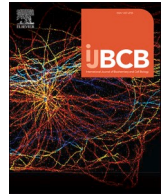


Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

International Journal of Biochemistry and Cell Biology

journal homepage: www.elsevier.com/locate/biociel

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

Paulina Kazmierska-Grebowska^{a,*}, Witold Żakowski^b, Dorota Myślińska^b, Ravindra Sahu^c, Maciej M. Jankowski^{c,**}

^a Department of Neurobiology, Faculty of Biology and Environmental Protection, University of Lodz, Lodz, Poland

^b Department of Animal and Human Physiology, Faculty of Biology, University of Gdansk, Gdansk, Poland

^c BioTechMed Center, Multimedia Systems Department, Faculty of Electronics, Telecommunications and Informatics, Gdansk University of Technology, Gdansk, Poland

ARTICLE INFO

Keywords:

Serotonin
5-HT
Spatial memory
Behavior
Theta rhythm
Spatially tuned cells

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

* Correspondence to: Department of Neurobiology, Faculty of Biology and Environmental Protection, University of Lodz, Lodz 90-236, Poland

** Correspondence to: BioTechMed Center, Multimedia Systems Department, Faculty of Electronics, Telecommunications and Informatics, Gdansk University of Technology, Gdansk 80-233, Poland

E-mail addresses: paulina.kazmierska@biol.uni.lodz.pl (P. Kazmierska-Grebowska), maciej.jankowski@pg.edu.pl (M.M. Jankowski).

<https://doi.org/10.1016/j.biociel.2024.106663>

Received 14 March 2024; Received in revised form 17 September 2024; Accepted 17 September 2024

Available online 24 September 2024

1357-2725/© 2025 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

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; Cesuglio, 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; Heinzl 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 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, 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 Maseck (2023) failed to reproduce these results possibly due to different genetically modified mouse models used in both studies. In Gerdey and Maseck (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 Maseck, 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)

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

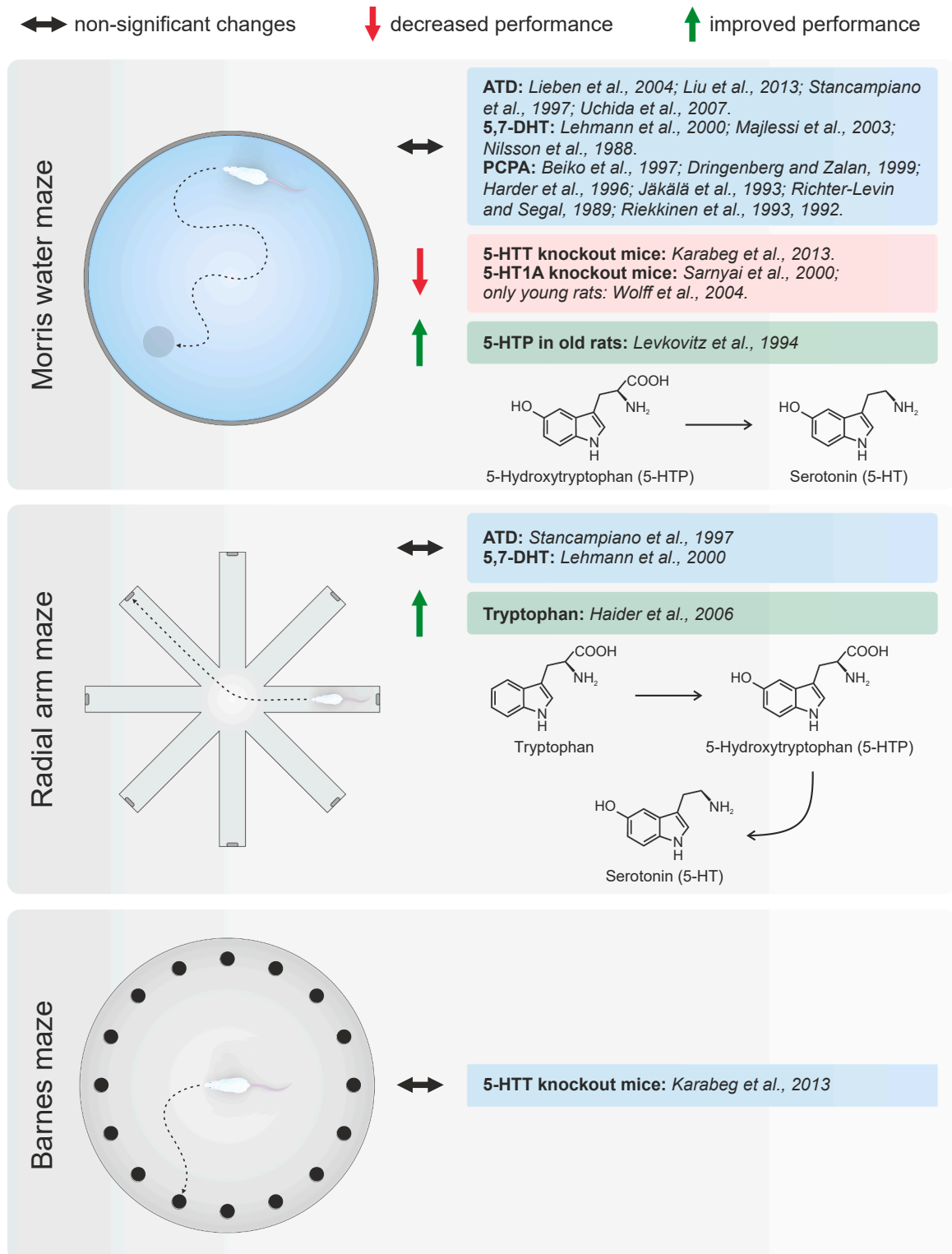


Fig. 1. This figure summarizes research on how changes in global serotonin levels affect spatial memory in rodents across various tasks, such as the Morris water maze, radial arm maze, and Barnes maze. It depicts three main outcomes observed in previous studies: non-significant changes, decreased performance, 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/2C 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

