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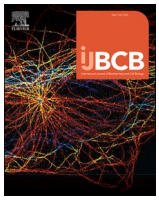

Revisiting serotonin's role in spatial memory: A call for sensitive analytical approaches

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ABSTRACT

The serotonergic system is involved in various psychiatric and neurological conditions, with serotonergic drugs often used in treatment. These conditions frequently affect spatial memory, which can serve as a model of declarative memory due to well-known cellular components and advanced methods that track neural activity and behavior with high temporal resolution. However, most findings on serotonin's effects on spatial learning and memory come from studies lacking refined analytical techniques and modern approaches needed to uncover the underlying neuronal mechanisms. This In Focus review critically investigates available studies to identify areas for further exploration. It finds that well-established behavioral models could yield more insights with modern tracking and data analysis approaches, while the cellular aspects of spatial memory remain underexplored. The review highlights the complex role of serotonin in spatial memory, which holds the potential for better understanding and treating memory-related disorders.

1. 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).

2. 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 within abstract spatiotemporal frameworks (Eichenbaum and Cohen, 2014; Galvez-Pol et al., 2021; Guelton, 2023; Neupane et al., 2024). 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

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specifically focus on spatial memory as a framework to examine the impact of serotonin on this distinct category of memory.

3. 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 (Elmer et al., 2024; Parrott, 2002), microdosing (Cavanna et al., 2022), and other recently emerging fields of prescribed or self-prescribed neuro-enhancement (Daubner et al., 2021; Jannini et al., 2022; Marazziti et al., 2021; Sakakibara, 2020), which aim to improve human mood, well-being, creativity, and the balance between wakefulness and sleep (Cavanna et al., 2022; Cespuglio, 2018; Daubner et al., 2021; Elmer et al., 2024; 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).

4. Spatial memory in mental health disorders linked to serotonin

Psychiatric conditions such as depression, bipolar disorder, anxiety, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), and even schizophrenia are associated with deficits in spatial memory (Cornwell et al., 2010; Galkin et al., 2020; Heinzel et al., 2021; Hørlyck et al., 2022; Lamy et al., 2008; Marlatte et al., 2022; Park, 1992; Smith et al., 2015; Vance and Winther, 2021; Vytal et al., 2013). Many of these conditions, which affect spatial cognition, are commonly treated with selective serotonin reuptake inhibitors (SSRIs) (Murphy et al., 2021; Vaswani et al., 2003).

Various aspects of spatial memory impairment have been observed in individuals with depression. Depressed patients often exhibit difficulties with spatial navigation (Cornwell et al., 2010), while those with mild depressive disorders tend to show decreased spatial working memory (Galkin et al., 2020). In children diagnosed with major depressive disorder, there is a more pronounced impairment in spatial working memory (Vance and Winther, 2021). Additionally, a selective impairment in high-load allocentric spatial memory, which is more affected than egocentric memory was found in patients with remitted unipolar depression and bipolar disorder (Hørlyck et al., 2022). This suggests a potential link to impaired hippocampal function. Interestingly, implicit memory impairments in depressed individuals appear to be specific to spatial context, as these patients generally show normal improvement with practice, normal color priming, and even stronger location priming effects compared to healthy controls (Lamy et al., 2008). Overall, these findings suggest that depression impacts different facets of spatial memory, particularly those related to hippocampal dysfunction.

In anxiety disorders, spatial working memory is frequently impaired (Vytal et al., 2013), and anxiety in general has been shown to affect the hippocampus and spatial memory (Bannerman et al., 2014). PTSD patients also exhibit significant spatial memory deficits. When tested on tasks that rely on hippocampus-dependent processing, individuals with PTSD were selectively impaired in allocentric spatial processing, which involves understanding the position of objects in relation to one another (Smith et al., 2015). Some studies suggest that PTSD patients struggle not only with navigating complex spatial environments but also with imagining neutral, spatially coherent scenes. Those with broader impairments in spatial processing tend to have reduced hippocampal volumes and abnormalities in white matter tracts involved in multisensory integration (Marlatte et al., 2022). Animal models of PTSD show similar trends, with impaired spatial memory and enhanced habit memory observed in rats (Goodman and McIntyre, 2017).

