Revista Médica del
Hospital General de México

PERMANYER

Check for updates

Is the ventral tegmental area the main anatomical structure of memory storage?

Hüseyin Çaksen

Divisions of Pediatric Neurology and Genetics and Behavioral-Developmental Pediatrics, Department of Pediatrics, Faculty of Medicine, Necmettin Erbakan University, Meram, Konya, Türkiye

Abstract

Memory is a complex brain function that permits individuals to store and retrieve information. Although it has been suggested that many brain structures are responsible for memory, it is still unknown where memory information is stored in the brain. In this article, based on the current literature data, we briefly reviewed the structures and pathways in the brain responsible for memory to determine the main anatomical structure of memory storage in humans. Although many types of memories, such as short-term, working, sensory, episodic, semantic, procedural, and prospective memories, have been reported in the literature, all of them are nothing more than activated long-term memory. Recent studies have shown that in humans, not only the prefrontal cortex, midbrain, amygdala, hippocampus, and cerebellum, but also the whole brain, including the entire cerebral cortex of six brain lobes, subcortical structures and brainstem, are involved in the management, execution and functioning of memory systems and encoding, consolidation and storage of memories. However, there is only one area of memory storage the size of a lentil (or a mustard-seed) in the human brain. Considering its size, anatomical location, connections, and interactions with other areas of the brain, neural structure and functions, and cellular properties, we propose that the ventral tegmental area is the main anatomical structure of memory storage in humans.

Keywords: *Memory. Memory storage. Human. Midbrain. Ventral tegmental area.*

Introduction

Memory is a complex brain function that permits individuals to store and retrieve information. Our memory systems in the brain are capable of storing massive amounts of information over extended periods of time, in some cases, as long as a lifetime. The information stored in our memories informs our sense of identity, our understanding of the world around us, and our future actions[1]. Memory activation mechanisms, attentional and executive mechanisms, and long-term retrieval mechanisms all work together in processing to form an effective working memory system[2]. In the human brain, the neural networks are organized into distributed systems, which collaborate with other systems, both sensory and associative, to produce the total working effect[3]. A memory system is usually defined as a neural structure (or network of structures) and its interconnections, which together operate on a particular type of information and then participate in the storage of that information, either within the structure itself or elsewhere[4].

Despite ongoing research efforts since the 1940s, when the field of neuropsychology emerged, the question of where memory information is stored in the brain remains unresolved by medicine, neuroscience, psychiatry, psychology, sociology, and philosophy. Many scientists have argued that the prefrontal cortex, basal ganglia,

Correspondence:
Hüseyin Çaksen
E-mail: huseyincaksen@hotmail.com

Date of reception: 18-01-2025
Date of acceptance: 20-02-2025
DOI: 10.24875/HGMX.25000005
Available online: 03-11-2025
Rev Med Hosp Gen Mex. 2026;89(2):114-118
www.hospitalgeneral.mx

0185-1063/© 2025 Sociedad Médica del Hospital General de Mexico. Published by Permanyer. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

midbrain (or mesencephalon), hippocampus, amygdala, and cerebellum are all important for different aspects of memory, but some authors have noted the specific center of memory storage in humans. On the other hand, although some authors suggested short-term and long-term memory subsystems, a commonly expressed view is that short-term memory is nothing more than activated long-term memory. This conception of the relation between short-term memory and long-term memory has become increasingly popular in neuroimaging research[5]. Although it has been suggested that many brain structures are responsible for memory, it is still unknown where memory information is stored in the brain. Herein, based on the current literature data, we briefly reviewed the structures and pathways in the brain responsible for memory to determine the main anatomical structure of memory storage in humans.

Memory systems and storage in humans

The prefrontal cortex, basal ganglia, midbrain, hippocampus, amygdala, and cerebellum are all important for different aspects of memory. The human brain has two prefrontal cortices, two basal ganglia, two thalami, two hippocampi, two amygdalae, and two cerebellar hemispheres, one on each side of the brain, but one midbrain. The midbrain, the shortest part of the brainstem, is the most rostral part of the brainstem that connects the pons and cerebellum with the forebrain. The midbrain includes two substantiae nigrae and two retrorubral fields, one on each side of the midline. However, the ventral tegmental area (VTA), which consists of a group of neurons located in the midline at the floor of the midbrain, is a single piece[6] (Fig. 1).

The neurons in the midbrain tegmentum aggregate in several tiers or laminae oriented longitudinally in the midbrain, traversing its entire mediolateral extent. The VTA and retrorubral fields contain mixed populations of neurons and are organized into two additional tiers, the ventromedial VTA regions and a dorsolateral VTA/retrorubral fields continuum situated dorsal to the substantia nigra[7]. The midbrain contains many important structures that make it essential for the proper functioning of the body. It consists of features that are intimately connected to human emotion and the shaping of memory through neural connections to the lobes of the cortex.