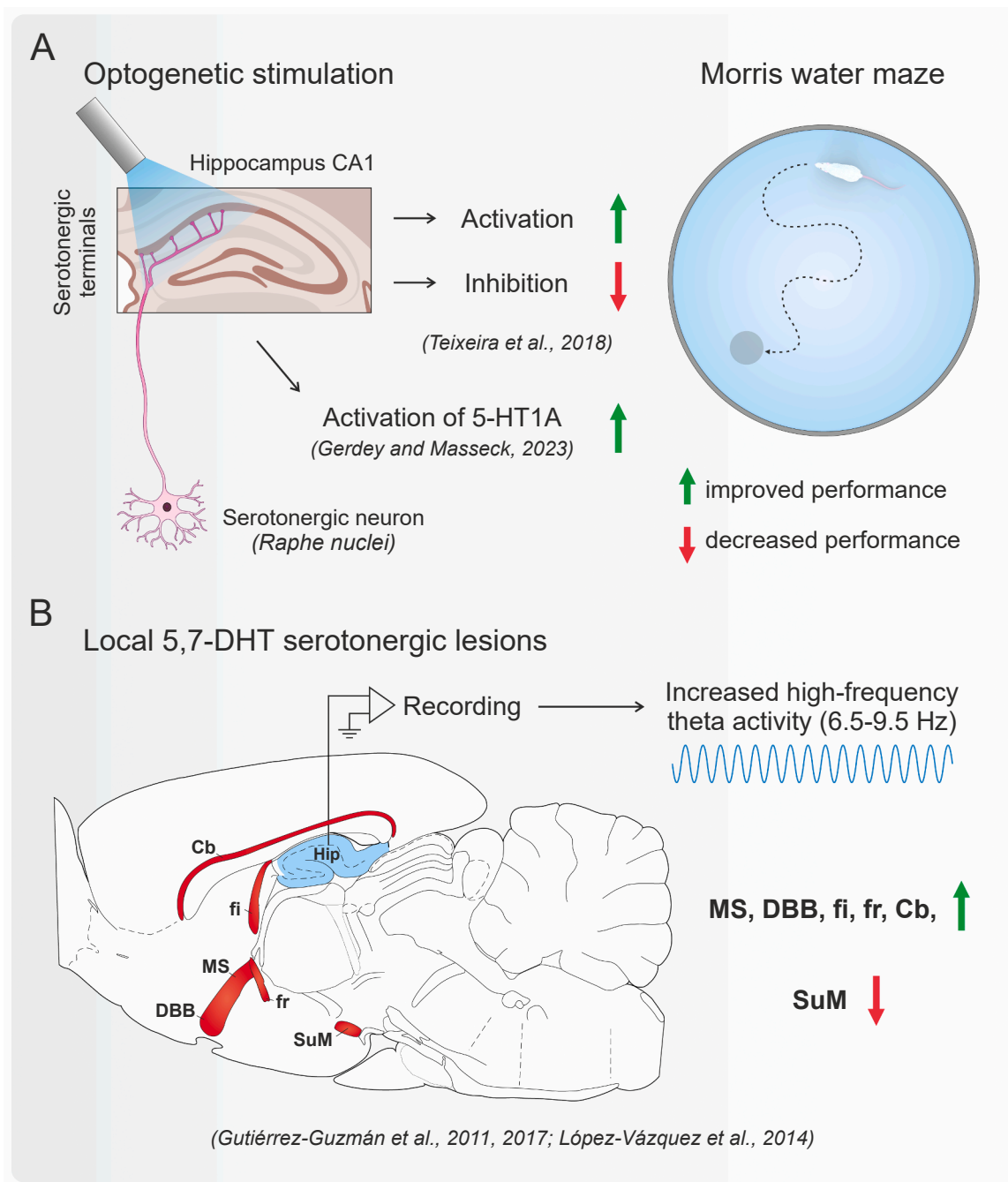


Fig. 2. Impact of targeted serotonergic system manipulations on spatial memory in the Morris water maze task: (A) Optogenetic activation of serotonergic terminals or 5-HT1A receptors in the hippocampal CA1 region of the hippocampus enhanced performance of mice in water maze, while inhibition of serotonin 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-HT₃ 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 pedunclopontine 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 administered 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. Tansospirone 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 (Herrerias, 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 serotonergic 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. Janowski:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Conceptualization. **Paulina Kazmierska-Grebowska:** 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.

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.

References

- Alonso, A., Rodriguez, L.A.G., Logroscino, G., Herman, M.A., 2009. Use of antidepressants and the risk of Parkinson's disease: a prospective study. *J. Neurol., Neurosurg. Psychiatr* 80, 671–674. <https://doi.org/10.1136/jnnp.2008.152983>.
- Amir, N., Suliman-Lavie, R., Tal, M., Shifman, S., Tishby, N., Nelken, I., 2020. Value-complexity tradeoff explains mouse navigational learning. *PLoS Comput. Biol.* 16, e1008497. <https://doi.org/10.1371/journal.pcbi.1008497>.
- Andersen, K.A.A., Carhart-Harris, R., Nutt, D.J., Erritzoe, D., 2021. Therapeutic effects of classic serotonergic psychedelics: A systematic review of modern-era clinical studies. *Acta Psychiatr. Scand.* 143, 101–118. <https://doi.org/10.1111/acps.13249>.
- Aronov, D., Nevers, R., Tank, D.W., 2017. Mapping of a non-spatial dimension by the hippocampal-entorhinal circuit. *Nature* 543, 719–722. <https://doi.org/10.1038/nature21692>.
- Bannerman, D.M., Sprengel, R., Sanderson, D.J., McHugh, S.B., Rawlins, J.N.P., Monyer, H., Seeburg, P.H., 2014. Hippocampal synaptic plasticity, spatial memory and anxiety. *Nat. Rev. Neurosci.* 15, 181–192. <https://doi.org/10.1038/nrn3677>.
- Barkus, C., Line, S.J., Huber, A., Capito, L., Lima, J., Jennings, K., Lowry, J., Sharp, T., Bannerman, D.M., McHugh, S.B., 2014. Variation in Serotonin Transporter Expression Modulates Fear-Evoked Hemodynamic Responses and Theta-Frequency Neuronal Oscillations in the Amygdala. *Biol. Psychiatry* 75, 901–908. <https://doi.org/10.1016/j.biopsych.2013.09.003>.
- Beaudet, G., Bouet, V., Jozet-Alves, C., Schumann-Bard, P., Dauphin, F., Paizanis, E., Boulouard, M., Freret, T., 2015. Spatial memory deficit across aging: current insights of the role of 5-HT7 receptors. *Front. Behav. Neurosci.* 8. <https://doi.org/10.3389/fnbeh.2014.00448>.
- Beiko, J., Candusso, L., Cain, D.P., 1997. The effect of nonspatial water maze pretraining in rats subjected to serotonin depletion and muscarinic receptor antagonism: a detailed behavioural assessment of spatial performance. *Behav. Brain Res.* 88, 201–211. [https://doi.org/10.1016/S0166-4328\(97\)02298-5](https://doi.org/10.1016/S0166-4328(97)02298-5).
- Bellmund, J.L.S., Gärdenfors, P., Moser, E.I., Doeller, C.F., 2018. Navigating cognition: Spatial codes for human thinking. *Science* 362, eaat6766. <https://doi.org/10.1126/science.aat6766>.
- Bertrand, F., Lehmann, O., Lazarus, C., Jeltsch, H., Cassel, J.-C., 2000. Intraseptal infusions of 8-OH-DPAT in the rat impairs water-maze performances: effects on memory or anxiety? *Neurosci. Lett.* 279, 45–48. [https://doi.org/10.1016/S0304-3940\(99\)00948-9](https://doi.org/10.1016/S0304-3940(99)00948-9).
- Bicanski, A., Burgess, N., 2018. A neural-level model of spatial memory and imagery. *eLife* 7, e33752. <https://doi.org/10.7554/eLife.33752>.
- Buhot, M.-C., Patra, S.K., Naïli, S., 1995. Spatial memory deficits following stimulation of hippocampal 5-HT1B receptors in the rat. *Eur. J. Pharmacol.* 285, 221–228. [https://doi.org/10.1016/0014-2999\(95\)00407-C](https://doi.org/10.1016/0014-2999(95)00407-C).
- Buzsáki, G., 2002. Theta Oscillations in the Hippocampus. *Neuron* 33, 325–340. [https://doi.org/10.1016/S0896-6273\(02\)00586-X](https://doi.org/10.1016/S0896-6273(02)00586-X).
- Buzsáki, G., Moser, E.I., 2013. Memory, navigation and theta rhythm in the hippocampal-entorhinal system. *Nat. Neurosci.* 16, 130–138. <https://doi.org/10.1038/nn.3304>.
- Buzsáki, G., McKenzie, S., Davachi, L., 2022. Neurophysiology of Remembering. *Annu. Rev. Psychol.* 73, 187–215. <https://doi.org/10.1146/annurev-psych-021721-110002>.
- Cai, X., Kallarackal, A.J., Kvarita, M.D., Goluskin, S., Gaylor, K., Bailey, A.M., Lee, H.-K., Hagan, R.L., Thompson, S.M., 2013. Local potentiation of excitatory synapses by serotonin and its alteration in rodent models of depression. *Nat. Neurosci.* 16, 464–472. <https://doi.org/10.1038/nn.3355>.
- Carhart-Harris, R., Nutt, D., 2017. Serotonin and brain function: a tale of two receptors. *J. Psychopharmacol.* 31, 1091–1120. <https://doi.org/10.1177/0269881117725915>.
- Carli, M., Samanin, R., 1992. 8-Hydroxy-2-(di-n-propylamino)tetrinalin impairs spatial learning in a water maze: role of postsynaptic 5-HT_{1A} receptors. *Br. J. Pharmacol.* 105, 720–726. <https://doi.org/10.1111/j.1476-5381.1992.tb09045.x>.
- Carli, M., Lazarova, M., Tatarczynska, E., Samanin, R., 1992. Stimulation of 5-HT_{1A} receptors in the dorsal hippocampus impairs acquisition and performance of a spatial task in a water maze. *Brain Res.* 595, 50–56. [https://doi.org/10.1016/0006-8993\(92\)91451-J](https://doi.org/10.1016/0006-8993(92)91451-J).
- Carli, M., Luschki, R., Garofalo, P., Samanin, R., Samanin, R., 1995. 8-OH-DPAT impairs spatial but not visual learning in a water maze by stimulating 5-HT_{1A} receptors in

