Preprint of: Kaźmierska-Grębowska, P., Żakowski, W., Myślińska, D., Sahu, R., & Jankowski, M. (2024). Revisiting serotonin's role in spatial memory: A call for sensitive analytical approaches. INTERNATIONAL JOURNAL OF BIOCHEMISTRY & CELL BIOLOGY, 176, 106663. **https://doi.org/10.1016/j.biocel.2024.106663**

Serotonin and Spatial Navigation: What's known and what's missing

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Abstract

In the broader context of modern society, the activity of the serotonergic system has been implicated in the etiology of various psychiatric conditions and mental disorders, with serotonergic drugs commonly used in their treatment. It has been documented that serotonin can modify neural pathways and synaptic connections, which are essential for cognitive functions and memory processing. Spatial memory has emerged as one of the valuable models for understanding general declarative memory functions. Hence, in this In Focus review, our attention is solely devoted to understanding how serotonin affects spatial memory and learning. We aim to identify and highlight the existing gaps in research, offering new insights into serotonin's function and plan for further research in both spatial navigation and the broader spectrum of declarative memory.

Keywords: serotonin, 5-HT, spatial memory, behavior, theta rhythm, spatially tuned cells

Key Facts:

- Serotonin (5-hydroxytryptamine, 5-HT), an indolamine neurotransmitter, has been implicated in the etiology of various psychiatric conditions and mental disorders.
- Spatial memory has become a model for exploring the functions of declarative memory.
- The serotonergic system modulates spatial memory via diverse mechanisms, with effectiveness varying by manipulation type, experimental method, and data analysis approach.
- Further progress in understanding the effects of serotonin on spatial memory at both behavioral and cellular levels requires the use of modern, high-resolution methods.

Remembering Space and Time

Our self is constantly shaped by experiences as we encounter them across various physical spaces at different moments of our lives (Klein and Nichols, 2012). These events, typically intertwined with cues from sensory domains, become embedded in our preexisting neural networks (Buzsáki et al., 2022). This implies that space and time are fundamental elements for our declarative memory and, therefore, crucial building components of our self-identity (Buzsáki et al., 2022; Eichenbaum, 2017; Grilli and Verfaellie, 2015; Klein and Nichols, 2012; Martinelli et al., 2013). Losing the ability to encode and retain information about space and time can have dramatic outcomes on our ability to function in daily life. This is often observed in patients with severe dementia of various etiology. At some point in the disease, we may lose the ability to recognize our own home or loved ones (Jetten et al., 2010; Rose Addis and Tippett, 2004; Strikwerda-Brown et al., 2019).

Mental maps

Spatial memory has been proposed as one of the mnemonic mechanisms providing a general framework for the functioning of declarative memory (Bellmund et al., 2018; Bicanski and Burgess, 2018; Buzsáki et al., 2022; Buzsáki and Moser, 2013; Eichenbaum and Cohen, 2014; Tolman, 1948; Varga et al., 2024; Viganò and Piazza, 2020). Not only does this concept apply to environmental frames that physically exist and are experienced through the senses, but it is also proposed to involve the creation of abstract cognitive maps, or as some refer to them, mental maps (Aronov et al., 2017; Buzsáki and Moser, 2013; Constantinescu et al., 2016; Eichenbaum and Cohen, 2014; Guelton, 2023; Tolman, 1948). These putative mental maps would organize our memories, including events, episodes, solutions to problems, emotional states, and internal sensations, along with some generalizations and semantic facts, within abstract spatiotemporal

frameworks (Eichenbaum and Cohen, 2014; Guelton, 2023). Thus, we can travel mentally through abstract spaces of interconnected memories, further process all stored information, and produce new associations (Fragueiro et al., 2021). In this In Focus review, we will specifically focus on spatial memory as a framework to examine the impact of serotonin on this distinct category of memory.

Why serotonin?