The retrorubral fields project to the VTA and substantiae nigrae. The substantiae nigrae is also connected with the VTA in the brain. Hence, the VTA is connected with both the retorubral field and the substantia nigra.

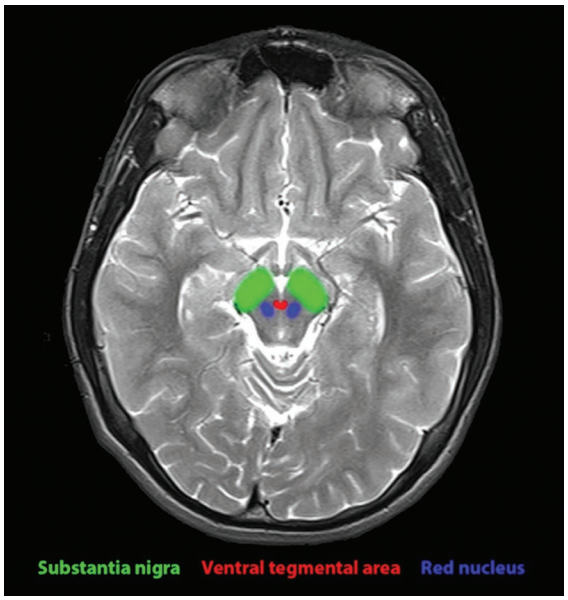


Figure 1. Axial cranial magnetic resonance imaging shows two substantiae nigrae, two red nuclei, and one ventral tegmental area.

Kwon and Jang[6] reported that the VTA showed 100% connectivity to the red nucleus, thalamus, and pontine tegmentum in healthy adult subjects. It revealed over 70% connectivity in the following brain regions: globus pallidus, posterior lobe of cerebellum, prefrontal cortex, primary motor cortex, and amygdala. In all subjects, the substantia nigra showed 100% connectivity to the red nucleus, thalamus, globus pallidus, corpus callosum, primary motor cortex, primary somatosensory cortex, premotor cortex, pontine tegmentum, and posterior lobe of cerebellum. The following brain regions showed over 70% connectivity of the substantia nigra: caudate nucleus, putamen, nucleus accumbens, prefrontal cortex, temporal lobe, amygdala, pontine basis, occipital lobe, and anterior lobe of cerebellum[6]. These findings clearly show that the VTA is connected to all areas of the brain, including the brainstem and cerebellum, either directly or via the substantiae nigrae.

Nursi[8] reported that the center of memory storage in humans occupies a small space the size of a lentil (or a mustard-seed) in the brain; however, he did not describe its location in the brain. The faculty of memory, which is the size of a mustard-seed in a head from the manifest world (visible material world), takes on an existence the size of a library from the world of meaning. The world of meaning is the understanding and description of truths through the mind[8]. Kwon and

Jang[6] recorded that the sizes of the region of interest for the VTA in the brain were 10.8 ± 1.9 mm, the size of a lentil. This shows that the main anatomical structure of memory storage mentioned by Nursi[8] might be the VTA.

Recently, Cohen et al.[9] found that reward-related memory benefits were linked to age-varying neural mechanisms in participants aged 8-25 years old using functional magnetic resonance imaging. During encoding, interactions between the prefrontal cortex and VTA were associated with better high-reward memory to a greater degree with increasing age. Pre-encoding to post-encoding changes in functional connectivity between the anterior hippocampus and VTA were also associated with better high-reward memory, but more so at younger ages[9]. While many core facets of executive function may reach maturation in childhood, these processes continue to be refined and stabilized during adolescence. This is mediated, in part, by interactions between the hippocampus and prefrontal cortex. Specifically, the development of this circuit refines adolescents' ability to extract relevant information from prior experience to support task-relevant behavior[10].

Neurotransmitters, memory pathways, and VTA

Single-neuron analysis revealed that significant subpopulations of dopamine and gamma-aminobutyric acid neurons responded differently between left and right trials in the memory delay in mice. Firing rate differences are linked to short-term memory-dependent decisions and cannot be explained by reward-related processes, motivated behavior, or motor-related activities[11]. Recently, Sayegh et al.[12] discovered that stimulating the Schaffer collaterals – the glutamatergic axons connecting CA3 and CA1 regions – of the dorsal hippocampus concomitantly with midbrain dopamine terminals within a 200 ms time window triggers long-term potentiation at glutamatergic synapses in male DAT::Cre mice. They also showed that the stimulation of this dopaminergic pathway facilitates contextual learning in awake behaving mice, while its inhibition hinders it. Thus, activation of midbrain dopamine can operate as a teaching signal that triggers NeoHebbian long-term potentiation and promotes supervised learning[12]. Lima et al.[13] found that alpha7 nicotinic acetylcholine receptor-mediated cholinergic interactions between the pedunculopontine tegmental nucleus and the medial prefrontal cortex modulate the duration of fear-motivated memories in rats, maybe by regulating the activation state of VTA-hippocampus dopamine connections.