OCD is another condition treated with SSRIs, and studies have shown that individuals with OCD experience impairments in spatial working memory performance (Heinzel et al., 2021). Similarly, patients with schizophrenia display significant deficits in spatial working memory (Park, 1992). These findings across different psychiatric conditions further underscore the connection between spatial memory impairments and the hippocampal dysfunction commonly associated with the disorders treated with SSRIs. Moreover, a systematic review of modern-era clinical studies on the therapeutic effects of classic serotonergic psychedelics highlights their use in treating major depressive disorder, substance use disorders, OCD, and anxiety disorders (Andersen et al., 2021).

5. Spatial memory in neurological conditions treated or supplemented with SSRIs

In neurological disorders like chronic pain syndromes (Moriarty et al., 2017; Xia et al., 2020), sleep disorders (Piber, 2021; Simon et al., 2022), and Parkinson's disease (Harrington et al., 2022; Possin et al., 2008) spatial memory is also often impaired. In epilepsy, animal models of temporal lobe epilepsy (TLE) have demonstrated deficits in spatial learning and memory (Chauvière et al., 2009; Murphy, 2013). In humans, the impact on spatial memory varies depending on the severity of the condition. Some studies report no significant impairment (Maidenbaum et al., 2019), while others suggest mild deficits in specific aspects of spatial memory, particularly in patients with temporal lobe epilepsy (Rosas et al., 2013), reflecting the patterns seen in animal models. Patients with these conditions frequently receive SSRIs, either for the primary neurological disorder (Patetsos and Horjales-Araujo, 2016; Wiegand, 2008) or for comorbid conditions like mood disorders, which commonly accompany epilepsy and Parkinson's disease (Górska et al., 2018; Lemke et al., 2004; Tallarico et al., 2023). SSRIs have shown good effectiveness in treating depression in Parkinson's disease (PD) patients, improving daily activities and motor function, though adverse effects are unneglectable (Lemke et al., 2004). Intriguingly, research suggests that starting antidepressant therapy in non-Parkinsonian patients may increase the risk of developing Parkinson's disease (PD) within two years, indicating that in some cases depressive symptoms could be an early sign of the disease, appearing before motor symptoms (Alonso et al., 2009). Some SSRIs have been shown to improve spatial memory and learning both in healthy animals (Tao et al., 2016) and in animal models of Alzheimer's disease (Wei et al., 2017).

This brief review explores serotonin's roles in modulating spatial memory and its neuronal correlates. Despite the widespread use of serotonergic drugs for mental health conditions, a significant gap remains in understanding the mechanisms by which serotonin affects spatial memory. We propose that future studies use advanced analytical techniques to integrate behavioral and electrophysiological approaches for a comprehensive understanding of serotonin's impact on this type of declarative memory.

6. Global changes in brain serotonin and spatial memory – 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 standard, well-established 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 1 A 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, systemic administration of 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 (Table 1) (Beaudet et al., 2015; Coray and Quednow, 2022; Dale et al., 2016; De Filippis et al., 2015; Wingen et al., 2007).

Based on Table 1, it is evident that acute systemic manipulation of specific 5-HT receptors can affect animals' ability to solve spatial memory tasks, unlike long-term changes in global serotonin levels. This is particularly notable given that the results are often inconsistent and occasionally contradictory. For instance, systemic administration of the 5-HT1A and 5-HT7 receptor agonist, 8-Hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT), impaired performance in the Delayed Non-Matching to Position test in rats (Warburton, et al., 1997), yet improved performance in a radial maze task in mice (Miheau and Van Marrewijk, 1999). This highlights the complexity of the effects of systemic administration of this particular 5-HT agonist on spatial memory, which may be influenced by multiple factors, including the behavioral tests employed and the animal species used. However, the majority of these studies rely on coarse measures of behavior in standard 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 memory 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). Those include open-source tools such as DeepLabCut (Mathis et al., 2018), LEAP (Pereira et al., 2020, 2019), LabGym (Hu et al., 2023), a method for 3D reconstruction of the mouse body, enabling quantification of various motor actions (Storchi et al., 2020), and many other open-source resources (Isik and Unal, 2023).

7. Local changes in brain serotonin affect spatial memory

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. The systemic action on specific serotonergic receptors, though more effective, produces inconsistent and sometimes contradictory results. 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 spatial memory. 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 (Fig. 2A) (Gerdey and Masseck, 2023).

