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Commentary Paper

Seven Ambiguities in Explaining the Human Memory System in the Principles of Neural Science Book

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ABSTRACT

Memory is probably one of the most complex human cognitive functions, and in many years, thousands of studies have helped us better recognize this brain function. Professor Kandel and his colleagues have written one of the reference textbooks in neuroscience, which has also elaborated on the memory function. In this book, I encountered several ambiguities while explaining the memory system. Here, I share those points, either to find an answer to them or to let them be a suggestion for our future works. Professor Kandel has spent most of his meritorious lifetime studying the memory system; however, the brain is extremely complex, and as a result, we still have many years to comprehensively understand the neural mechanisms of brain functions.

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Highlights

- The human memory system is not yet well identified.
- Imaging studies are not able to locate the memory storage sites of the brain.
- Current theories cannot explain the huge amount of memory storage in the brain.
- Episodic memories of animals should be different with a human episodic memory?

Plain Language Summary

The human memory system is very complex, and we still have many questions on that. One of the questions is about the location of episodic memory storage in humans. Is that really happening in the brain? One other question is about studying the episodic memory in animals: do they really have an episodic memory similar to the humans? Prof. Kandel in his very valuable book has explained the memory system; however, many ambiguities are still unsolved. For example, the neuroimaging methods are nearly never able to speak of the site of memory "storage" in the brain, whereas many of their results are used as evidence for identifying the location of memory storage in the brain. Also, the hippocampus is emphasized to be responsible for the storage of episodic memories in animals, whereas a human whore hippocampus is resected is still able to retrieve his memories from before the surgery. As a result, we speculate that, despite all the very precious findings of Prof. Kandel, we still have to work in this field to reveal its mysteries.

1. Commentary

Professor Eric R Kandel, as provided his lifetime story in his "in search of memory" book (Kandel, 2007), was born in Vienna, in 1929. He received the nobel prize in physiology or medicine in 2000 for all his contributions and achievements in the study of the mechanism of memory storage in the brain. Around twenty years before receiving Nobel Prize, in 1981, he and his colleague, Professor James H Schwartz, wrote the book principles of neural science. This book is currently in its fifth edition and is more than 3 times larger than its first edition (Kandel et al., 2012). I always considered the principles of neuroscience a holy book in neuroscience; to my astonishment, I noticed similar expressions about this book elsewhere, such as calling it the "bible of neuroscience".

As a researcher who is interested in human memory (Batouli et al., 2020, Batouli et al., 2021; Batouli & Sisakhti, 2019; Batouli & Sisakhti, 2020; Rafei et al., 2021; Razavi et al., 2021; Sisakhti et al., 2021; Sisakhti et al., 2023). I studied this book (the fifth edition) and in particular, its three chapters (chapters 65, 66, 67) which are on memory. During my studies, some parts of these chapters seemed ambiguous to me, i.e. being insufficiently explained or in contradiction with the other parts of the book. As a result, here, I share with you my questions about this book, and I hope to find some answers to these questions either in the next edition of this book or in others' future works.

The focus of the current manuscript has merely been on this book. In other words, the answers to my questions may be found in other references; however, regarding such a textbook should be independent, I did not refer to other resources. The aim here is only to open a discussion on the different aspects of the human memory system, and I would be grateful if there could be explanations for these questions. The quotations from the book are marked with "asterisks", with the page numbers mentioned in [brackets]. A total of 10 questions exist in seven categories, as provided below.

Site of memory storage

It is raised in the book that "the brain does not have a single long-term store of explicit memories" [p.1446]; however "memory storage involves different parts of the brain" [p.1442]. Kandel et al. also added that "the ultimate storage site for all declarative memories is thought to be in the cerebral cortex" [p.1487], "knowledge is stored distributedly in the neocortex" [p.1451], "storage of any item is widely distributed among many brain regions" [p.1446], and "over time, explicit memories are transferred to different regions of the neocortex" [p.1461]. It is also read that "old memories are not stored

in the medial temporal lobe (MTL), but in various other cortical regions" [p.1448], and "MTL plays a temporary role in consolidating memories, and after a long period, the MTL is not needed because memories can be retrieved directly from cortical regions" [p.1448].

Question/Suggestion 1: The above statements are about the site of long-term memory storage in the brain, and suggest it to be over the cortex. However, I cannot observe any evidence in the book for these claims; neither an animal nor a human study. The site of LTM storage is a substantial issue, and it is suggested that appropriate evidence for this claim be provided in future editions of the book.

Using neuroimaging devices

The answer to my above question may be derived from the neuroimaging works. It is mentioned in the book that "positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) allow us to scan the healthy brain in the process of building new memories or retrieving existing memories, and thus to identify the specific regions that are active during different processes" [p.1447]. Examples in the book were "fMRI in healthy people showed increased activity in the right hippocampus when recalling spatial information, and in the left hippocampus when recalling words, objects, or people" [p.1445], or "positron emission tomography (PET) and fMRI studies of subjects asked to recall or recognize previously studied words or pictures showed activity in the anterior and lateral prefrontal cortex" [p.1449].

