardman JG, Limbird LE (Editors in Chief), International Edition, McGraw Hill, pp 581-616, 1996.

- Baddeley AD, Hitch G. Working memory. In: GH Bower (Editor), The Psychology of Learning and Motivation: Advances in Research and Theory, Vol 8, Academic Press, New York, 1974, pp 47-89.
- Baddeley AD. The episodic buffer: a new component of working memory? Trends Cogn Neurosci 4: 417-423, 2000.
- Barnes CA. Spatial learning and memory processes: the search for their neurobiological mechanisms in the rat. Trends Neurosci 1988; 11: 163-169.
- Bayliss DA, Wang YM, Zahnow CA, Joseph DR, Milhorn DE. Localization of histidine decarboxylase mRNA in rat brain. Mol Cell Neurosci 1990; 1: 3-9.
- Blakemore C. Mechanics of the mind, Cambridge MA, Cambridge University Press, 1977.
- Bekinschtein P, Cammarota M, Izquierdo I, Medina JH. BDNF and memory formation and storage. Neuroscientist 2008; 14: 147-156.
- Blandina P, Efoudebe M, Cenni G, Mannaioni P, Passani MB. Acetylcholine, histamine, and cognition: two sides of the same coin. Learn Mem 2004; 11: 1-8.
- Bouton ME. Conditioning, remembering, and forgetting. J Exp Psychol 1994; 20: 219-231.
- Brown RE, Stevens DR, Haas HL. The physiology of brain histamine. Prog Neurobiol 2001; 637-672.
- Brunelli M, García-Gil M, Mozzachiodi R, Scuri R, Zaccardi ML. Neurobiological principles of learning and memory. Arch Italliennes Biologie 1997; 135: 15-36.
- Byrne JH, Baxter DA, Buonomano DV, McCleary LJ, Eskin A, Goldsmith JR, McClendon E, Nazif FA, Noel F, Scholz P. Neural and molecular bases of

nonassociative and associative learning in Aplysia. Ann NY Acad Sci 1991; 627: 124-149.

- Cacabelos R, Alvarez XA. Histidine decarboxylase inhibition induced by alpha-fluormethylhistidine provokes learning-related hypokinetic activity. Agents and Actions 1991; 33: 131-134.
- Cambon K, Hansen SM, Venero C, Herrero AI, Skibo G, Berezin V, Bock E, Sandi C. A synthetic neural cell adhesion molecule mimetic peptide promotes synaptogenesis, enhances presynaptic function, and facilitates memory consolidation. J Neurosci 2004; 24: 4197-4204.
- Cammarota M, Bevilaqua LR, Medina JH, Izquierdo I. ERK1/2 and CaMKII-mediated events in memory formation: is 5HT regulation involved? Behav Brain Res 2008; 195: 120-128.
- Cangioli I, Baldi E, Mannaioni PF, Bucherelli C, Blandina P, Passani MB. Activation of histaminergic H_3 receptors in the rat basolateral amygdala improves expression of fear memory and enhances acetylcholine release. Eur J Neurosci 2002; 16: 521-528.
- Cherkin A. Kinetics of memory consolidation: role of amnesic treatment parameters. Proc Natl Acad Sci USA 1968; 63: 1094-1101.
- Chun MM, Turk-Browne NB. Interactions between attention and memory. Curr Opinion Neurobiol 2007; 17: 177-184.
- Courtney SM, Ungerleider LG, Keil K, Haxby JV. Transient and sustained activity in a distributed neural system for human working memory. Nature 1997; 386:608-611.

- Dai H, Kaneko K, Kato H, Fujii S, Jing Y, Xu A, Sakurai E, Kato M, Okamura N, Kuramasu A, Yanai K. Selective cognitive dysfunction in mice lacking histamine H_1 and H_2 receptors. Neurosci Res 2007; 57: 306-313.
- Davis H. Transitive inference in rats (Rattus norvegicus). J Comp Psychol 1992; 106: 342-349.
- Dere E, Huston JP, De Souza Silva MA. The pharmacology, neuroanatomy and neurogenetics of one-trial object recognition in rodents. Neurosci Biobehav Rev 2007; 31: 673-704.
- Dere E, Kart-Teke E, Huston JP, De Souza Silva MA. The case for episodic memory in animals. Neurosci Biobehav Rev 2006; 30: 1206-1224
- Dere E, Huston JP, De Souza Silva MA. Episodic-like memory in mice: simultaneous assesment of object, place and temporal order memory. Brain Res Brain Res Protocol 2005; 16: 10-19
- Dere E, Zlomuzica A, Huston JP, De Souza Silva MA. Animal episodic memory. In Handbook of Episodic Memory 18. Dere E, Easton A, Nadel L, Huston JP (Editors), handbook of Behavioural Neuroscience Series, 2008, Elsevier.
- Devinsky O, Farah MJ, Barr WB. Visual agnosia (Chapter 21). Handbook of Clinical Neurology 2008; 88: 417-427
- Deutsch SI, Rosse RB, Schwartz BL. Histamine H_2 receptor antagonists in schizophrenia: rationale for use and therapeutic potential. CNS Drugs 1997; 8: 276-284.
- Diehl F, Furstenau de Oliveira L, Sanchez G, Camboim C, de Olivera Alvares L, Lanziotti VB, Cervenasky C, Kornisiuk E, Jerusalinky D., Quillfeldt JA. Facilitatory effect of the intra-hippocampal pre-test administration of MT3 in the inhibitory avoidance task. Behav Brain Res 2007; 177: 227-231.