- the hippocampus. *Behav. Brain Res.* 67, 67–74. [https://doi.org/10.1016/0166-4328\(94\)00105-0](https://doi.org/10.1016/0166-4328(94)00105-0).
- Cavanna, F., Muller, S., de la Fuente, L.A., Zamberlan, F., Palmucci, M., Janeckova, L., Kuchar, M., Pallavicini, C., Tagliacozzi, E., 2022. Microdosing with psilocybin mushrooms: a double-blind placebo-controlled study. *Transl. Psychiatry* 12, 307. <https://doi.org/10.1038/s41398-022-02039-0>.
- Cesapuglio, R., 2018. Serotonin: its place today in sleep preparation, triggering or maintenance. *Sleep. Med.* 49, 31–39. <https://doi.org/10.1016/j.sleep.2018.05.034>.
- Chauvière, L., Raftani, N., Thinus-Blanc, C., Bartolomei, F., Esclapez, M., Bernard, C., 2009. Early Deficits in Spatial Memory and Theta Rhythm in Experimental Temporal Lobe Epilepsy. *J. Neurosci.* 29, 5402–5410. <https://doi.org/10.1523/JNEUROSCI.4699-08.2009>.
- Constantinescu, A.O., O'Reilly, J.X., Behrens, T.E.J., 2016. Organizing conceptual knowledge in humans with a gridlike code. *Science* 352, 1464–1468. <https://doi.org/10.1126/science.aaf0941>.
- Coray, R., Quednow, B.B., 2022. The role of serotonin in declarative memory: A systematic review of animal and human research. *Neurosci. Biobehav. Rev.* 139, 104729. <https://doi.org/10.1016/j.neubiorev.2022.104729>.
- Cornwell, B.R., Salvatore, G., Colon-Rosario, V., Latov, D.R., Holroyd, T., Carver, F.W., Coppola, R., Manji, H.K., Zarate, C.A., Grillon, C., 2010. Abnormal Hippocampal Functioning and Impaired Spatial Navigation in Depressed Individuals: Evidence From Whole-Head Magnetoencephalography. *AJP* 167, 836–844. <https://doi.org/10.1176/appi.ajp.2009.09050614>.
- Correia, K., Walker, R., Pittenger, C., Fields, C., 2024. A comparison of machine learning methods for quantifying self-grooming behavior in mice. *Front. Behav. Neurosci.* 18, 1340357. <https://doi.org/10.3389/fnbeh.2024.1340357>.
- Correia, P.A., Lottem, E., Banerjee, D., Machado, A.S., Carey, M.R., Mainen, Z.F., 2017. Transient inhibition and long-term facilitation of locomotion by phasic optogenetic activation of serotonin neurons. *eLife* 6, e20975. <https://doi.org/10.7554/eLife.20975>.
- Dale, E., Pehrson, A.L., Jeyarajah, T., Li, Y., Leiser, S.C., Smagin, G., Olsen, C.K., Sanchez, C., 2016. Effects of serotonin in the hippocampus: how SSRIs and multimodal antidepressants might regulate pyramidal cell function. *CNS Spectr.* 21, 143–161. <https://doi.org/10.1017/S1092852915000425>.
- Daubner, J., Arshad, M.I., Henseler, C., Hescheler, J., Ehninger, D., Broich, K., Rawashdeh, O., Papazoglou, A., Weiergräber, M., 2021. Pharmacological Neuroenhancement: Current Aspects of Categorization, Epidemiology, Pharmacology, Drug Development, Ethics, and Future Perspectives. *Neural Plast.* 2021, 1–27. <https://doi.org/10.1155/2021/8823383>.
- De Filippis, B., Chiodi, V., Adriani, W., Lacivita, E., Mallozzi, C., Leopoldo, M., Domenici, M.R., Fusco, A., Laviola, G., 2015. Long-lasting beneficial effects of central serotonin receptor 7 stimulation in female mice modeling Rett syndrome. *Front. Behav. Neurosci.* 9. <https://doi.org/10.3389/fnbeh.2015.00086>.
- Deakin, J., 2013. The origins of '5-HT and mechanisms of defence' by Deakin and Graeff: A personal perspective. *J. Psychopharmacol.* 27, 1084–1089. <https://doi.org/10.1177/0269881113503508>.
- Dringenberg, H.C., Zalan, R.M., 1999. Serotonin-dependent maintenance of spatial performance and electroencephalography activation after cholinergic blockade: effects of serotonergic receptor antagonists. *Brain Res.* 837, 242–253. [https://doi.org/10.1016/S0006-8993\(99\)01669-8](https://doi.org/10.1016/S0006-8993(99)01669-8).
- Dringenberg, H.C., Hargreaves, E.L., Baker, G.B., Cooley, R.K., Vanderwolf, C.H., 1995. p-Chlorophenylalanine-induced serotonin depletion: reduction in exploratory locomotion but no obvious sensory-motor deficits. *Behav. Brain Res.* 68, 229–237. [https://doi.org/10.1016/0166-4328\(94\)00174-E](https://doi.org/10.1016/0166-4328(94)00174-E).
- Egashira, N., Yano, A., Ishigami, N., Mishima, K., Iwasaki, K., Fujioka, M., Matsushita, M., Nishimura, R., Fujiwara, M., 2006. Investigation of mechanisms mediating 8-OH-DPAT-induced impairment of spatial memory: Involvement of 5-HT_{1A} receptors in the dorsal hippocampus in rats. *Brain Res.* 1069, 54–62. <https://doi.org/10.1016/j.brainres.2005.10.103>.
- Eichenbaum, H., 2017. On the Integration of Space, Time, and Memory. *Neuron* 95, 1007–1018. <https://doi.org/10.1016/j.neuron.2017.06.036>.
- Eichenbaum, H., Cohen, N.J., 2014. Can we reconcile the declarative memory and spatial navigation views on hippocampal function? *Neuron* 83, 764–770. <https://doi.org/10.1016/j.neuron.2014.07.032>.
- Elmer, T., Vannoy, T.K., Studerus, E., Lyubomirsky, S., 2024. Subjective long-term emotional and social effects of recreational MDMA use: the role of setting and intentions. *Sci. Rep.* 14, 3434. <https://doi.org/10.1038/s41598-024-51355-6>.
- Foley, A.G., Murphy, K.J., Hirst, W.D., Gallagher, H.C., Hagan, J.J., Upton, N., Walsh, F. S., Regan, C.M., 2004. The 5-HT₆ Receptor Antagonist SB-271046 Reverses Scopolamine-Disrupted Consolidation of a Passive Avoidance Task and Ameliorates Spatial Task Deficits in Aged Rats. *Neuropsychopharmacol* 29, 93–100. <https://doi.org/10.1038/sj.npp.1300332>.
- Fontana, D.J., Daniels, S.E., Wong, E.H.F., Clark, R.D., Eglén, R.M., 1997. The Effects of Novel, Selective 5-Hydroxytryptamine (5-HT)₄ Receptor Ligands in Rat Spatial Navigation. *Neuropharmacology* 36, 689–696. [https://doi.org/10.1016/S0028-3908\(97\)00055-5](https://doi.org/10.1016/S0028-3908(97)00055-5).
- Fraguero, A., Tosoni, A., Frisoni, M., Di Matteo, R., Sestieri, C., Committeri, G., 2021. Travel in the Physical and Mental Space: A Behavioral Assessment of the Phylogenetic Continuity Hypothesis Between Egocentric Navigation and Episodic Memory, 147470492110408. *Evol. Psychol.* 19. <https://doi.org/10.1177/14747049211040823>.
- Galkin, S.A., Peshkovskaya, A.G., Simutkin, G.G., Vasil'eva, S.N., Roshchina, O.V., Ivanova, S.A., Bokhan, N.A., 2020. Impairments to the Functions of Spatial Working Memory in Mild Depression and their Neurophysiological Correlates. *Neurosci. Behav. Physiol.* 50, 825–829. <https://doi.org/10.1007/s11055-020-00973-4>.