Several studies have investigated the role of the serotonergic system in spatial memory through local injections of 5-HT receptor agonists or antagonists, primarily into the dorsal hippocampus, but also into the medial septum - a structure known for its strong influence on hippocampal activity (e.g. Müller and Remy, 2018). In most of these studies, the agonist 8-OH-DPAT, targeting 5-HT1A and 5-HT7 receptors, was used. These two 5-HT receptor types are highly concentrated in brain regions involved in spatial learning and memory (Mengod et al., 2010), and are thought to play an important role in memory formation (Roberts and Hedlund, 2012; Teixeira et al., 2018). Both receptor types have been implicated in memory deficits and have been suggested as potential therapeutic targets (for review see Meneses, 2013). In general, infusion of 8-OH-DPAT into the hippocampus or medial septum impairs spatial memory in rats tested in various behavioral tests, such as the radial-arm maze or Morris water maze (Table 2) (Bertrand et al., 2000; Carli et al., 1992; Egashira et al., 2006; Jeltsch et al., 2004; Koenig et al., 2008; Warburton et al., 1997). Interestingly, in one study the administration of 8-OH-DPAT produced opposite effects depending on the targeted brain structure. Infusion into the median raphe nucleus improved performance in the Delayed Non-Matching to Position test, while administration into the dorsal hippocampus impaired performance in the same test (Warburton, et al., 1997). These findings suggest that the final outcome may depend on whether the stimulated serotonergic receptors are located presynaptically or postsynaptically.

The role of the serotonergic system in spatial memory becomes even more enigmatic when considering other types of serotonergic receptors in the hippocampal system. For example, Naghdi and Harooni (2005)