Question/Suggestion 2: I believe that when a brain area is observed to be active during the retrieval of a memory, that area is not necessarily eloquent for the memory, and can only be involved in a cognitive function associated with the memory. For example, recalling a scene activates or needs the visual processing areas of the brain to process that information; however, this activation should not be interpreted as that area being the "site" of memory storage. As mentioned in the book, "storage refers to the neural mechanisms and sites by which memory is retained over time" [p.1447]; however, it seems neuroimaging studies can only provide evidence about "how different categories of knowledge are represented in the human brain" [p.1451], and not the site of memory storage.

Here is an example: If we can fill a glass by opening a water tap, and if opening a tap is always significantly associated with filling the glass, can we deduce that the tap is the place of water "storage"? Similarly, in assessing the human memory system, if running a memory task is statistically associated with the activation of a particular brain area, can we infer that the active brain area is the site of memory "storage", or should we conclude that it is only part of a chain of brain functions for a successful memory?

Hippocampus role in episodic memory

The book reports rodent studies that assessed spatial memory and the role of the hippocampus in these tasks. These studies considered spatial memory tasks as a kind of episodic memory. It is read in the book that the "hippocampus is crucial for spatial representation; in mice and rats, lesions of the hippocampus interfere with memory for space and context, and single neurons in the hippocampus encode specific spatial information" [p.1445]. It is also stated that in the water maze test, "if the mouse locates the platform and remembers its position based on the spatial contextual cues- markings on the walls of the room that the pool is located, this task requires hippocampus" [p.1503], while "in the non-contextual version that the platform is raised above the water level or marked with a visible flag, permitting the mouse to directly navigate to the platform using brain pathways, the task does not require hippocampus" [p.1503]. Furthermore, it is mentioned that the "hippocampal pyramidal neurons fire in place fields even if the long-term potentiation (LTP) is blocked, which shows the sensitivity of these cells to the spatial location" [p.1510].

Question/Suggestion 3: Episodic memory is a vital human function; however, the book seems to have a very narrow look into that: only rodent studies and only spatial tasks are considered. It is mentioned in the book that "long-term memory of a stably formed place field requires the animal to attend to its environment, as is the case for explicit memory in humans" [p.1511]. It seems that we need much further information particularly, about other aspects of episodic memory in humans. In addition, based on the above statements in the book, the hippocampus seems to be the central brain structure in episodic memory; however, this seems to be in contrast with the other parts of the book, as provided below:

The book mentions several examples of the patient H.M., whose hippocampus was resected in surgery. Despite a lack of hippocampus, and the hippocampus mentioned in the above rat studies to be critical for retrieving episodic memory, he had a flawless ability to retrieve his older episodic memory: "he had LTM for events that occurred before the operation" [p.1443], "his semantic memory was preserved" [p.1445], and "he can recall

childhood memories, as well as many experiences of his lifetime" [p.1448].

It is also added that the main distortion in H.M. was not his working memory (WM): "H.M had normal WM, for example, he can repeat a telephone number for seconds to minutes due to his intact WM" [p.1445], "indicating that the MTL is not necessary for transient memory" [p.1443]; however, his problem was in the ability to form new memories or the encoding ability. "He could not recognize people after surgery, even he met them several times" [p.1445], and "he had difficulty in forming and retaining new conscious (episodic and semantic) memories of their personal experience or the meaning of new concepts" [p.1446]. "The activation of MTL in the encoding of stimuli that were later remembered is observed compared to those that were forgotten" [p.1448], suggesting the role of MTL in the encoding process.

Question/Suggestion 4: Is the hippocampus necessary for accessing older episodic memory? H.M. did not have this brain structure but could remember his older memories, while the animal studies suggest that an impaired hippocampus deteriorates retrieval of episodic memory. Kandel mentions that "the observations in H.M. and other amnesic patients with damage to the MTL suggest that old memories are not stored in MTL" [p.1448]. This contradicts the results of animal studies which report the spatial information (as a kind of episodic memory) to be stored in the hippocampus: "The hippocampus stores declarative information in a more stable form for periods ranging from days to weeks to years, up to a lifetime" [p.1487], and "PKM (protein kinase Mzeta) is required for the maintenance of LTP but is not involved in its initial induction" [p.1503]. As a result, it is suggested that future editions of the book respond to these conflicting statements.

Question/Suggestion 5: It is mentioned that "the hippocampus stores declarative information in a more stable form for periods ranging from days to weeks to years, up to a lifetime" [p.1487]. It seems H.M. is a counterexample for this claim.

Question/Suggestion 6: The book pointed out that "the retrieval of contextual or event details associated with episodic memory showed activity in the MTL, particularly in the hippocampus" [p.1449]. How can this be interpreted when the hippocampus was not necessary for the retrieval of episodic memory in patient H.M.? Is it only because "MTL activity is thought to facilitate the activation of neocortical representations that were present during encoding" [p.1449]?