Despite less than 0.1% of neurons in the mammalian brain having the ability to synthesize and release serotonin (5-hydroxytryptamine, 5-HT) (Okaty et al., 2019), much discussion has centered on how it can alter and potentially enhance our quality of life in a variety of mental health disorders. This includes moderating anxiety and stress, promoting patience and coping mechanisms, and opening the window for greater neural plasticity, depending on the type of receptors involved (Carhart-Harris and Nutt, 2017; Deakin, 2013; Miyazaki et al., 2012, 2014). Serotonergic drugs have been proposed and are widely used in treating a broad spectrum of mental health conditions, particularly mood disorders (Hieronymus et al., 2016; Moncrieff et al., 2023; Pourhamzeh et al., 2022). This is despite controversies regarding serotonin dysregulation being the major cause of these conditions (Kirsch, 2019; Moncrieff et al., 2023). Furthermore, serotonergic drugs are also found in the realms of recreational drug use, microdosing, and other recently emerging fields of self-prescribed neuro-enhancement, which aim to improve human mood, well-being, efficiency, creativity, and the balance between wakefulness and sleep (Cavanna et al., 2022; Cespuglio, 2018; Daubner et al., 2021; Gandotra et al., 2022; Jannini et al., 2022; Marazziti et al., 2021; Monti, 2011; Parrott, 2002; Sakakibara, 2020; Schmitt et al., 2006). Reflecting on these widespread applications, substances acting on the brain's serotonin system have become prevalent across all age groups in our society (Giovannini et al., 2020;

Jannini et al., 2022). Given the extensive scope of serotonin research, particularly within pharmacology, this brief review will focus on selected topics that we believe would benefit from re-examination using more advanced approaches.

Global changes in brain serotonin – missing bits and pieces

The serotonergic system has been identified as capable of modulating spatial memory through various mechanisms, although its effectiveness can vary depending on the type of manipulation applied, the experimental method, and the approach to data analysis (Fig. 1) (Coray and Quednow, 2022; Dale et al., 2016; Glikmann-Johnston et al., 2015). The majority of earlier studies investigating serotonin's role in spatial memory relied on simple behavioral tests, such as the Morris water maze, radial arm maze, Barnes maze, and similar assays. These studies often employed basic behavioral analyses, focusing on metrics such as the time required to locate a target location or the duration spent in the chosen area. Results were typically presented as average time in seconds. For instance, a global decrease in serotonin levels induced by acute tryptophan depletion (ATD) (Hood et al., 2005; Van Donkelaar et al., 2011; Young et al., 1989) did not significantly impact spatial memory in rats and mice across several studies (Lieben et al., 2004; Liu et al., 2013; Stancampiano et al., 1997; Uchida et al., 2007). Similarly, nonspecific neurotoxic lesions targeting serotonin neurons using 5,7-dihydroxytryptamine (5,7-DHT) did not significantly alter outcomes in those basic behavioral models (Lehmann et al., 2000; Majlessi et al., 2003; Nilsson et al., 1988). The serotonin depletion induced by inhibiting tryptophan hydroxylase with Para-chlorophenylalanine (PCPA) (Dringenberg et al., 1995; Miczek et al., 1975) also did not affect significantly the learning performance of rats in water maze (Fig. 1) (Beiko et al., 1997; Dringenberg and Zalan, 1999; Harder et al., 1996; Jäkälä et al., 1993; Richter-Levin and Segal, 1989; Riekkinen et al., 1993, 1992) and active place avoidance, a

spatial task that requires allothetic mapping and cognitive coordination and is highly dependent on the hippocampus (Petrásek and Stuchlík, 2009).

On the other hand, several studies have shown that global decrease in serotonin levels altered certain aspects of spatial memory (Fig. 1). In the Barnes maze, the performance of the serotonin transporter (5-HTT) knockout (-/-) mice was indistinguishable from that of heterozygous (+/-) and wild-type (+/+) mice. However, they performed worse in the Morris water maze. Nevertheless, over the course of repeated water maze trials, 5-HTT knockout (-/-) mice improved to reach the performance level of wild-type mice (Karabeg et al., 2013). The serotonin 1A receptor (5-HT1A) knockout animals exhibited deficits in hippocampal-dependent learning and memory tasks, including Morris water maze and a version of the Y maze (Sarnyai et al., 2000). In the other experiments, young adult 5-HT1A knockouts, but not aged ones, exhibited impaired learning and retention in the Morris water maze (Wolff et al., 2004).