- Galvez-Pol, A., Nadal, M., Kilner, J.M., 2021. Emotional representations of space vary as a function of peoples' affect and interoceptive sensibility. *Sci. Rep.* 11, 16150. <https://doi.org/10.1038/s41598-021-95081-9>.
- Gandra, K., Jaskiw, G., Fuller, M., Vaidya, P., Chiang, A., Konicki, E., Strohl, K.P., 2022. Sertraline as an adjunctive treatment for insomnia comorbid with other mental health disorders. *J. Affect. Disord. Rep.* 10, 100389. <https://doi.org/10.1016/j.jadr.2022.100389>.
- Gasbarri, A., Cifariello, A., Pompili, A., Meneses, A., 2008. Effect of 5-HT7 antagonist SB-269970 in the modulation of working and reference memory in the rat. *Behav. Brain Res.* 195, 164–170. <https://doi.org/10.1016/j.bbr.2007.12.020>.
- Gener, T., Tauste Campo, A., Alemany-González, M., Nebot, P., Delgado-Sallent, C., Chanovas, J., Puig, M.V., 2019. Serotonin 5-HT1A, 5-HT2A and dopamine D2 receptors strongly influence prefronto-hippocampal neural networks in alert mice: Contribution to the actions of risperidone. *Neuropharmacology* 158, 107743. <https://doi.org/10.1016/j.neuropharm.2019.107743>.
- Gerdey, J., Maseck, O.A., 2023. Linking serotonergic median raphe input to dorsal CA1 with mnemonic functions (preprint). *Neuroscience*. <https://doi.org/10.1101/2023.09.04.556213>.
- Giovannini, S., Onder, G., Van Der Roest, H.G., Topinkova, E., Gindin, J., Cipriani, M.C., Denking, M.D., Bernabei, R., Liperoti, R., on behalf of the SHELTER Study Investigators, 2020. Use of antidepressant medications among older adults in European long-term care facilities: a cross-sectional analysis from the SHELTER study. *BMC Geriatr.* 20, 310. <https://doi.org/10.1186/s12877-020-01730-5>.
- Glikman-Johnston, Y., Saling, M.M., Reutens, D.C., Stout, J.C., 2015. Hippocampal 5-HT1A receptor and spatial learning and memory. *Front. Pharmacol.* 6. <https://doi.org/10.3389/fphar.2015.00289>.
- Glyns, N.G., Huels, E.R., Nelson, A., Kim, Y., Kennedy, R.T., Mashour, G.A., Pal, D., 2024. Neurochemical and Neurophysiological Effects of Intravenous Administration of *N,N*-dimethyltryptamine in Rats. <https://doi.org/10.1101/2024.04.19.589047>.
- Goodman, J., McIntyre, C.K., 2017. Impaired Spatial Memory and Enhanced Habit Memory in a Rat Model of Post-traumatic Stress Disorder. *Front. Pharmacol.* 8, 663. <https://doi.org/10.3389/fphar.2017.00663>.
- Gordon, J.A., Lacefield, C.O., Kentros, C.G., Hen, R., 2005. State-Dependent Alterations in Hippocampal Oscillations in Serotonin 1A Receptor-Deficient Mice. *J. Neurosci.* 25, 6509–6519. <https://doi.org/10.1523/JNEUROSCI.1211-05.2005>.
- Górska, N., Stupski, J., Cudala, W.J., Wigłusz, M.S., Gałuszko-Wegielnik, M., 2018. Antidepressants in epilepsy. *Neurol. i Neurochir. Pol.* 52, 657–661. <https://doi.org/10.1016/j.pjnns.2018.07.005>.
- Grieves, R.M., Jeffery, K.J., 2017. The representation of space in the brain. *Behav. Process.* 135, 113–131. <https://doi.org/10.1016/j.beproc.2016.12.012>.
- Grilli, M.D., Verfaellie, M., 2015. Supporting the self-concept with memory: insight from amnesia. *Soc. Cogn. Affect. Neurosci.* 10, 1684–1692. <https://doi.org/10.1093/scan/nsv056>.
- Guelton, B., 2023. Mental maps: Between memorial transcription and symbolic projection. *Front. Psychol.* 14, 1142238. <https://doi.org/10.3389/fpsyg.2023.1142238>.
- Gutiérrez-Guzmán, B.E., Hernández-Pérez, J.J., González-Burgos, I., Ferial-Velásco, A., Medina, R., Guevara, M.Á., López-Vázquez, M.Á., Olvera-Cortés, M.E., 2011. Hippocampal serotonin depletion facilitates place learning concurrent with an increase in CA1 high frequency theta activity expression in the rat. *Eur. J. Pharmacol.* 652, 73–81. <https://doi.org/10.1016/j.ejphar.2010.11.014>.
- Gutiérrez-Guzmán, B.E., Hernández-Pérez, J.J., Olvera-Cortés, M.E., 2017. Serotonergic modulation of septo-hippocampal and septo-mammillary theta activity during spatial learning, in the rat. *Behav. Brain Res.* 319, 73–86. <https://doi.org/10.1016/j.bbr.2016.11.017>.
- Haider, S., Khalilq, S., Ahmed, S.P., Haleem, D.J., 2006. Long-term tryptophan administration enhances cognitive performance and increases 5HT metabolism in the hippocampus of female rats. *Amino Acids* 31, 421–425. <https://doi.org/10.1007/s00726-005-0310-x>.
- Harder, J.A., Kelly, M.E., Cheng, C.H.K., Costall, B., 1996. Combined pCPA and muscarinic antagonist treatment produces a deficit in rat water maze acquisition. *Pharmacol. Biochem. Behav.* 55, 61–65. [https://doi.org/10.1016/0091-3057\(96\)00049-4](https://doi.org/10.1016/0091-3057(96)00049-4).
- Harrington, D.L., Shen, Q., Wei, X., Litvan, I., Huang, M., Lee, R.R., 2022. Functional topologies of spatial cognition predict cognitive and motor progression in Parkinson's. *Front. Aging Neurosci.* 14, 987225. <https://doi.org/10.3389/fnagi.2022.987225>.
- Heinzel, S., Bey, K., Grützmann, R., Klawohn, J., Kaufmann, C., Lennertz, L., Wagner, M., Kathmann, N., Riesel, A., 2021. Spatial working memory performance in people with obsessive-compulsive disorder, their unaffected first-degree relatives and healthy controls. *BJPsych Open* 7, e208. <https://doi.org/10.1192/bjo.2021.1052>.
- Hernández-Pérez, J.J., Gutiérrez-Guzmán, B.E., López-Vázquez, M.Á., Olvera-Cortés, M.E., 2015. Supramammillary serotonin reduction alters place learning and concomitant hippocampal, septal, and supramammillary theta activity in a Morris water maze. *Front. Pharm.* 6. <https://doi.org/10.3389/fphar.2015.00250>.
- Herreras, O., 2016. Local Field Potentials: Myths and Misunderstandings. *Front. Neural Circuits* 10. <https://doi.org/10.3389/fnirc.2016.00101>.
- Herrik, K.F., Mørk, A., Richard, N., Bundgaard, C., Bastlund, J.F., de Jong, I.E.M., 2016. The 5-HT6 receptor antagonist idalopirdine potentiates the effects of acetylcholinesterase inhibition on neuronal network oscillations and extracellular acetylcholine levels in the rat dorsal hippocampus. *Neuropharmacology* 107, 351–363. <https://doi.org/10.1016/j.neuropharm.2016.03.043>.
- Hieronymus, F., Emilsson, J.F., Nilsson, S., Eriksson, E., 2016. Consistent superiority of selective serotonin reuptake inhibitors over placebo in reducing depressed mood in patients with major depression. *Mol. Psychiatry* 21, 523–530. <https://doi.org/10.1038/mp.2015.53>.