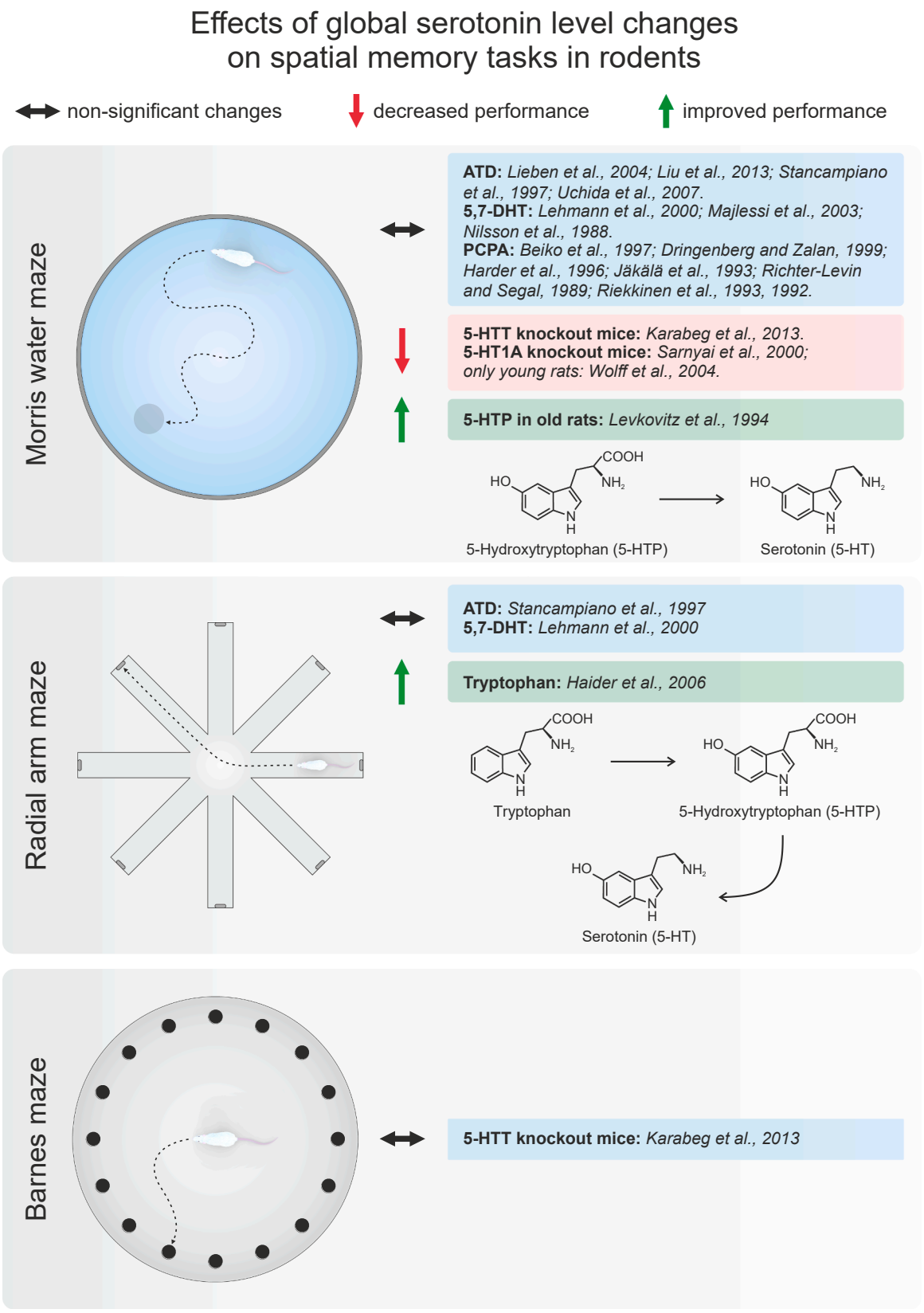

Fig. 1. This figure summarizes research on how changes in global serotonin levels affect spatial memory in rodents across various tasks, such as the Morris water maze, radial arm maze, and Barnes maze. It depicts three main outcomes observed in previous studies: non-significant changes, decreased performance, 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 1 A 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.

Table 1
Effects of systemic administration of various serotonergic receptor agonists and antagonists on chosen aspects of spatial memory in animal behavioral models.

Receptor type	Agonist / Antagonist	Species	Administration site	Behavioral test	Effect	References
5-HT1A/7	Agonist (8-OH-DPAT)	Rat	Systemic	Water maze	Impairment	(Carli et al., 1995; Carli and Samanin, 1992)
5-HT1A/7	Agonist (8-OH-DPAT) (+muscarinic receptor antagonist)	Rat	Systemic	Water maze	Impairment	(Riekkinen et al., 1995)
5-HT1A/7	Agonist (8-OH-DPAT)	Mouse	Systemic	Radial maze	Improvement	(Miheau and Van Marrewijk, 1999)
5-HT1A/7	Agonist (8-OH-DPAT)	Rat	Systemic	Delayed Non-Matching to Position	Impairment	(Warburton, et al., 1997)
5-HT1A	Antagonist (WAY−101405)	Rat	Systemic	Water maze	Improvement	(Hirst et al., 2008)
5-HT 1B	Antagonist (SB−216641)	Rat	Systemic	Water maze	Improvement	(Cai et al., 2013)
5-HT2A	Agonist (TCB−2)	Mouse	Systemic	Water maze	Impairment	(Zhang et al., 2017)
5-HT3	Antagonist (ondansetron)	Rat	Systemic	Radial maze	Improvement	(Staubli and Xu, 1995)
5-HT4	Agonist (BIMU8)	Rat	Systemic	Water maze	Improvement	(Teixeira et al., 2018)
5-HT4	Antagonist (GR125487)	Rat	Systemic	Water maze	Impairment	(Teixeira et al., 2018)
5-HT4	Agonist (RS67333)	Rat	Systemic	Water maze	Improvement	(Fontana et al., 1997)
5-HT6R	Antagonist (SB−271046-A, or SB−357134-A)	Rat	Systemic	Water maze	Improvement	(Rogers and Hagan, 2001)
5-HT6	Antagonist (SB−271046)	Rat (aged)	Systemic	Water maze	Improvement	(Foley et al., 2004)
5-HT 7	Antagonist (SB−269970)	Rat	Systemic	Radial maze	Improvement	(Gasbarri et al., 2008)

reported varying effects on rats' performance in the Morris water maze, depending on which receptor antagonist was infused into the dorsal hippocampus: a 5-HT2A/2 C receptor antagonist led to improvement, while a 5-HT3 receptor antagonist caused impairment. Although some possible explanations have been proposed, the authors conclude that the precise mechanism by which these two receptor types affect spatial memory remains unclear. Furthermore, in studies by Staubli and Xu (1995), systemic administration of a 5-HT3 antagonist improved memory performance in the radial maze, producing effects opposite to those observed in the water maze after local infusion into the hippocampus (Naghdi and Harooni, 2005). This suggests that, in the case of 5-HT3 receptor antagonists, their effects on spatial memory may also depend on the route of administration and the type of behavioral test used.