Explicit memory in animal

As observed in the book, episodic memory was mostly studied in rodents, and by assessing spatial memory. One feature of explicit memory is that it is declarative, and since it cannot be assessed in animals, the book points out that episodic memory is identified in animals by the being-conscious feature of it. Since "consciousness cannot be studied empirically in the mouse" [p.1511] either, "selective attention, which is required for conscious recall, is examined instead" [p.1511].

Question/Suggestion 7: Regarding the "being declarable" feature of episodic memory, and since animals cannot "declare" anything, should we name this memory differently when it is studied in animals?

Size of memory storage

It is stated in the book that "one of the features of LTM is that it seems to have an almost unlimited capacity; no known limit exists to the amount of information in LTM storage" [p.1447]. One piece of evidence provided for that claim was "a memory system that automatically retained every detail of every experience, such as what happened in Shereshevski, who was filled with highly detailed memories of his past experiences" [p.1458].

However, based on the mechanisms reported for the storage of explicit memory in the book, "if synaptic connections can only be enhanced and never attenuated, the synaptic transmission may rapidly saturate, the strength of the synaptic connection may reach a point beyond which further enhancement is not possible" [p.1513]. Since "individuals can learn and store new memories throughout a lifetime" [p.1513], the book suggests that the solution for this paradox is "a mechanism to down-regulate synaptic function to counteract LTP" [p.1513], which is called long-term depression. "The LTD suggests an anti-Hebbian learning rule; synapses that do not contribute to the firing of a cell are weakened" [p.1513].

Question/Suggestion 8: Should we consider an unlimited LTM capacity in humans? If yes, probably the current mechanisms which explain the storage of LTM need further modifications, as apparently, and based on the book, the current mechanisms need the LTD for continuous memory storage, and this equals the erasure of our older memories, which does not seem to necessarily happen.

Differences between implicit and explicit memories

"Implicit memory, also known as procedural or non-declarative memory, takes the form of an unconscious memory, and is an automatic manner" [p.1446, 1461]; it includes "knowledge that is acquired without conscious effort, and guides behaviour unconsciously" [p.1452]. "Implicit memory can only be retrieved during performance and not consciously" [p.1485]. On the other hand, "explicit memory, also known as declarative, is conscious" [p.1446, 1461], and "is the conscious recall of information" [p.1487].

As mentioned in the book, it seems that episodic memory depends on the MTL structures, while implicit memory does not. Evidence includes a "greater activity in the MTL during encoding of stimuli that were subsequently remembered compared to those that were forgotten" [p.1448], and the "episodic learning being dependent on the interaction between cognitive control processes in the PFC and associative binding mechanisms in the MTL" [p.1448]. The disabled encoding ability in patient H.M. is another evidence, and similarly the musician, Clive Wearing, whose hippocampus and temporal cortex were affected, "did not have memory for events or people he met a few minutes earlier" [p.1461], which showed "impairments in his episodic memory encoding", while he "could still play on the piano, showing his intact procedural memory" [p.1461].

On the other hand, "priming, as a type of implicit memory, does not depend on the MTL" [p.1452]. "The implicit memory is independent of the hippocampus, such as patients with MTL damage who can learn to read mirror-reversed text" [p.1453]. Other evidence were the "neural circuits that initiate habit, motor skills and conditioned learning are independent of the medial temporal lobe system is responsible for explicit memory" [p.1453]; "learning of sensorimotor depending on basal ganglia, cerebellum, and neocortex; dysfunction of the basal ganglia impairing learning of motor skills; and lesions in the cerebellum impairing motor learning" [p.1453]; "skills to depend on structural changes in the motor neocortex, such as the expansion of the cortex relevant to fingers in musicians" [p.1453]; and "long term storage of implicit memory requiring neocortex for priming, striatum for skills and habits, amygdala for learned fear, cerebellum for learned motor skills, and reflex pathways for non-associative learning" [1461].

Question/Suggestion 9: Based on the above statements, the implicit and explicit memories have at least two differences: being dependent on the MTL structures, and being conscious. Those memories which are processed in the MTL become conscious, and the memories that do not pass through the MTL are unconscious. Can we conclude that the MTL structures are central organs for consciousness?

Differences between semantic and episodic memories

"Episodic memory is the memory of personal experiences or autobiographical memory, and semantic memory is the memory for facts" [p.1446]. Also, "semantic knowledge is distinguished from episodic knowledge in that it is typically unrelated to the context in which the information was acquired" [p.1451].

Question/Suggestion 10: Is it reasonable to infer that semantic memory is a special kind of episodic memory that is independent of temporal and spatial constraints? An episode, in which the information content is more vital than the temporal and spatial features of the data collection event, becomes semantic knowledge.

Conclusion

Once again, I insist here that my goal was not to criticize all scientific endeavours and achievements of great scientists, such as Professor Kandel and his colleagues. However, to achieve a more comprehensive understanding of the human memory system, I am searching for the answers to my above questions, and any assistance from the experts in the field would be appreciated.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Conflict of interest

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