- Hirst, W.D., Andree, T.H., Aschmies, S., Childers, W.E., Comery, T.A., Dawson, L.A., Day, M., Feingold, I.B., Grauer, S.M., Harrison, B.L., Hughes, Z.A., Kao, J., Kelly, M.G., Van Der Lee, H., Rosenzweig-Lipson, S., Saab, A.L., Smith, D.L., Sullivan, K., Rizzo, S.J.S., Tio, C., Zhang, M.-Y., Schechter, L.E., 2008. Correlating Efficacy in Rodent Cognition Models with in Vivo 5-Hydroxytryptamine 1A Receptor Occupancy by a Novel Antagonist, (R)-N-(2-Methyl-(4-indolyl-1-piperazinyl)ethyl)-N-(2-pyridinyl)-cyclohexane Carboxamide (WAY-101405). *J. Pharm. Exp. Ther.* 325, 134–145. <https://doi.org/10.1124/jpet.107.133082>.
- Hood, S.D., Bell, C.J., Nutt, D.J., 2005. Acute Tryptophan Depletion. Part I: Rationale and Methodology. *Aust. N. Z. J. Psychiatry* 39, 558–564. <https://doi.org/10.1080/j.1440-1614.2005.01627.x>.
- Hørlyck, L.D., Jespersen, A.E., King, J.A., Ullum, H., Miskowiak, K.W., 2022. Impaired allocentric spatial memory in patients with affective disorders. *J. Psychiatr. Res.* 150, 153–159. <https://doi.org/10.1016/j.jpsychires.2022.01.042>.
- Hu, Y., Ferrario, C.R., Maitland, A.D., Ionides, R.B., Ghimire, A., Watson, B., White, H., Xi, Y., Zhou, J., Ye, B., 2023. LabGym: Quantification of user-defined animal behaviors using learning-based holistic assessment. *Cell Rep. Methods* 3, 100415. <https://doi.org/10.1016/j.crmeth.2023.100415>.
- Isik, S., Unal, G., 2023. Open-source software for automated rodent behavioral analysis. *Front. Neurosci.* 17, 1149027. <https://doi.org/10.3389/fnins.2023.1149027>.
- Ivan, V., Tomas-Cuesta, D., Esteves, I., Luczak, A., Mohajerani, M., McNaughton, B., Gruber, A., 2024. Psilocybin reduces functional connectivity and the encoding of spatial information by neurons in mouse retrosplenial cortex. <https://doi.org/10.22541/au.171378690.00112411.v1>.
- Jäkälä, P., Mazurkiewicz, M., Sirviö, J., Riekkinen, P., Riekkinen, P., 1993. The behavioral effects of serotonin synthesis inhibition and quisqualic acid induced lesions of the nucleus basalis magnocellularis in rats. *Gen. Pharmacol.: Vasc. Syst.* 24, 1141–1148. [https://doi.org/10.1016/0306-3623\(93\)90361-Z](https://doi.org/10.1016/0306-3623(93)90361-Z).
- Jankowski, M.M., Polterovich, A., Kazakov, A., Niediek, J., Nelken, I., 2023. An automated, low-latency environment for studying the neural basis of behavior in freely moving rats. *BMC Biol.* 21, 172. <https://doi.org/10.1186/s12915-023-01660-9>.
- Jannini, T.B., Lorenzo, G.D., Bianciardi, E., Niolu, C., Toscano, M., Ciocca, G., Jannini, E.A., Siracusano, A., 2022. Off-label use of Selective Serotonin Reuptake Inhibitors (SSRIs). *CN* 20, 693–712. <https://doi.org/10.2174/1570159X19666210517150418>.
- Jeltsch, H., Bertrand, F., Galani, R., Lazarus, C., Schimchowitsch, S., Cassel, J.-C., 2004. Intraseptal injection of the 5-HT1A/5-HT7 agonist 8-OH-DPAT and working memory in rats. *Psychopharmacology* 175. <https://doi.org/10.1007/s00213-004-1783-0>.
- Jetten, J., Haslam, C., Pugliese, C., Tonks, J., Haslam, S.A., 2010. Declining autobiographical memory and the loss of identity: Effects on well-being. *J. Clin. Exp. Neuropsychol.* 32, 408–416. <https://doi.org/10.1080/13803390903140603>.
- Jones, M.W., Wilson, M.A., 2005. Phase precession of medial prefrontal cortical activity relative to the hippocampal theta rhythm. *Hippocampus* 15, 867–873. <https://doi.org/10.1002/hipo.20119>.
- Karabeg, M.M., Grauthoff, S., Kollert, S.Y., Weidner, M., Heiming, R.S., Jansen, F., Popp, S., Kaiser, S., Lesch, K.-P., Sachser, N., Schmitt, A.G., Lewejohann, L., 2013. 5-HTT Deficiency Affects Neuroplasticity and Increases Stress Sensitivity Resulting in Altered Spatial Learning Performance in the Morris Water Maze but Not in the Barnes Maze. *PLoS ONE* 8, e78238. <https://doi.org/10.1371/journal.pone.0078238>.
- Kazmierska, P., Konopacki, J., 2015. Development of theta rhythm in hippocampal formation slices perfused with 5-HT1A antagonist, (S)WAY 100135. *Brain Res.* 1625, 142–150. <https://doi.org/10.1016/j.brainres.2015.08.041>.
- Kirsch, I., 2019. Placebo effect in the treatment of depression and anxiety. *Front. Psychiatry* 10, 407. <https://doi.org/10.3389/fpsyg.2019.00407>.
- Klein, S.B., Nichols, S., 2012. Memory and the Sense of Personal Identity. *Mind* 121, 677–702.
- Koenig, J., Cosquer, B., Cassel, J., 2008. Activation of septal 5-HT_{1A} receptors alters spatial memory encoding, interferes with consolidation, but does not affect retrieval in rats subjected to a water-maze task. *Hippocampus* 18, 99–118. <https://doi.org/10.1002/hipo.20368>.
- Könings, M., Blokkeel, M., Kapusta, K., Claassen, T., Buitelaar, J.K., Glennon, J.C., Bielczyk, N.Z., 2019. Quantifying free behaviour in an open field using k-motif approach. *Sci. Rep.* 9, 19873. <https://doi.org/10.1038/s41598-019-56482-z>.
- Kudina, T.A., Sudnitsyn, V.V., Kutyreva, E.V., Kichigina, V.F., 2004. The Serotonin Reuptake Inhibitor Fluoxetine Suppresses Theta Oscillations in the Electroencephalogram of the Rabbit Hippocampus. *Neurosci. Behav. Physiol.* 34, 929–933. <https://doi.org/10.1023/B:NEAB.0000042576.39132.f5>.
- Lamy, D., Goshen-Kosover, A., Aviani, N., Harari, H., Levkovitz, H., 2008. Implicit memory for spatial context in depression and schizophrenia. *J. Abnorm. Psychol.* 117, 954–961. <https://doi.org/10.1037/a0013867>.
- Lehmann, O., Jeltsch, H., Lehnardt, O., Pain, L., Lazarus, C., Cassel, J., 2000. Combined lesions of cholinergic and serotonergic neurons in the rat brain using 192 IgG-saporin and 5,7-dihydroxytryptamine: neurochemical and behavioural characterization. *Eur. J. Neurosci.* 12, 67–79. <https://doi.org/10.1046/j.1460-9568.2000.00881.x>.
- Lemke, Matthias R., Fuchs, G., Gemende, I., Herting, B., Oehlwein, C., Reichmann, H., Rieke, J., Volkman, J., 2004. Depression and Parkinson's disease. *J. Neurol.* 251. <https://doi.org/10.1007/s00415-004-1606-6>.
- Levkovitz, Y., Richter-Levin, G., Segal, M., 1994. Effect of 5-hydroxytryptophan on behavior and hippocampal physiology in young and old rats. *Neurobiol. Aging* 15, 635–641. [https://doi.org/10.1016/0197-4580\(94\)00058-1](https://doi.org/10.1016/0197-4580(94)00058-1).
- Lieben, C.K.J., Oorsouw, K.V., Deutz, N.E.P., Blokland, A., 2004. Acute tryptophan depletion induced by a gelatin-based mixture impairs object memory but not affective behavior and spatial learning in the rat. *Behav. Brain Res.* 151, 53–64. <https://doi.org/10.1016/j.bbr.2003.08.002>.