- Dringenberg HC, De Souza-Silva MA, Rossmüller J, Huston JP, Schwarting RK. Histamine H1 receptor antagonists produce increases in extracellular acetylcholine in the rat frontal cortex and hippocampus. J Neurochem 1998; 70: 1750-1758
- Dusek JA, Eichenbaum H. The hippocampus and memory for orderly stimulus relations. Proc Natl Acad Sci USA 1997; 94: 7109-7114.
- Eichenbaum H, Otto T. The hippocampus-what does it do? Behav Neural Biol 1992; 57: 2-36.
- Eichenbaum HB. Learning and memory: brain systems, in Squire LR, Bloom FE, McConnell SK, Roberts JL, Spitzer NC, Zigmond MJ (Editors), Fundamental Neuroscience, 2º edition, pp.1299-1327, Academic Press, 2003.
- Eidi M, Zarrindast MR, Eidi A, Oryan S, Parivar K. Effects of histamine and cholinergic on memory retention of passive avoidance learning in rats. Eur J Pharmacol 2003; 465: 91-96.
- Eisenstein EM. Selecting a model system for neurobiological studies of learning and memory. Behav Brain res 1997; 82: 121-132.
- Ericsson KA, Kintsch W. Long-term working memory. Psychol Rev 1995; 102: 211-245
- Ericson H, Watanabe T, Köhler C. Morphological analysis of the tuberomammillary nucleus in the rat brain: delineation of subgroups with antibody against L-histidine decarboxylase as a marker. J Comp Neurol 1987; 263:1-24.
- Esbenshade TA, Fox GB, Cowart MD. Histamine H_3 receptor antagonists. Preclinical promise for treating obesity and cognitive disorders. Mol Interventions 2006; 6: 77-88.
- Farah M. Visual Agnosia, Cambridge, MA, 1990, MIT Press.

- Frisch C, Hasenöhrl RU, Haas HL, Weiller HT, Steinbusch HWM, Huston JP. Facilitation of learning after lesions of the tuberomammillary nucleus region in adult and aged rats. Exp Brain Res 1998; 118: 447-456.
- Frisch C, Hasenöhrl RU, Huston JP. Memory improvement by post-trial injection of lidocaine into the tuberomammillary nucleus, the source of neuronal histamine. Neurobiol Learn Mem 1999; 72: 69-77.
- Frisch C, Hasenöhrl RU, Huston JP. The histamine H_1-antagonist chlorpheniramine facilitates learning in aged rats. Neurosci Lett 1997; 229: 89-92.
- Funahashi S, Kubota K. Working memory and prefrontal cortex. Neurosci res 1994; 21: 1-11.
- Glenberg AM. What memory is for. Behav Brain Sci 1997; 20: 1-55.
- Gold PE, McGaugh JL. A single trace, two process view of memory storage processes. In: Deutsch D, Deutsch JA (Editors), Short-term Memory, Academic Press, New York, 1975, pp 355-378.
- Green JP, Histamine receptors in the brain, in Handbook of Psychopharmacology, Vol 17, pp- 385-420, Iversen L, Iversen SD, Snyder SH (Editors), Plenum Press, 1983.
- Haas H, Panula P. The role of histamine and the tuberomammillary nucleus in the nervous system. Nature Rev Neuroscience 2003; 4: 121-130.
- Haas HL, Konnerth A. Histamine and noradrenaline decrease calcium-activated potassium conductance in hippocampal pyramidal cells. Nature 1983; 302: 432-434.
- Hanley JR, Davies ADM, Downes JJ, Roberts JN, Gong QY, Mayes AR. Remembering and knowing in a patient with preserved recognition and impaired recall. Neuropsychologia 2001; 39: 1003-1010.