8. Serotonin, theta rhythm, and spatial memory

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 (6.5–9.5 Hz) (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).

Some studies indicate that the serotonergic system plays a role in the tonic modulation of theta rhythms in septo-hippocampal network (Gordon et al., 2005; Kazmierska and Konopacki, 2015; Kudina et al., 2004; Olvera-Cortés et al., 2013; Sörman et al., 2011; Vertes, 2010). Mice lacking the 5-HT1A receptor exhibit increased anxiety-related behavior, with the hippocampus implicated as a key modulatory structure. Local field potential recordings showed increased hippocampal theta oscillations in knock-outs, particularly in anxiety-provoking situations (Gordon et al., 2005). Studies on freely behaving rabbits showed that serotonergic manipulation via fluoxetine, a serotonin reuptake blocker, decreased the magnitude of hippocampal theta oscillations. This provided evidence of the inhibitory control of rhythmic theta activity by the serotonergic system (Kudina et al., 2004). Serotonergic manipulation via the 5-HT2C receptor agonist mCPP also suppressed hippocampal theta rhythm in rats, with a stronger effect observed during REM sleep than waking theta states. This suppression was dose-dependent and reversible by the 5-HT2C receptor antagonist SB-242084, highlighting the role of 5-HT2C receptors in the modulation of hippocampal theta oscillations (Sörman et al., 2011). On the other hand, serotonergic manipulation via the 5-HT1A receptor antagonist (S) WAY 100135 induced theta rhythm in hippocampal slices, providing evidence that these serotonergic receptors are involved in the modulation of hippocampal theta oscillations in rats *in vitro* (Kazmierska and Konopacki, 2015). Serotonin modulates hippocampal theta activity by desynchronizing it through its action on medial septal neurons, which affects both cholinergic and GABAergic inputs. Earlier studies indicate that serotonin depletion may alter theta rhythm generation and influences spatial learning and memory formation by decreasing hippocampal theta power under certain conditions, highlighting its role in regulating cognitive processes related to theta oscillations (Olvera-Cortés et al., 2013).

Hippocampal theta frequency and power were evaluated before and after subcutaneous administration of the 5-HT6 antagonist (SAM-531) and agonist (EMD386088) in both urethane-anesthetized and freely moving rats. EMD386088 suppressed sleep and reduced theta peak frequency in a dose-dependent manner during awake theta states, while in anesthetized rats, it selectively decreased theta frequency without altering theta power; this effect was effectively blocked by coadministration of SAM-531 (Ly et al., 2013). Gener et al. (2019) investigated how selective pharmacological activation and inhibition of 5-HT1A, 5-HT2A and dopaminergic D2 receptors influence prefrontal cortex