There is also evidence suggesting that global long-term increase in serotonin levels can improve particular aspects of spatial memory (Fig. 1). A daily injection of the serotonin precursor, 5-hydroxytryptophane (5-HTP), prior to training sessions, improved considerably the performance of the old rats in the water maze but had no effect on the behavior of the young rats (Levkovitz et al., 1994). Enhanced performance in radial maze was also observed in rats treated with tryptophan (Haider et al., 2006). Furthermore, various agonists and antagonists of the large family of serotonergic receptors had different effects on spatial memory in animal models using water maze and radial arm maze tests, and in human spatial memory tasks (Beaudet et al., 2015; Coray and Quednow, 2022; Dale et al., 2016; De Filippis et al., 2015; Wingen et al., 2007).

Considering the data discussed above, it can be inferred that long-term changes in global serotonin levels are unlikely to affect spatial memory and learning. However, the majority of

these studies rely on coarse measures of behavior in simplistic tests, an approach that significantly reduces our capability to quantify the rich and dynamic nature of behaviors occurring at sub-second time scales. Recent high-resolution animal tracking methods, automated behavior recognition, data-driven and hierarchical approaches for behavioral data analysis, and other available resources could help to shed new light on the role of serotonin in spatial navigation that seems to be more complex and will require more sensitive analytical methods (Amir et al., 2020; Correia et al., 2024, 2017; Hu et al., 2023; Jankowski et al., 2023; Könings et al., 2019; Mathis et al., 2018; Pereira et al., 2020, 2019; Ryait et al., 2019; Storchi et al., 2020; Van Dam et al., 2023).

Local changes in brain serotonin and their impact on hippocampal theta rhythm-related learning

So far, attempts to change global serotonin levels have most frequently failed to produce significant effects. However, in some cases, they have either impaired or improved spatial memory and learning. When we examine experiments involving more targeted, localized changes in serotonin levels within specific brain structures, it appears to be a more effective approach (Fig. 2). Optogenetic activation of serotonergic terminals in the CA1 region of the hippocampus enhanced water maze memory formation, while inhibition of these terminals in the CA1 region impaired it (Fig. 2A) (Teixeira et al., 2018). Recent study by Gerdey and Masseck (2023) failed to reproduce these results possibly due to different genetically modified mouse models used in both studies. In Gerdey and Masseck (2023) study, manipulating median raphe serotonin input to the dorsal CA1 subfield, whether through activation or inhibition at CA1 fiber terminals, did not affect significantly object recognition, spatial memory, or anxiety behavior. However, activation of serotonergic fibers to the CA1 region altered strategies used in the Barnes Maze. Moreover, activation of 5-HT1A receptors, abundant in CA1's pyramidal neurons,

significantly enhanced spatial memory without impacting object recognition or avoidance behavior (Fig. 2A) (Gerdey and Masseck, 2023).

Following lesions in the fimbria, fornix, and cingulate bundle of adult rats with 5,7-DHT to deplete hippocampal serotonin, Gutiérrez-Guzmán et al. (2011) observed a facilitation of place learning. This effect was associated with dominant high-frequency theta activity (6.5-9.5Hz) (Gutiérrez-Guzmán et al., 2011). Similarly, serotonin depletion in the medial septum facilitated learning in Morris water maze and increased the frequency of the hippocampal theta activity during the first days of training to 8.5 Hz (Gutiérrez-Guzmán et al., 2017). The depletion of serotonin in the medial septum and Broca's diagonal band (MS/DBB) facilitated working memory also in the radial arm maze and again induced a higher expression of high-frequency (6.5–9.5 Hz) theta activity (López-Vázquez et al., 2014). On the other hand, depletion of serotonin in the supramammillary nucleus impaired learning in Morris water maze and altered the expression of hippocampal high-frequency theta activity (Fig. 2B) (Hernández-Pérez et al., 2015).