- Liu, H., Zhou, J., Fang, L., Liu, Z., Fan, S., Xie, P., 2013. Acute tryptophan depletion reduces nitric oxide synthase in the rat hippocampus. *Neurochem Res* 38, 2595–2603. <https://doi.org/10.1007/s11064-013-1177-y>.
- López-Vázquez, M.Á., López-Loeza, E., Lajud Ávila, N., Gutiérrez-Guzmán, B.E., Hernández-Pérez, J.J., Reyes, Y.E., Olvera-Cortés, M.E., 2014. Septal serotonin depletion in rats facilitates working memory in the radial arm maze and increases hippocampal high-frequency theta activity. *Eur. J. Pharmacol.* 734, 105–113. <https://doi.org/10.1016/j.ejphar.2014.04.005>.
- Ly, S., Pishdari, B., Lok, L.L., Hajos, M., Kocsis, B., 2013. Activation of 5-HT6 Receptors Modulates Sleep–Wake Activity and Hippocampal Theta Oscillation. *ACS Chem. Neurosci.* 4, 191–199. <https://doi.org/10.1021/cn300184t>.
- Maidenbaum, S., Patel, A., Stein, E., Jacobs, J., 2019. Spatial Memory Rehabilitation in Virtual Reality – Extending findings from Epilepsy Patients to the General Population, in: 2019 International Conference on Virtual Rehabilitation (ICVR). Presented at the 2019 International Conference on Virtual Rehabilitation (ICVR), IEEE, Tel Aviv, Israel, pp. 1–7. <https://doi.org/10.1109/ICVR46560.2019.8994573>.
- Majlessi, N., Kaddhodaie, M., Parviz, M., Naghdi, N., 2003. Serotonin depletion in rat hippocampus attenuates l-NAME-induced spatial learning deficits. *Brain Res.* 963, 244–251. [https://doi.org/10.1016/S0006-8993\(02\)03987-2](https://doi.org/10.1016/S0006-8993(02)03987-2).
- Marazziti, D., Avella, M.T., Ivaldi, T., Palermo, S., Massa, L., Vecchia, A.D., Basile, L., Mucci, F., 2021. Neuroenhancement: State of the Art and Future Perspectives. *Clin. Neuropsychiatry* 18, 137–169. <https://doi.org/10.36131/cnforitieditore20210303>.
- Marlatte, H., Beaton, D., Adler-Luzon, S., Abo-Ahmad, L., Gilboa, A., 2022. Scene Construction and Spatial Processing in Post-traumatic Stress Disorder. *Front. Behav. Neurosci.* 16, 888358. <https://doi.org/10.3389/fnbeh.2022.888358>.
- Martinielli, P., Sperduti, M., Piolino, P., 2013. Neural substrates of the self-memory system: New insights from a meta-analysis. *Hum. Brain Mapp.* 34, 1515–1529. <https://doi.org/10.1002/hbm.22008>.
- Mathis, A., Mamidanna, P., Cury, K.M., Abe, T., Murthy, V.N., Mathis, M.W., Bethge, M., 2018. DeepLabCut: markerless pose estimation of user-defined body parts with deep learning. *Nat. Neurosci.* 21, 1281–1289. <https://doi.org/10.1038/s41593-018-0209-y>.
- Meneses, A., 2013. 5-HT systems: emergent targets for memory formation and memory alterations. *Rev. Neurosci.* 24. <https://doi.org/10.1515/revneuro-2013-0026>.
- Mengod, G., Cortés, R., Vilaró, M.T., Hoyer, D., 2010. Distribution of 5-HT Receptors in the Central Nervous System. *Handbook of Behavioral Neuroscience*. Elsevier, pp. 123–138. [https://doi.org/10.1016/S1569-7339\(10\)70074-6](https://doi.org/10.1016/S1569-7339(10)70074-6).
- Miczek, K.A., Altman, J.L., Appel, J.B., Boggan, W.O., 1975. Para-chlorophenylalanine, serotonin and killing behavior. *Pharmacol. Biochem. Behav.* 3, 355–361. [https://doi.org/10.1016/0091-3057\(75\)90043-X](https://doi.org/10.1016/0091-3057(75)90043-X).
- Miheau, J., Van Marrewijk, B., 1999. Stimulation of 5-HT1A receptors by systemic or medial septum injection induces anxiogenic-like effects and facilitates acquisition of a spatial discrimination task in mice. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 23, 1113–1133. [https://doi.org/10.1016/S0278-5846\(99\)00057-3](https://doi.org/10.1016/S0278-5846(99)00057-3).
- Miyazaki, K., Miyazaki, K.W., Doya, K., 2012. The Role of Serotonin in the Regulation of Patience and Impulsivity. *Mol. Neurobiol.* 45, 213–224. <https://doi.org/10.1007/s12035-012-8232-6>.
- Miyazaki, K.W., Miyazaki, K., Tanaka, K.F., Yamanaka, A., Takahashi, A., Tabuchi, S., Doya, K., 2014. Optogenetic Activation of Dorsal Raphe Serotonin Neurons Enhances Patience for Future Rewards. *Curr. Biol.* 24, 2033–2040. <https://doi.org/10.1016/j.cub.2014.07.041>.
- Moncrieff, J., Cooper, R.E., Stockmann, T., Amendola, S., Hengartner, M.P., Horowitz, M. A., 2023. The serotonin theory of depression: a systematic umbrella review of the evidence. *Mol. Psychiatry* 28, 3243–3256. <https://doi.org/10.1038/s41380-022-01661-0>.
- Monti, J.M., 2011. Serotonin control of sleep-wake behavior. *Sleep. Med. Rev.* 15, 269–281. <https://doi.org/10.1016/j.smrv.2010.11.003>.
- Moriarty, O., Ruane, N., O’Gorman, D., Maharaj, C.H., Mitchell, C., Sarma, K.M., Finn, D. P., McGuire, B.E., 2017. Cognitive Impairment in Patients with Chronic Neuropathic or Radicular Pain: An Interaction of Pain and Age. *Front. Behav. Neurosci.* 11, 100. <https://doi.org/10.3389/fnbeh.2017.00100>.
- Müller, C., Remy, S., 2018. Septo-hippocampal interaction. *Cell Tissue Res* 373, 565–575. <https://doi.org/10.1007/s00441-017-2745-2>.
- Murphy, G.G., 2013. Spatial Learning and Memory—What’s TLE Got to Do with It?: Spatial Learning/Memory and TLE. *Epilepsy Curr.* 13, 26–29. <https://doi.org/10.5698/1535-7511-13.1.26>.
- Murphy, S.E., Capitão, L.P., Giles, S.L.C., Cowen, P.J., Stringaris, A., Harmer, C.J., 2021. The knowns and unknowns of SSRI treatment in young people with depression and anxiety: efficacy, predictors, and mechanisms of action. *Lancet Psychiatry* 8, 824–835. [https://doi.org/10.1016/S2215-0366\(21\)00154-1](https://doi.org/10.1016/S2215-0366(21)00154-1).
- Naghdi, N., Harooni, H., 2005. The effect of intrahippocampal injections of ritanserin (5HT antagonist) and granisetron (5HT antagonist) on learning as assessed in the spatial version of the water maze. *Behav. Brain Res.* 157, 205–210. <https://doi.org/10.1016/j.bbr.2004.06.024>.
- Neupane, S., Fiete, I., Jazayeri, M., 2024. Mental navigation in the primate entorhinal cortex. *Nature*. <https://doi.org/10.1038/s41586-024-07557-z>.
- Nilsson, O.G., Strecker, R.E., Daszuta, A., Björklund, A., 1988. Combined cholinergic and serotonergic denervation of the forebrain produces severe deficits in a spatial learning task in the rat. *Brain Res.* 453, 235–246. [https://doi.org/10.1016/0006-8993\(88\)90163-1](https://doi.org/10.1016/0006-8993(88)90163-1).
- Núñez, A., Buño, W., 2021. The Theta Rhythm of the Hippocampus: From Neuronal and Circuit Mechanisms to Behavior. *Front. Cell. Neurosci.* 15, 649262. <https://doi.org/10.3389/fncel.2021.649262>.
- Okaty, B.W., Commons, K.G., Dymecki, S.M., 2019. Embracing diversity in the 5-HT neuronal system. *Nat. Rev. Neurosci.* 20, 397–424. <https://doi.org/10.1038/s41583-019-0151-3>.