- Hartley T, Bird CM, Chan D, Cipolotti L, Husain M, Vargha-Khadem F, Burgess N. The hippocampus is required for short-term topographical memory in humans. Hippocampus 2007; 17: 34-48.
- Henke K, Buck A, Weber B, Wieser HG. Human hippocampus establishes associations in memory. Hippocampus 1997; 7: 249-256.
- Holdstock JS, Mayes AR, Isaac CL, Gong Q, Roberts N. Differential involvement of the hippocampus and temporal lobe cortices in rapid and slow learning of new semantic information. Neuropsychologia 2002; 40: 748-768.
- Honrubia MA, Vilaró MT, Palacios JM, Mengod GD. Distribution of the histamine H_2 receptor in monkey brain and its mRNA localization in monkey and human brain. Synapse 2000; 38: 343-354.
- Horel JA. Some comments on the special cognitive functions claimed for the hippocampus. Cortex 1994; 30: 269-280.
- Horton JC. The central visual pathways. In Adler's Physiology of the Eye. Hart WM (Editor), 1992, St louis, Mosby Yearbook.
- Hough LB, Khandelwal JK, Green JP. Histamine turnover in regions of rat brain. Brain Res 1984; 291: 103-109.
- Hough LB. Cellular localization and possible functions for brain histamine: recent progress. Prog Neurobiol 1988; 30: 469-505.
- HurlemannR, Hawellek B, Matusch A, Kolsch H, Wollersen H, Madea B, Vogeley K, Maier W, Dolan RJ. Noradrenergic modulation of emotion-induced forgetting and remembering. J Neurosci 2005; 25: 6343-6349.
- Izquierdo I, Medina JH, Vianna MRM, Izquierdo LA, Barros DM. Separate mechanisms for short- and long-term memory. Behav Brain Res 1999; 103: 1-11.

- Jager G, Van Hell HH, De Win MM, Kahn RS, Van den Brink W, Van Ree JM, Ramsey NF. Effects of frequent cannabis use on hippocampal activity during an associative memory task. Eur Neuropsychopharmacol 2007; 17: 289-297.
- Kamei C, Chung YH, Tasaka K. Influence of certain H_1-blockers on the step-through active avoidance response in rats. Psychopharmacology 1990; 102: 312-318.
- Kamei C, Okumura Y, Tasaka K. Influence of histamine depletion on learning and memory recollection in rats. Psychopharmacology (Berl) 1993; 111: 376-382.
- Kamei C, Tasaka K. Participation of histamine in the step-through active avoidance response and its inhibition by H_1-blockers. Japan J Pharmacol 1991; 57: 473-482.
- Kandel ER, Kupfermann I, Iversen S. Learning and memory, in Principles of Neural Science, 4th edition, Kandel ER, Schwartz JH, Jessell TM (Editors), 2000, pp1209-1226, McGraw Hill.
- Kato T, Erhard P, Takayama Y, Strupp J, Le TH, Oganawa S, Ugurbil K. Human hippocampal long-term sustained response during word memory processing. Neuroreport 1998; 9: 1041-1047.
- Koriat A. How do we know that we know? The accessibility model of the feeling of knowing. Psychol Rev 1993; 100: 609-639
- Koriat A. The feeling of knowing: some metatheoretical implications for consciousness and control. Conscious Cogn 2000; 9: 149-171.
- Koriat A, Levy-Sadot R. The combined contribution of the cue-familiarity and accessibility heuristics to feelings of knowing. J Exp Psychol Learn Mem Cogn 2001; 27: 34-53
- Lee JL, Everitt BJ, Thomas KL Independent cellular processes for hippocampal memory consolidation and reconsolidation. Science 2004; 304: 829-830.

- Liu L, Zhang S, Zhu Y, Fu Q, Zhu Y, Gong Y, Ohtsu H, Luo J, Wei E, Chen Z. Improved learning and memory of contextual fear conditioning and hippocampal CA_1 long-term potentiation in histidine decarboxylase knock-out mice. Hippocampus 2007; 17: 634-641
- Livingston RB. Sensorial processing, in: *Best and Taylor's Physiological Basis of Medical Practice*, Beck JB (Editor), 12th edition, 1991, Section 9, Chapter 62, William and Wilkins.
- Martinez JL, Derrick BE. Long-term potentiation and learning. Annu Rev Psychol 1996; 47: 173-203.
- Martinez-Mir MI, Pollard H, Moreau J, Arrang JM, Ruat M, Traiffort E, Schwartz JC, Palacios JM. Loss of striatal histamine H_2 receptors in Huntington' chorea but not in Parkinson's disease. Comparison with animal models. Synapse 1993; 15: 209-220.
- Maxwell JP, Masters RSW, Eves FF. The role of working memory in motor learning and performance. Consciousness Cog 2003; 12: 376-402.
- Mazurkiewicz-Kwilecki IM, Nsonwah S. Changes in the regional brain histamine and histidine levels in postmorten brains of Alzheimer patients. Can J Physiol Pharmacol 1989; 67: 75-78.
- McGaugh JL, Introini-Collison IB, Cahill LF, Castellano C, Dalmaz C, Parent MB, Williams CL. Neuromodulatory systems and memory storage: role of the amygdala. Behav Brain Res 1993; 58: 81-90.
- McGaugh JL. A multi-trace view of memory storage processes. Accademia Nazionale dei Lincei 1968; 109: 13-28
- McGaugh JL. Time-dependent processes in memory storage. Science 1966; 153: 1351-1359