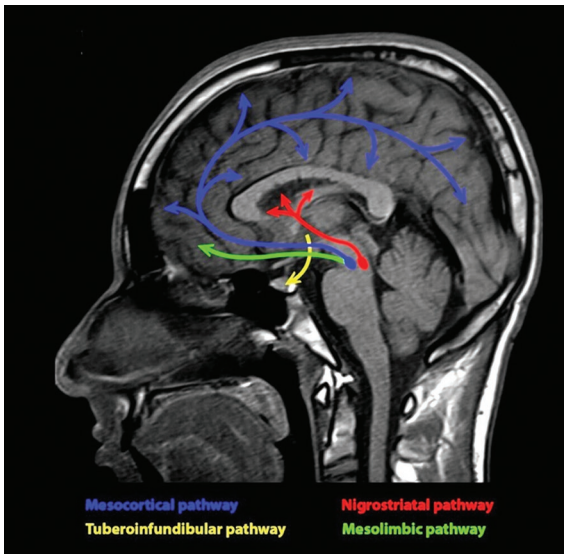


Figure 2. Sagittal cranial magnetic resonance imaging appears as dopaminergic pathways.

In humans, there are four dopaminergic pathways: mesocortical, nigrostriatal, mesolimbic, and tuberoinfundibular. The majority of the estimated 400,000 dopamine-producing neurons reside in the midbrain and consist of three cell groups: the retrorubral field, the substantia nigra pars compacta, and VTA[14] (Fig. 2). These cell groups are largely continuous, with VTA and the retrorubral field forming dorso-medial and caudo-lateral protrusions of the substantia nigra pars compacta, respectively. At caudal levels of substantia nigra pars compacta, the retrorubral field, and VTA are continuous with each other. Given this continuity, the terms substantia nigra pars compacta primarily specify subdivisions of one coherent dopaminergic cell complex. Further dopamine neurons are located in nearby regions such as the hypothalamus, peria-queductal grey, rostral linear nucleus, and dorsal raphe[14]. Furthermore, the prefrontal cortex and thalamus interact to regulate dopaminergic neuron acti-vity[15]. Dopamine, one of the major neurotransmitters in the brain, is a key regulator involved in cognition, learning, and memory[6,15]. In particular, encoding and consolidation of memories require the stimulation of dopamine receptors as part of a hippocampal-striatal-prefrontal loop that orchestrates the formation of new memories[16].

The VTA, a pivotal brain region of the mesocorticolimbic dopaminergic system, is substantially innervated and modulated by cholinergic projections from

the pedunculopontine tegmental nucleus and laterodorsal tegmental nucleus[17]. The VTA contains diverse populations of dopamine-, glutamate-, and gamma-aminobutyric acid-releasing neurons, as well as combinatorial neurons that release more than one neurotransmitter[18]. The VTA glutamate neurons are known to form asymmetrical synapses and evoke excitatory post-synaptic currents in the prefrontal cortex and the dorsal hippocampus, both of which are known to regulate learning and memory. Thus, VTA glutamate neurons play a role in memory consolidation, at least through projecting to the prefrontal cortex and dorsal hippocampus[19]. Recently, GABA+/creatine levels were found to be positively correlated with long-delayed verbal memory and immediate non-verbal memory in the brain of older adults with high-Alzheimer's disease risk using magnetic resonance spectroscopy[20].

Conclusion

Although many types of memories, such as short-term, working, sensory, episodic, semantic, procedural, and prospective memories, have been reported in the literature, all of them are nothing more than activated long-term memory. The human midbrain and pons contain nuclei of major neurotransmitter systems that send long-range projections to regulate brain activity in cortical and subcortical structures. Despite being small structures, these nuclei are critically implicated in a very wide range of cognitive and bodily functions[9]. Recent studies have shown that in humans, not only the prefrontal cortex, midbrain, amygdala, hippocampus, and cerebellum, but also the whole brain, including the entire cerebral cortex of six brain lobes, subcortical structures and brainstem, are involved in the management, execution and functioning of memory systems and encoding, consolidation and storage of memories. However, there is only one area of memory storage the size of a lentil (or a mustard-seed) in the human brain. Considering its size, anatomical location, connections, and interactions with other areas of the brain, neural structure and functions, and cellular properties, we propose that the VTA is the main anatomical structure of memory storage in humans. Further comprehensive studies using neurochemical analyses, electrophysiological, and neuroimaging techniques should be conducted to determine whether the VTA is the main memory storage in the brain.