- Olvera-Cortés, M.E., Gutiérrez-Guzmán, B.E., López-Loeza, E., Hernández-Pérez, J.J., López-Vázquez, M.Á., 2013. Serotonergic modulation of hippocampal theta activity in relation to hippocampal information processing. *Exp. Brain Res* 230, 407–426. <https://doi.org/10.1007/s00221-013-3679-x>.
- Park, S., 1992. Schizophrenics Show Spatial Working Memory Deficits. *Arch. Gen. Psychiatry* 49, 975. <https://doi.org/10.1001/archpsyc.1992.01820120063009>.
- Parrott, A.C., 2002. Recreational Ecstasy/MDMA, the serotonin syndrome, and serotonergic neurotoxicity. *Pharmacol. Biochem. Behav.* 71, 837–844. [https://doi.org/10.1016/S0091-3057\(01\)00711-0](https://doi.org/10.1016/S0091-3057(01)00711-0).
- Patetsos, E., Horjales-Araujo, E., 2016. Treating Chronic Pain with SSRIs: What Do We Know? *Pain. Res. Manag.* 2016, 1–17. <https://doi.org/10.1155/2016/2020915>.
- Pereira, T.D., Aldarondo, D.E., Willmore, L., Kislin, M., Wang, S.S.-H., Murthy, M., Shaevitz, J.W., 2019. Fast animal pose estimation using deep neural networks. *Nat. Methods* 16, 117–125. <https://doi.org/10.1038/s41592-018-0234-5>.
- Pereira, T.D., Shaevitz, J.W., Murthy, M., 2020. Quantifying behavior to understand the brain. *Nat. Neurosci.* 23, 1537–1549. <https://doi.org/10.1038/s41593-020-00734-z>.
- Petrásek, T., Stuchlík, A., 2009. Serotonin-depleted rats are capable of learning in active place avoidance, a spatial task requiring cognitive coordination. *Physiol. Res* 299–303. <https://doi.org/10.33549/physiolres.931729>.
- Piber, D., 2021. The role of sleep disturbance and inflammation for spatial memory. *Brain, Behav., Immun. - Health* 17, 100333. <https://doi.org/10.1016/j.bbih.2021.100333>.
- Possin, K.L., Filoteo, J.V., Song, D.D., Salmon, D.P., 2008. Spatial and object working memory deficits in Parkinson’s disease are due to impairment in different underlying processes. *Neuropsychology* 22, 585–595. <https://doi.org/10.1037/a0012613>.
- Pourhamzeh, M., Moravej, F.G., Arabi, M., Shahriari, E., Mehrabi, S., Ward, R., Ahadi, R., Joghataei, M.T., 2022. The Roles of Serotonin in Neuropsychiatric Disorders. *Cell Mol. Neurobiol.* 42, 1671–1692. <https://doi.org/10.1007/s10571-021-01064-9>.
- Richter-Levin, G., Segal, M., 1989. Spatial performance is severely impaired in rats with combined reduction of serotonergic and cholinergic transmission. *Brain Res.* 477, 404–407. [https://doi.org/10.1016/0006-8993\(89\)91437-6](https://doi.org/10.1016/0006-8993(89)91437-6).
- Riekkinen, M., Sirviö, J., Riekkinen, P., 1993. Pharmacological consequences of nicotinic plus serotonergic manipulations. *Brain Res.* 622, 139–146. [https://doi.org/10.1016/0006-8993\(93\)90812-2](https://doi.org/10.1016/0006-8993(93)90812-2).
- Riekkinen, M., Sirviö, J., Toivanen, T., Riekkinen, P., 1995. Combined treatment with a 5HT1A receptor agonist and a muscarinic acetylcholine receptor antagonist disrupts water maze navigation behavior. *Psychopharmacology* 122, 137–146. <https://doi.org/10.1007/BF02246088>.
- Riekkinen, P., Riekkinen, M., Sirviö, J., Riekkinen, P., 1992. Effects of concurrent nicotinic antagonist and PCPA treatments on spatial and passive avoidance learning. *Brain Res.* 575, 247–250. [https://doi.org/10.1016/0006-8993\(92\)90086-0](https://doi.org/10.1016/0006-8993(92)90086-0).
- Roberts, A.J., Hedlund, P.B., 2012. The 5-HT₇ receptor in learning and memory. *Hippocampus* 22, 762–771. <https://doi.org/10.1002/hipo.20938>.
- Rogers, D., Hagan, J., 2001. 5-HT₆ receptor antagonists enhance retention of a water maze task in the rat. *Psychopharmacology* 158, 114–119. <https://doi.org/10.1007/s002130100840>.
- Rosas, K., Parrón, I., Serrano, P., Cimadevilla, J.M., 2013. Spatial recognition memory in a virtual reality task is altered in refractory temporal lobe epilepsy. *Epilepsy Behav.* 28, 227–231. <https://doi.org/10.1016/j.yebeh.2013.05.010>.
- Rose Addis, D., Tippett, L., 2004. Memory of myself: Autobiographical memory and identity in Alzheimer’s disease. *Memory* 12, 56–74. <https://doi.org/10.1080/09658210244000423>.
- Ryait, H., Bermudez-Contreras, E., Harvey, M., Faraji, J., Mirza Agha, B., Gomez-Palacio Schjetnan, A., Gruber, A., Doan, J., Mohajerani, M., Metz, G.A.S., Whishaw, I.Q., Luczak, A., 2019. Data-driven analyses of motor impairments in animal models of neurological disorders. *PLoS Biol.* 17, e3000516. <https://doi.org/10.1371/journal.pbio.3000516>.
- Sakakibara, E., 2020. The polysemy of psychotropic drugs: continuity and overlap between neuroenhancement, treatment, prevention, pain relief, and pleasure-seeking in a clinical setting. *BMC Med Ethics* 21, 54. <https://doi.org/10.1186/s12910-020-00497-z>.
- Sandoval, K., McDaniel, K.M., Murawski, N.J., Doerr, C.E., Calton, J.L., 2008. Combined blockade of serotonergic and muscarinic transmission disrupts the anterior thalamic head direction signal. *Behav. Neurosci.* 122, 1226–1235. <https://doi.org/10.1037/a0013138>.
- Sarnyai, Z., Sibille, E.L., Pavlides, C., Fenster, R.J., McEwen, B.S., Tóth, M., 2000. Impaired hippocampal-dependent learning and functional abnormalities in the hippocampus in mice lacking serotonin_{1A} receptors. *Proc. Natl. Acad. Sci. U. S. A.* 97, 14731–14736. <https://doi.org/10.1073/pnas.97.26.14731>.
- Schmitt, J., Wingen, M., Ramaekers, J., Evers, E., Riedel, W., 2006. Serotonin and Human Cognitive Performance. *CPD* 12, 2473–2486. <https://doi.org/10.2174/13816120677698909>.
- Siapas, A.G., Lubenov, E.V., Wilson, M.A., 2005. Prefrontal Phase Locking to Hippocampal Theta Oscillations. *Neuron* 46, 141–151. <https://doi.org/10.1016/j.neuron.2005.02.028>.
- Simon, K.C., Clemenson, G.D., Zhang, J., Sattari, N., Shuster, A.E., Clayton, B., Alzueta, E., Dulai, T., De Zambotti, M., Stark, C., Baker, F.C., Mednick, S.C., 2022. Sleep facilitates spatial memory but not navigation using the Minercraft Memory and Navigation task. *Proc. Natl. Acad. Sci. U. S. A.* 119, e2202394119. <https://doi.org/10.1073/pnas.2202394119>.
- Skaggs, W.E., McNaughton, B.L., Wilson, M.A., Barnes, C.A., 1996. Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences. *Hippocampus* 6, 149–172. [https://doi.org/10.1002/\(SICI\)1098-1063\(1996\)6:2<149::AID-HIPO6>3.0.CO;2-K](https://doi.org/10.1002/(SICI)1098-1063(1996)6:2<149::AID-HIPO6>3.0.CO;2-K).
- Skovgård, K., Agerskov, C., Kohlmeier, K.A., Herrik, K.F., 2018. The 5-HT₃ receptor antagonist ondansetron potentiates the effects of the acetylcholinesterase inhibitor