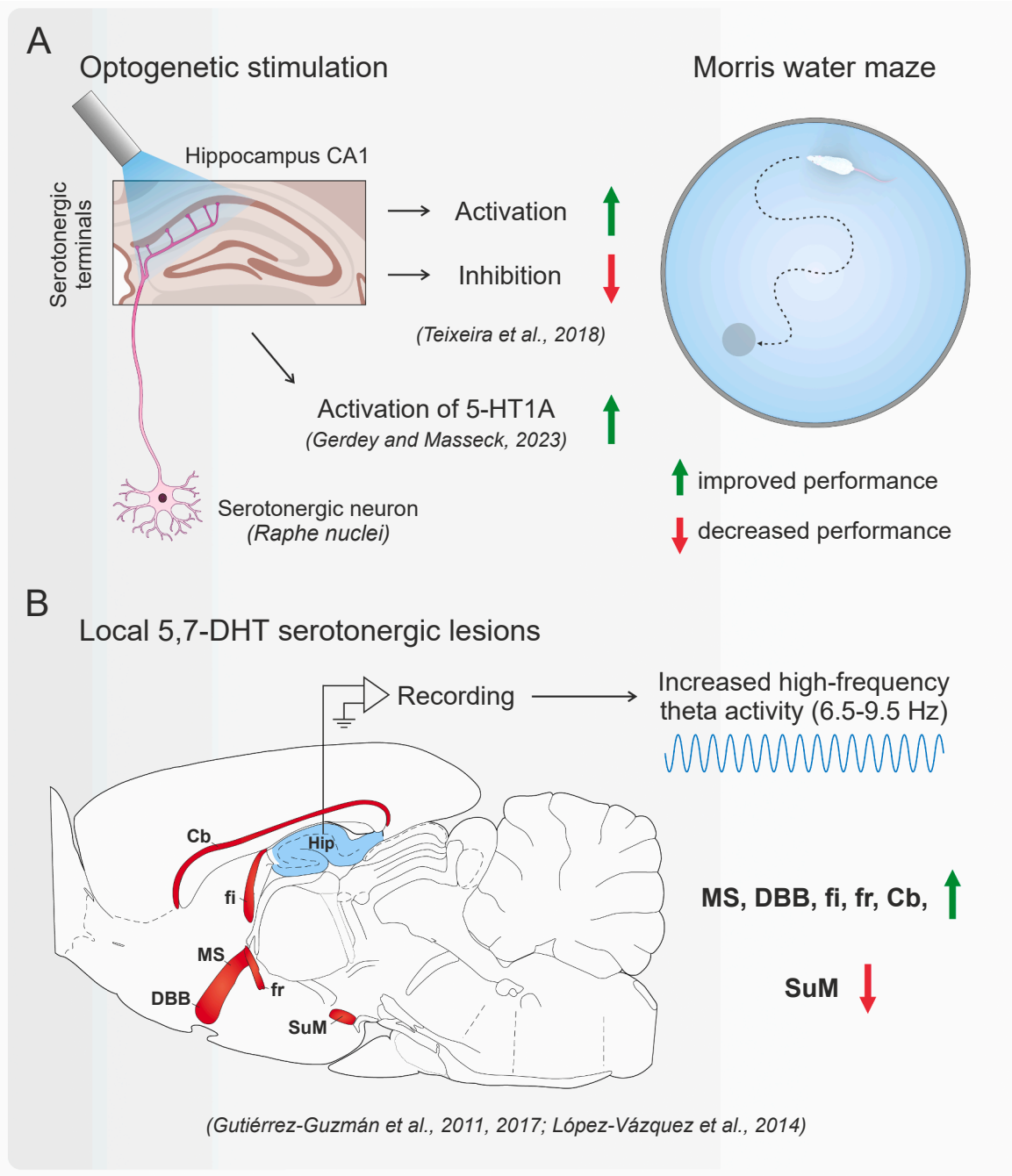

Fig. 2. Impact of targeted serotonergic system manipulations on spatial memory in the Morris water maze task: (A) Optogenetic activation of serotonergic terminals or 5-HT1A receptors in the hippocampal CA1 region of the hippocampus enhanced performance of mice in water maze, while inhibition of serotonin 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.

and hippocampal neural activity and phase synchronization between those structures in freely moving mice. They found that acute administration of risperidone, 5-HT1AR agonist 8-OH-DPAT, 5-HT2AR antagonist M100907, and D2R antagonist haloperidol reduced locomotor activity, neural spiking, theta and gamma oscillations, and theta phase synchronization between hippocampus and prefrontal cortex. The effects of the selective 5-HT_3 receptor antagonist, ondansetron alone and combined with donepezil (cholinesterase inhibitor) on hippocampal oscillations were studied using in vivo electrophysiology in urethane-anesthetized rats. During brainstem pedunculopontine tegmental nucleus stimulation, donepezil dose-dependently increased hippocampal theta and gamma power, while ondansetron further potentiated these responses (Skovgård et al., 2018). A similar result was obtained in anesthetized rats during electrical stimulation of the nucleus pontis oralis when selective 5-HT6 receptor antagonist idalopirdine was administrated in combination with donepezil (Herrik et al., 2016). A study performed on a visceral hypersensitivity rat model induced by chronic water avoidance stress revealed that rats showed increased 5-HT levels, reduced 5-HT1A receptor expression, and enhanced theta oscillations in the anterior cingulate cortex (ACC). Activation of 5-HT1A receptors via the agonist 8-OH-DPAT reduced theta enhancement in ACC of stressed rats, while the antagonist WAY100135 increased theta oscillations in normal rats. Tandospirone suppressed theta band enhancement in ACC both in vitro and in vivo, alleviating anxiety-like

Table 2
Effects of local administration of various serotonergic receptor agonists and antagonists on chosen aspects of spatial memory in animal behavioral models.