- Meneses A. Stimulation of 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{2A/2C}$, 5-HT$_3$ and 5-HT$_4$ receptors or 5-HT uptake inhibition: short- and long-term memory. Behav Brain Res 2007; 184: 81-90.
- Milner B. Amnesia following operation on the temporal lobe. In: Whitty CWM and Zang OL (Editors), Amnesia, London: Butterworth & Co., 1966, pp109-133
- Molinari SP, Kaminski R, Di Rocco A, Yahr MD. The use of famotidine in the treatment of Parkinson's disease: a pilot study. J Neural Transm 1995; 9: 243-247.
- Murray E, Gaffan D. Removal of the amygdala plus subjacent cortex disrupts the retention of both intramodal and crossmodal associative memories in monkeys. Behav Neurosci 1994; 108: 494-500.
- Pannula P, Pirvola U, Auvinen S, Airaksinen MS. Histamine-immunoreactive nerve fibres in the rat brain. Neuroscience 1989; 28: 585-610.
- Pannula P, Yang H, DeCosta E. Histamine-containing neurons in the rat hypothalamus. Proc Natl Acad Sci USA 1984; 81: 2572-2576.
- Parson ME, Ganellin CR. Histamine and its receptors. Br J Pharmacol 2006; 147: S127-S135.
- Passani MB, Bacciottini L, Mannaioni PF, Blandina P. Central histaminergic system and cognition. Neurosci Biobehav Rev 2000; 24: 107-113.
- Passani MB, Giannoni P, Bucherelli C, Baldi E, Blandina P. Histamine in the brain: beyond sleep and memory. Biochem Pharmacol 2007; 73: 1113-1122.
- Patterson K, Nestor PJ, Rogers TT. Where do you know what you know? The representation of semantic knowledge in the human brain. Nature Rev Neuroscience 2007; 8: 976-987.
- Pontecorvo MJ, Sahgal A, Steckler T. Further developments in the measurements of working memory in rodents. Cogn Brain res 1996; 3: 205-213.

- Prast H, Argyriou A, Philippu A. Histaminergic neurons facilitate social memory in rats. Brain res 1996; 734: 316-318.
- Privou C, Li JS, Hasenöhrl RU, Huston JP. Enhanced learning by posttrial injection of H_1- but not H_2-histaminergic antagonists into the nucleus basalis magnocellularis region. Neurobiol Learn Mem 1999; 71: 308-324.
- Ridley RM, Baker HF, Harder JA, Pearson C. Effects of lesions of different parts of the septo-hippocampal system in primates on learning and retention of information acquired before or after surgery. Brain Res Bull 1996; 40: 21-32.
- Ruarte MB, Orofino AG, Alvarez EO. Hippocampal histamine receptors and conflictive exploration in the rat: studies using the elevated asymmetric plus-maze. Br J Med Biol Res 1997; 30: 1451-1461.
- Schmajuk NA, DiCarlo JJ. Stimulus configuration, classical conditioning, and hippocampal function. Psychol Rev 1992; 99: 268-305.
- Schwartz JC. Histamine as a transmitter in the brain. Life Sci 1975; 17: 503-518.
- Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry 1957; 20: 11-21
- Selbach O, Brown RE, Haas HL. Longterm increase of hippocampal excitability by histamine and cyclic AMP. Neuropharmacology 1997; 36:1539-1548.
- Shen Y, Specht SM, De Saint Ghislain I, Li R. The hippocampus: a biological model for studying learning and memory. Prog Neurobiol 1994; 44: 485-496.
- Smith BN, Amstrong WE. The ionic dependence of the histamine-induced depolarization of vasopressin neurones in the supraoptic J Physiol (Lon) nucleus. 1996; 495: 465-478.