Acknowledgments

The author would like to thank his colleague, Dr. Ö. Yaz, MD, for helping him to prepare the images for the article.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Chiew KS, Bowen HJ. Neurobiological mechanisms of selectivity in motivated memory. In: Elliot AJ, editor. Advances in Motivation Science. Vol. 9. Amsterdam: Elsevier; 2022. p. 57-87.
2. Cowan N. An embedded process model of working memory. In: Miyake A, Shah P, editors. Models of Working Memory: Mechanisms of Active Maintenance and Executive Control. Cambridge, UK: Cambridge University Press; 1999. p. 62-101.
3. Ackerman S. Discovering the brain. Washington: National Academies Press; 1992.
4. Kim JJ, Baxter MG. Multiple brain-memory systems: the whole does not equal the sum of its parts. Trends Neurosci. 2001;24:324-30.
5. Norris D. Short-term memory and long-term memory are still different. Psychol Bull. 2017;143:992-1009.
6. Kwon HG, Jang SH. Differences in neural connectivity between the substantia nigra and ventral tegmental area in the human brain. Front Hum Neurosci. 2014;8:41.
7. Halliday G, Reyes S, Double K. Substantia nigra, ventral tegmental area, and retrorubral fields. In: Mai JK, Paxinos G, editors. The Human Nervous System. Amsterdam: Elsevier; 2012. p. 439-55.
8. Nursi BS. From the Risale-I Nur Collection. Letters. The Twentieth Letter; 2012. Available from: https://www.erisale.com/index.jsp?locale=en#content.en.202.291 [Last accessed on 2025 Feb 19].
9. Cohen AO, Glover MM, Shen X, Phaneuf CV, Avallone KN, Davachi L, et al. Reward enhances memory via age-varying online and offline neural mechanisms across development. J Neurosci. 2022;42:6424-34.
10. Murty VP, Calabro F, Luna B. The role of experience in adolescent cognitive development: integration of executive, memory, and mesolimbic systems. Neurosci Biobehav Rev. 2016;70:46-58.
11. Glykos V, Fujisawa S. Memory-specific encoding activities of the ventral tegmental area dopamine and GABA neurons. Elife. 2024;12:RP89743.

12. Sayegh FJ, Mouledous L, Macri C, Pi Macedo J, Lejards C, Rampon C, et al. Ventral tegmental area dopamine projections to the hippocampus trigger long-term potentiation and contextual learning. Nat Commun. 2024;15:4100.
13. Lima RH, Radiske A, Köhler CA, Gonzalez MC, Bevilaqua LR, Rossato JI, et al. Nicotine modulates the long-lasting storage of fear memory. Learn Mem. 2013;20:120-4.
14. Düzel E, Guitart-Masip M, Maass A, Hämmerer D, Betts MJ, Speck O, et al. Midbrain fMRI: applications, limitations and challenges. In: Uludağ K, Uğurbil K, Berliner L, editors. *fMRI: From Nuclear Spins to Brain Functions*. Biological Magnetic Resonance. Boston, MA: Springer; 2015. p. 581-609.
15. Yang C, Hu Y, Talishinsky AD, Potter CT, Calva CB, Ramsey LA, et al. Medial prefrontal cortex and anteromedial thalamus interaction regulates goal-directed behavior and dopaminergic neuron activity. Nat Commun. 2022;13:1386.
16. Clos M, Bunzeck N, Sommer T. Dopamine is a double-edged sword: dopaminergic modulation enhances memory retrieval performance but impairs metacognition. Neuropsychopharmacology. 2019;44:555-63.
17. Zhang C, Liu X, Zhou P, Zhang J, He W, Yuan TF. Cholinergic tone in ventral tegmental area: functional organization and behavioral implications. Neurochem Int. 2018;114:127-33.
18. Morales M, Margolis EB. Ventral tegmental area: cellular heterogeneity, connectivity and behaviour. Nat Rev Neurosci. 2017;18:73-85.
19. Cai J, Tong Q. Anatomy and function of ventral tegmental area glutamate neurons. Front Neural Circuits. 2022;16:867053.
20. Murari G, Liang DR, Ali A, Chan F, Mulder-Heijstra M, Verhoeff NP, et al. Prefrontal GABA levels correlate with memory in older adults at high risk for Alzheimer's disease. Cereb Cortex Commun. 2020;1: tgaa022.