Serotonergic modulation of hippocampal theta rhythm has been described in several studies (Gordon et al., 2005; Kazmierska and Konopacki, 2015; Kudina et al., 2004; Olvera-Cortés et al., 2013; Sörman et al., 2011; Vertes, 2010). Theta activity plays a critical role in spatial navigation, particularly in the hippocampus, where place cells coordinate their firing with network oscillations and neurons in other brain regions through processes such as phase precession, phase locking, and phase rolling (Buzsáki, 2002; Jones and Wilson, 2005; Siapas et al., 2005; Skaggs et al., 1996; Sloin et al., 2022). Theta activity at its core is generated by the synchronous activity of multiple single neurons in specific neural networks, such as those in the medial septum and hippocampus (Herreras, 2016; Nuñez and Buño, 2021). Therefore we

expected that we will find numerous papers concerning the effects of serotonin on cellular substrates of spatial memory such as place cells, grid cells, boundary cells, head direction, or object and object-trace cells (Grieves and Jeffery, 2017). Despite the availability of advanced methods for studying spatial navigation at the single-cell level and its relations with theta rhythm in both rodents and, increasingly, humans, we found it challenging to locate studies that detail such research. Our investigation uncovered research conducted by Zhang et al. (2017) demonstrating that the administration of the phenylalkylamine hallucinogen TCB-2, a selective agonist of 5-HT2A receptors (5-HT2ARs), increased the latency for trained mice to initiate goal-directed swimming in the Morris water maze. This effect could be prevented by the 5-HT2AR antagonist MDL 11,939. TCB-2 did not affect previously established place fields of CA1 neurons in mice exploring a familiar environment, nor did it impact the remapping of place cells in a novel environment. However, it did impair the long-term stability of place fields for the novel environment initially encoded under the influence of TCB-2, an effect that could also be prevented by 5-HT2AR antagonist MDL 11,939 (Zhang et al., 2017). In a study by Sandoval et al. (2008), the serotonergic antagonist methiothepin altered the directional characteristics of head direction cells in the anterior dorsal thalamus only when combined with the muscarinic antagonist scopolamine. These studies suggest that manipulating serotoninergic activity holds potential for modulation of the cellular substrates of spatial memory and could be further investigated.

Conclusions

In summary, the serotonergic system has the potential to modulate spatial memory, though its effects are complex and require more advanced experimental and data analysis methods for thorough understanding. Current behavioral experiments often report no significant effects,

possibly due to the reliance on coarse measures. Meanwhile, the interplay between cellular substrates of spatial memory and serotonin remains poorly explored. Both domains offer promising avenues for research, which could be pursued concurrently with plenty of tools available at hand.

Acknowledgements

This work was supported by the National Science Centre and the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 945339, Polonez Bis 3, project No. 2022/47/P/NZ4/03358; Principal Investigator: dr. Maciej M. Jankowski. The publication of this article was supported by National Science Centre, Poland Grant, Sonata 13, project No. 2017/26/D/NZ4/00159, Principal Investigator: dr. Paulina Kazmierska-Grebowska.

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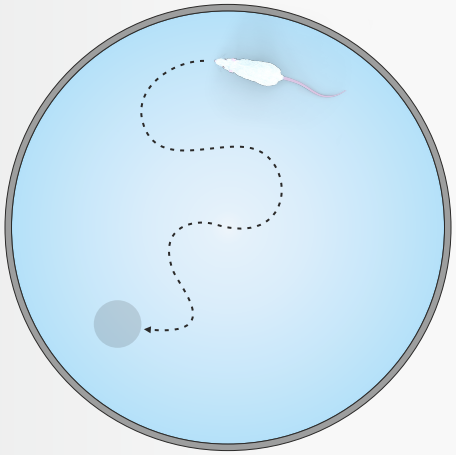
Figure 1. This figure summarizes research on how changes in global serotonin levels affect spatial memory in rodents across various tasks, such as the Morris water maze, radial arm maze, and Barnes maze. It depicts three main outcomes observed in previous studies: non-significant changes, decreased performance, and increased performance, marked by arrows in black, red, and green, respectively. Behavioral effects were produced through various experimental interventions. These included acute tryptophan depletion (ATD), neurotoxic lesions induced by 5,7-dihydroxytryptamine (5,7-DHT), serotonin depletion caused by inhibiting tryptophan hydroxylase with Para-chlorophenylalanine (PCPA), genetic manipulations such as knockouts of the serotonin transporter (5-HTT) or serotonin 1A receptor (5-HT1A) genes, as well as administration of serotonin precursors like 5-hydroxytryptophan (5-HTP) and tryptophan (TRP). Key studies are cited for each outcome, providing an overview of the role of serotonin in spatial memory.