- Spieler RE, Nelson CA, Huston JP, Mattioli R. Post-trial administration of H_1 histamine receptor blocker improves appetitive reversal learning and memory in goldfish, Carassius auratus. Neurosci Lett 1999; 277: 5-8.
- Squire LR, Bayley PJ. The neuroscience of remote memory. Curr Opinion Neurobiol 2007; 17: 185-196.
- Squire LR, Wixted JT, Clark RE. Recognition memory and the medial temporal lobe: a new perspective. Nature Rev Neuroscience 2007; 8: 872-883
- Squire LR. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. Psychol Rev 1992; 99: 195-231.
- Squire LR, Bayley PJ. The neuroscience of remote memory. Curr Opinion Neurobiol 2007; 17: 185-196.
- Steckler T, Muir JL. Measurement of cognitive function: relating rodent performance with human minds. Cogn Brain Res 1996; 3: 299-308.
- Sutherland RJ, McDonald RJ. Hippocampus, amygdala, and memory deficits in rats. Behav Brain Res 1990; 37: 57-79.
- Tavares MCH, Tomaz C. Working memory in capuchin monkeys (Cebus apella). Behav Brain Res 2002; 131: 131-137.
- Tulving E. In Organization of Memory, Tulving E and Donalson W (Editors), 1972, pp 381-403, Academic Press, New York
- Volpe BT, Davis HP, Towle A, Dunlap WP. Loss of hippocampal CA1 pyramidal neurons correlates with memory impairment in rats with ischemic or neurotoxin lesions. Behav Neurosci 1992; 106: 457-464
- Wagar BM, Dixon MJ. Past experience influences object representation in working memory. Brain Cogn 2005; 57: 248-256.

- Wada H, Inagaki N, Yamatodani A, Watanabe T. Is the histaminergic neuron system a regulatory center for whole-brain activity?. Trends in Neurosci 1991; 14: 415-418.
- Warrington EK, Weiskrantz L. A new method of testing long-term retention with special reference to amnesic patients. Nature 1968; 217: 972-974
- Warrington EK, Weiskrantz L. Further analysis of the prior learning effect in amnesic patients. Neuropsychologia 1978; 16: 169-177.
- Warrington EK, Weiskrantz L. The amnesic syndrome . Consolidation or retieval? Nature 1970; 228: 628-630.
- Warrington EK, Weiskrantz L. The effect of prior learning on subsequent retention in amnesic patients. Neuropsychologia 1974; 12: 419-428
- Watanabe T, Taguchi Y, Shiosaka S, Tanaka J, Kubota H, Terano Y, Wada H. Distribution of the histaminergic neuron system in the central nervous system of the rat; a fluorescent immunohistochemical analysis with histidine decarboxylase as a marker. Brain res 1984; 295: 13-25.
- Weiger T, Stevens DR, Wunder L, Haas HL. Histamine H_1- receptors in C6 glial cells are coupled to calcium-dependent potassium channels via release of calcium from internal stores. Naunyn Schmiedebergs Arch Pharmacol 1997; 355: 559-565.
- Wolfman C, Fin C, Dias M, Bianchin M, Da Silva RC, Schmitz PK, Medina JH, Izquierdo I. Intrahippocampal or intraamygdala infusion of KN62, a specific inhibitor of Calcium/Calmodulin-dependent protein kinase II, causes retrograde amnesia in the rat. Behav Neural Biol 1994; 61: 203-205
- Wood ER, Dudchenko PA, Eichenbaum H. The global record of memory in hippocampal neuronal activity. Nature 1999; 397: 613-616.

- Woolf NJ. A structural basis for memory storage in mammals. Prog Neurobiology 1998; 59-77.
- Wylie GR, Foxe JJ, Taylor TL. Forgetting as an active process: an fMRI investigation of item-method-directed forgetting. Cerebral Cortex 2008; 18: 670-682.
- Xu C, Michelsen KA, Wu M, Morozova E, Panula P, Alreja M. Histamine innervation and activation of septohippocampal GABAergic neuronas: involvement of local ACh release. J Physiol 2004; 561: 657-670.
- Xu LS, Yang L, Hu W, Yu X, Liu L, Wei E, Chen Z. Histamine ameliorates spatial memory deficits induced by MK-801 infusion into ventral hippocampus as evaluated by radial maze task in rats. Acta Pharmacol Sinica 2005; 26: 1448-1453.
- Zimmer HD. Visual and spatial working memory: from boxes to networks. Neurosci Biobehav Rev 32: 1373-1395, 2008
- Zola-Morgan S, Squire LR. Neuroanatomy of memory. Annu Rev Neurosci 1993; 16: 547-563.