- donepezil on neuronal network oscillations in the rat dorsal hippocampus. *Neuropharmacology* 143, 130–142. <https://doi.org/10.1016/j.neuropharm.2018.09.017>.
- Sloin, H.E., Levi, A., Someck, S., Spivak, L., Stark, E., 2022. High Fidelity Theta Phase Rolling of CA1 Neurons. *J. Neurosci.* 42, 3184–3196. <https://doi.org/10.1523/JNEUROSCI.2151-21.2022>.
- Smith, K.V., Burgess, N., Brewin, C.R., King, J.A., 2015. Impaired allocentric spatial processing in posttraumatic stress disorder. *Neurobiol. Learn. Mem.* 119, 69–76. <https://doi.org/10.1016/j.nlm.2015.01.007>.
- Sörman, E., Wang, D., Hajos, M., Kocsis, B., 2011. Control of hippocampal theta rhythm by serotonin: Role of 5-HT_{2c} receptors. *Neuropharmacology* 61, 489–494. <https://doi.org/10.1016/j.neuropharm.2011.01.029>.
- Stancampiano, R., Cocco, S., Melis, F., Cugusi, C., Sarais, L., Fadda, F., 1997. The decrease of serotonin release induced by a tryptophan-free amino acid diet does not affect spatial and passive avoidance learning. *Brain Res.* 762, 269–274. [https://doi.org/10.1016/S0006-8993\(97\)00506-4](https://doi.org/10.1016/S0006-8993(97)00506-4).
- Staubli, U., Xu, F., 1995. Effects of 5-HT₃ receptor antagonism on hippocampal theta rhythm, memory, and LTP induction in the freely moving rat. *J. Neurosci.* 15, 2445–2452. <https://doi.org/10.1523/JNEUROSCI.15-03-02445.1995>.
- Storchi, R., Milosavljevic, N., Allen, A.E., Zippo, A.G., Agnihotri, A., Cootes, T.F., Lucas, R.J., 2020. A High-Dimensional Quantification of Mouse Defensive Behaviors Reveals Enhanced Diversity and Stimulus Specificity. *Curr. Biol.* 30, 4619–4630.e5. <https://doi.org/10.1016/j.cub.2020.09.007>.
- Strikwerda-Brown, C., Grilli, M.D., Andrews-Hanna, J., Irish, M., 2019. All is not lost—Rethinking the nature of memory and the self in dementia. *Ageing Res. Rev.* 54, 100932. <https://doi.org/10.1016/j.arr.2019.100932>.
- Tallarico, M., Pisano, M., Leo, A., Russo, E., Citraro, R., De Sarro, G., 2023. Antidepressant Drugs for Seizures and Epilepsy: Where do we Stand? *CN* 21, 1691–1713. <https://doi.org/10.2174/1570159X20666220627160048>.
- Tao, C., Yan, W., Li, Y., Lu, X., 2016. Effect of antidepressants on spatial memory deficit induced by dizocilpine. *Psychiatry Res.* 244, 266–272. <https://doi.org/10.1016/j.psychres.2016.03.035>.
- Teixeira, C.M., Rosen, Z.B., Suri, D., Sun, Q., Hersh, M., Sargin, D., Dincheva, I., Morgan, A.A., Spivack, S., Krok, A.C., Hirschfeld-Stoler, T., Lambe, E.K., Siegelbaum, S.A., Ansorge, M.S., 2018. Hippocampal 5-HT Input Regulates Memory Formation and Schaffer Collateral Excitation. *Neuron* 98, 992–1004.e4. <https://doi.org/10.1016/j.neuron.2018.04.030>.
- Tolman, E.C., 1948. Cognitive maps in rats and men. *Psychol. Rev.* 55, 189–208. <https://doi.org/10.1037/h0061626>.
- Uchida, S., Umeeda, H., Kitamoto, A., Masushige, S., Kida, S., 2007. Chronic reduction in dietary tryptophan leads to a selective impairment of contextual fear memory in mice. *Brain Res.* 1149, 149–156. <https://doi.org/10.1016/j.brainres.2007.02.049>.
- Van Dam, E.A., Noldus, L.P.J.J., Van Gerven, M.A.J., 2023. Disentangling rodent behaviors to improve automated behavior recognition. *Front. Neurosci.* 17, 1198209. <https://doi.org/10.3389/fnins.2023.1198209>.
- Van Donkelaar, E.L., Blokland, A., Ferrington, L., Kelly, P.A.T., Steinbusch, H.W.M., Prickaerts, J., 2011. Mechanism of acute tryptophan depletion: is it only serotonin? *Mol. Psychiatry* 16, 695–713. <https://doi.org/10.1038/mp.2011.9>.
- Vance, A., Winther, J., 2021. Spatial working memory performance in children and adolescents with major depressive disorder and dysthymic disorder. *J. Affect. Disord.* 278, 470–476. <https://doi.org/10.1016/j.jad.2020.09.093>.
- Varga, V., Petersen, P., Zutshi, I., Huszar, R., Zhang, Y., Buzsáki, G., 2024. Working memory features are embedded in hippocampal place fields. *Cell Rep.* 43, 113807. <https://doi.org/10.1016/j.celrep.2024.113807>.
- Vaswani, M., Linda, F.K., Ramesh, S., 2003. Role of selective serotonin reuptake inhibitors in psychiatric disorders: a comprehensive review. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 27, 85–102. [https://doi.org/10.1016/S0278-5846\(02\)00338-X](https://doi.org/10.1016/S0278-5846(02)00338-X).
- Vertes, R.P., 2010. Serotonergic Regulation of Rhythmical Activity of the Brain, Concentrating on the Hippocampus. *Handbook of Behavioral Neuroscience*. Elsevier, pp. 277–292. [https://doi.org/10.1016/S1569-7339\(10\)70084-9](https://doi.org/10.1016/S1569-7339(10)70084-9).
- Viganò, S., Piazza, M., 2020. Distance and Direction Codes Underlie Navigation of a Novel Semantic Space in the Human Brain. *J. Neurosci.* 40, 2727–2736. <https://doi.org/10.1523/JNEUROSCI.1849-19.2020>.
- Vytal, K.E., Cornwell, B.R., Letkiewicz, A.M., Arkin, N.E., Grillon, C., 2013. The complex interaction between anxiety and cognition: insight from spatial and verbal working memory. *Front. Hum. Neurosci.* 7. <https://doi.org/10.3389/fnhum.2013.00093>.
- Warburton, E., Harrison, A.A., Robbins, T.W., Everitt, B.J., 1997. Contrasting effects of systemic and intracerebral infusions of the 5-HT_{1A} receptor agonist 8-OH-DPAT on spatial short-term working memory in rats. *Behav. Brain Res.* 84, 247–258. [https://doi.org/10.1016/S0166-4328\(96\)00154-4](https://doi.org/10.1016/S0166-4328(96)00154-4).
- Wei, Z., Junhong, G., Xiaoyuan, N., Jie, W., Zhaojun, W., Meina, W., Wei, Y., Jun, Z., Jinshun, Q., 2017. Citalopram Ameliorates Impairments in Spatial Memory and Synaptic Plasticity in Female 3xTgAD Mice. *BioMed. Res. Int.* 2017, 1–12. <https://doi.org/10.1155/2017/1238687>.
- Wiegand, M.H., 2008. Antidepressants for the Treatment of Insomnia: A Suitable Approach? *Drugs* 68, 2411–2417. <https://doi.org/10.2165/0003495-200868170-00001>.
- Wingen, M., Kuypers, K.P.C., Ramaekers, J.G., 2007. Selective verbal and spatial memory impairment after 5-HT_{1A} and 5-HT_{2A} receptor blockade in healthy volunteers pretreated with an SSRI. *J. Psychopharmacol.* 21, 477–485. <https://doi.org/10.1177/0269881106072506>.
- Wolff, M., Costet, P., Gross, C., Hen, R., Segu, L., Buhot, M.-C., 2004. Age-dependent effects of serotonin-1A receptor gene deletion in spatial learning abilities in mice. *Mol. Brain Res.* 130, 39–48. <https://doi.org/10.1016/j.molbrainres.2004.07.012>.
- Xia, S.-H., Hu, S.-W., Ge, D.-G., Liu, D., Wang, D., Zhang, S., Zhang, Q., Yuan, L., Li, Y.-Q., Yang, J.-X., Wu, P., Zhang, H., Han, M.-H., Ding, H.-L., Cao, J.-L., 2020. Chronic Pain Impairs Memory Formation via Disruption of Neurogenesis Mediated by Mesohippocampal Brain-Derived Neurotrophic Factor Signaling. *Biol. Psychiatry* 88, 597–610. <https://doi.org/10.1016/j.biopsych.2020.02.013>.
- Young, S.N., Ervin, F.R., Pihl, R.O., Finn, P., 1989. Biochemical aspects of tryptophan depletion in primates. *Psychopharmacology* 98, 508–511. <https://doi.org/10.1007/BF00441950>.
- Zhan, T.-T., Dong, Z.-Y., Yi, L.-S., Zhang, Y., Sun, H.-H., Zhang, H.-Q., Wang, J.-W., Chen, Y., Huang, Y., Xu, S.-C., 2022. Tansospirone prevents stress-induced anxiety-like behavior and visceral hypersensitivity by suppressing theta oscillation enhancement via 5-HT_{1A} receptors in the anterior cingulate cortex in rats. *Front. Cell. Neurosci.* 16, 922750. <https://doi.org/10.3389/fncel.2022.922750>.
- Zhang, G., Cinalli, D., Stackman, R.W., 2017. Effect of a hallucinogenic serotonin 5-HT_{2A} receptor agonist on visually guided, hippocampal-dependent spatial cognition in C57BL/6J mice. *Hippocampus* 27, 558–569. <https://doi.org/10.1002/hipo.22712>.