Figure 2. Impact of targeted serotonergic system manipulations on spatial memory in the Morris water maze task: (A) Optogenetic activation of serotonergic terminals or 5-HT1A receptors in the hippocampal CA1 region of the hippocampus enhanced performance in water maze, while inhibition of serotonin terminals in the CA1 region impaired it. (B) Local neurotoxic lesions induced by 5,7-dihydroxytryptamine (5,7-DHT) in the medial septum (MS), diagonal band of Broca (DBB), fimbria (fi), fornix (fr), and cingulate bundle (Cb) improved rats performance in water maze, while lesion in supramammillary nucleus (SuM) decreased performance.

Effects of global serotonin level changes on spatial memory tasks in rodents

↔ non-significant changes ↓ decreased performance ↑ improved performance

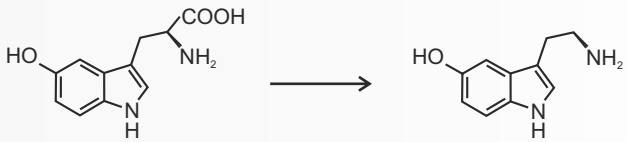
Morris water maze



↔ **ATD:** *Lieben et al., 2004; Liu et al., 2013; Stancampiano et al., 1997; Uchida et al., 2007.*
5,7-DHT: *Lehmann et al., 2000; Majlessi et al., 2003; Nilsson et al., 1988.*
PCPA: *Beiko et al., 1997; Dringenberg and Zalan, 1999; Harder et al., 1996; Jäkälä et al., 1993; Richter-Levin and Segal, 1989; Riekkinen et al., 1993, 1992.*

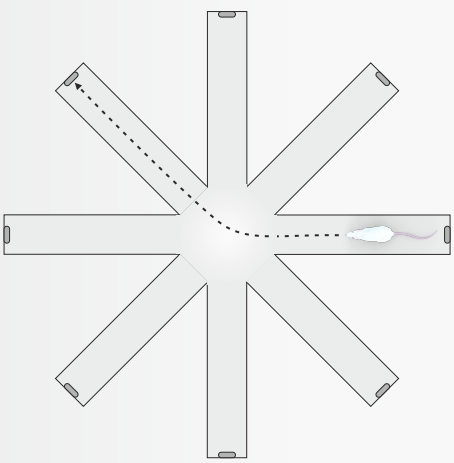
↓ **5-HTT knockout mice:** *Karabeg et al., 2013.*
5-HT1A knockout mice: *Sarnyai et al., 2000; only young rats: Wolff et al., 2004.*

↑ **5-HTP in old rats:** *Levkovitz et al., 1994*



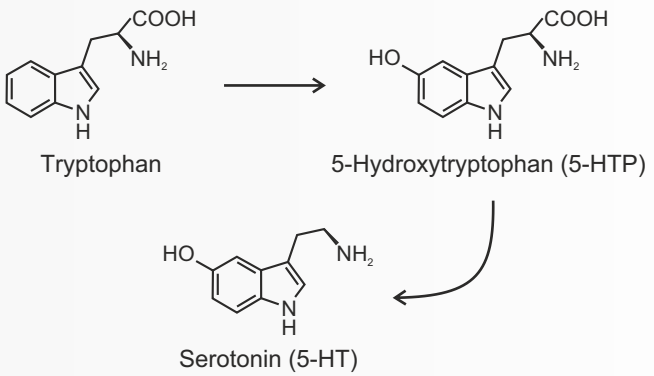
5-Hydroxytryptophan (5-HTP) — Serotonin (5-HT)