Receptor type	Agonist / Antagonist	**Species**	Administration site	Behavioral test	**Effect**	**References**
5-HT1A/7	Agonist (8-OH-DPAT)	Rat	Dorsal hippocampus	Water maze	Impairment	(Carli et al., 1992)
5-HT1A/7	Agonist (8-OH-DPAT)	Rat	Medial septum	Water maze	Impairment	(Bertrand et al., 2000)
5-HT1A/7	Agonist (8-OH-DPAT)	Rat	Dorsal hippocampus	Radial maze	Impairment	(Egashira et al., 2006)
5-HT1A/7	Agonist (8-OH-DPAT)	Rat	Dorsal hippocampus	Delayed Non-Matching to Position	Impairment	(Warburton, et al., 1997)
5-HT1A/7	Agonist (8-OH-DPAT)	Rat	Median raphe	Delayed Non-Matching to Position	Improvement	(Warburton, et al., 1997)
5-HT1A/7	Agonist (8-OH-DPAT)	Rat	Medial septum	Water maze	Impairment	(Koenig et al., 2008)
5-HT1A/7	Agonist (8-OH-DPAT)	Rat	Medial septum.	water maze	Impairment	(Jeltsch et al., 2004)
5-HT 1B	Agonist (CP−93,129)	Rat	CA1, Dorsal hippocampus	Radial maze	Impairment	(Buhot et al., 1995)
5-HT2A/2 C	Antagonist (ritanserin)	Rat	CA1, Dorsal hippocampus	Water maze	Improvement	(Naghdi and Harooni, 2005)
5-HT3	Antagonist (granisetron)	Rat	CA1 field of the dorsal hippocampus	Water maze	Impairment	(Naghdi and Harooni, 2005)

behavior in stressed rats by modulating 5-HT1A receptors (Zhan et al., 2022). Increased serotonin transporter (5-HTT) expression in male 5-HTTOE mice caused decrease in cue-evoked theta neuronal oscillations in basolateral amygdala during Pavlovian fear conditioning (Barkus et al., 2014). Continuous high-density global EEG recordings revealed significant changes in cortical neural dynamics following intravenous N,N dimethyltryptamine (DMT), a serotonergic psychedelic infusion, including a marked decrease in theta band spectral power (Glynos et al., 2024). These findings collectively indicate that serotonergic manipulations, whether via receptor modulation or alterations in transporter expression, consistently affect theta oscillations observed in global EEG recordings and within limbic structures.

9. Serotonin and spatially tuned neurons

Theta activity plays a critical role in spatial memory, 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 would 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 memory 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, increased the latency for trained mice to initiate goal-directed swimming in the Morris water maze. This effect could be prevented by the 5-HT2A receptor 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-HT2A receptor antagonist MDL 11,939 (Zhang et al., 2017). Recently, Ivan et al. (2024) investigated the effects of the classic psychedelic psilocybin on neural activity patterns and spatial encoding in the retrosplenial cortex of head-fixed mice navigating on a treadmill. Psilocybin reduced the place specificity of neurons to distinct locations along the belt and decreased the stability of place-related activity across trials and reduced functional connectivity among simultaneously recorded neurons. The 5-HT2A receptor antagonist ketanserin blocked most of these effects. These data support proposals that psychedelics increase the entropy of neural signaling and suggest a potential neural mechanism for the disorientation frequently reported by humans after taking psychedelics (Ivan et al., 2024). 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 merits further study.

10. 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 comprehensive understanding. Current behavioral experiments often report inconsistent or contradictory results, possibly due to reliance on sparse measures. This approach might lack the sensitivity or specificity required to detect subtle or complex interactions. Meanwhile, the interplay between the neuronal substrates of spatial memory and serotonin remains underexplored. Both areas present promising avenues for research that could be pursued with the extensive array of tools available at hand.

CRediT authorship contribution statement

Witold Żakowski: Writing – review & editing, Writing – original draft. **Ravindra Sahu:** Writing – review & editing, Writing – original draft. **Dorota Myślińska:** Writing – review & editing. **Maciej M. Jankowski:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Conceptualization. **Paulina Kaźmierska-Grębowska:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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