Radial arm maze

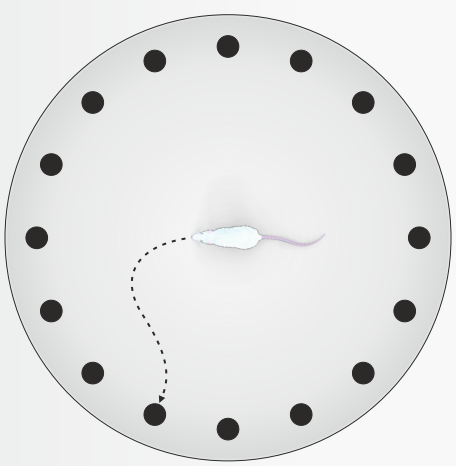


↔ **ATD:** *Stancampiano et al., 1997*
5,7-DHT: *Lehmann et al., 2000*

↑ **Tryptophan:** *Haider et al., 2006*



Tryptophan — 5-Hydroxytryptophan (5-HTP) — Serotonin (5-HT)



↔ **5-HTT knockout mice:** *Karabeg et al., 2013*

A

Optogenetic stimulation

Hippocampus CA1

Serotonergic terminals

→ Activation ↑

→ Inhibition ↓

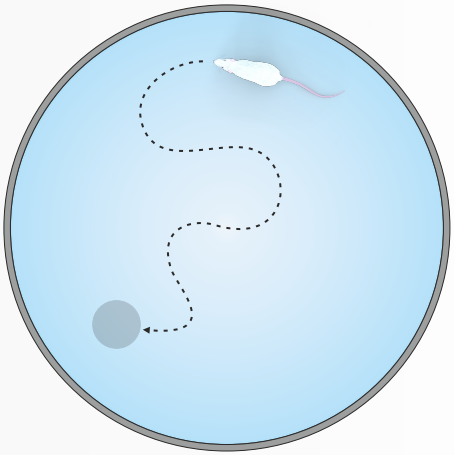
(Teixeira et al., 2018)

Activation of 5-HT1A ↑

(Gerdey and Masseck, 2023)

Serotonergic neuron
(Raphe nuclei)

Morris water maze



↑ improved performance

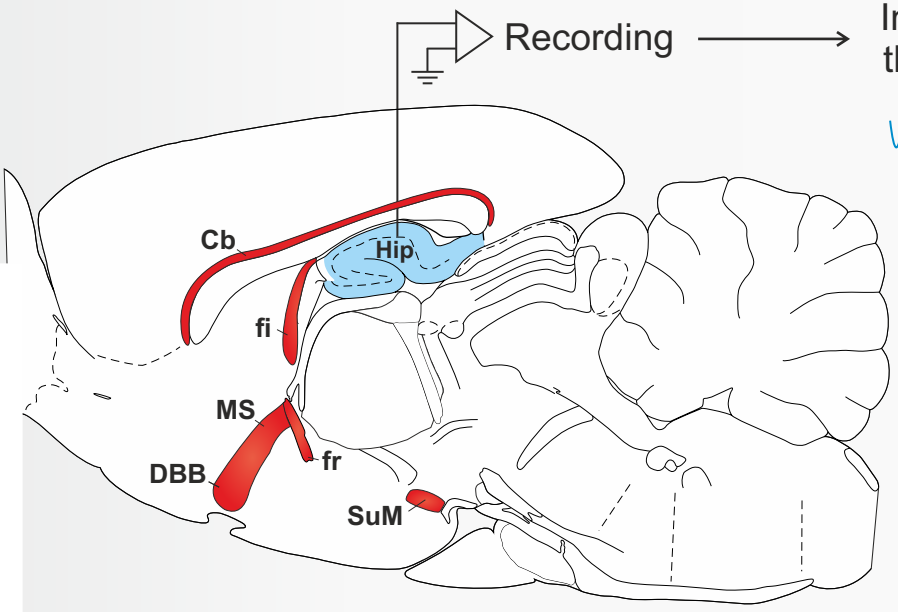
↓ decreased performance

B

Local 5,7-DHT serotonergic lesions

Recording →

Increased high-frequency theta activity (6.5-9.5 Hz)



MS, DBB, fi, fr, Cb, ↑

SuM ↓

(Gutiérrez-Guzmán et al., 2011, 2017; López-Vázquez et al., 2014)