

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

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1 **Abstract**

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

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

13 **Key Facts:**

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



21 *Remembering Space and Time*

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

33 *Mental maps*

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



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

49 *Why serotonin?*

50 Despite less than 0.1% of neurons in the mammalian brain having the ability to synthesize and
51 release serotonin (5-hydroxytryptamine, 5-HT) (Okaty et al., 2019), much discussion has
52 centered on how it can alter and potentially enhance our quality of life in a variety of mental
53 health disorders. This includes moderating anxiety and stress, promoting patience and coping
54 mechanisms, and opening the window for greater neural plasticity, depending on the type of
55 receptors involved (Carhart-Harris and Nutt, 2017; Deakin, 2013; Miyazaki et al., 2012, 2014).
56 Serotonergic drugs have been proposed and are widely used in treating a broad spectrum of
57 mental health conditions, particularly mood disorders (Hieronymus et al., 2016; Moncrieff et al.,
58 2023; Pourhamzeh et al., 2022). This is despite controversies regarding serotonin dysregulation
59 being the major cause of these conditions (Kirsch, 2019; Moncrieff et al., 2023). Furthermore,
60 serotonergic drugs are also found in the realms of recreational drug use, microdosing, and other
61 recently emerging fields of self-prescribed neuro-enhancement, which aim to improve human
62 mood, well-being, efficiency, creativity, and the balance between wakefulness and sleep
63 (Cavanna et al., 2022; Cespuoglio, 2018; Daubner et al., 2021; Gandotra et al., 2022; Jannini et
64 al., 2022; Marazziti et al., 2021; Monti, 2011; Parrott, 2002; Sakakibara, 2020; Schmitt et al.,
65 2006). Reflecting on these widespread applications, substances acting on the brain's serotonin
66 system have become prevalent across all age groups in our society (Giovannini et al., 2020;



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

70 *Global changes in brain serotonin – missing bits and pieces*

71 The serotonergic system has been identified as capable of modulating spatial memory through
72 various mechanisms, although its effectiveness can vary depending on the type of manipulation
73 applied, the experimental method, and the approach to data analysis (Fig. 1) (Coray and
74 Quednow, 2022; Dale et al., 2016; Glikmann-Johnston et al., 2015). The majority of earlier
75 studies investigating serotonin's role in spatial memory relied on simple behavioral tests, such as
76 the Morris water maze, radial arm maze, Barnes maze, and similar assays. These studies often
77 employed basic behavioral analyses, focusing on metrics such as the time required to locate a
78 target location or the duration spent in the chosen area. Results were typically presented as
79 average time in seconds. For instance, a global decrease in serotonin levels induced by acute
80 tryptophan depletion (ATD) (Hood et al., 2005; Van Donkelaar et al., 2011; Young et al., 1989)
81 did not significantly impact spatial memory in rats and mice across several studies (Lieben et al.,
82 2004; Liu et al., 2013; Stancampiano et al., 1997; Uchida et al., 2007). Similarly, nonspecific
83 neurotoxic lesions targeting serotonin neurons using 5,7-dihydroxytryptamine (5,7-DHT) did not
84 significantly alter outcomes in those basic behavioral models (Lehmann et al., 2000; Majlessi et
85 al., 2003; Nilsson et al., 1988). The serotonin depletion induced by inhibiting tryptophan
86 hydroxylase with Para-chlorophenylalanine (PCPA) (Dringenberg et al., 1995; Miczek et al.,
87 1975) also did not affect significantly the learning performance of rats in water maze (Fig. 1)
88 (Beiko et al., 1997; Dringenberg and Zalan, 1999; Harder et al., 1996; Jäkälä et al., 1993;
89 Richter-Levin and Segal, 1989; Riekkinen et al., 1993, 1992) and active place avoidance, a



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

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

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

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

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

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

123 So far, attempts to change global serotonin levels have most frequently failed to produce
124 significant effects. However, in some cases, they have either impaired or improved spatial
125 memory and learning. When we examine experiments involving more targeted, localized
126 changes in serotonin levels within specific brain structures, it appears to be a more effective
127 approach (Fig. 2). Optogenetic activation of serotonergic terminals in the CA1 region of the
128 hippocampus enhanced water maze memory formation, while inhibition of these terminals in the
129 CA1 region impaired it (Fig. 2A) (Teixeira et al., 2018). Recent study by Gerdey and Maseck
130 (2023) failed to reproduce these results possibly due to different genetically modified mouse
131 models used in both studies. In Gerdey and Maseck (2023) study, manipulating median raphe
132 serotonin input to the dorsal CA1 subfield, whether through activation or inhibition at CA1 fiber
133 terminals, did not affect significantly object recognition, spatial memory, or anxiety behavior.
134 However, activation of serotonergic fibers to the CA1 region altered strategies used in the Barnes
135 Maze. Moreover, activation of 5-HT1A receptors, abundant in CA1's pyramidal neurons,



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

138 Following lesions in the fimbria, fornix, and cingulate bundle of adult rats with 5,7-DHT
139 to deplete hippocampal serotonin, Gutiérrez-Guzmán et al. (2011) observed a facilitation of place
140 learning. This effect was associated with dominant high-frequency theta activity (6.5-9.5Hz)
141 (Gutiérrez-Guzmán et al., 2011). Similarly, serotonin depletion in the medial septum facilitated
142 learning in Morris water maze and increased the frequency of the hippocampal theta activity
143 during the first days of training to 8.5 Hz (Gutiérrez-Guzmán et al., 2017). The depletion of
144 serotonin in the medial septum and Broca's diagonal band (MS/DBB) facilitated working
145 memory also in the radial arm maze and again induced a higher expression of high-frequency
146 (6.5–9.5 Hz) theta activity (López-Vázquez et al., 2014). On the other hand, depletion of
147 serotonin in the supramammillary nucleus impaired learning in Morris water maze and altered
148 the expression of hippocampal high-frequency theta activity (Fig. 2B) (Hernández-Pérez et al.,
149 2015).

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



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

178 *Conclusions*

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



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

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498 **Figure 1.** This figure summarizes research on how changes in global serotonin levels affect
499 spatial memory in rodents across various tasks, such as the Morris water maze, radial arm maze,
500 and Barnes maze. It depicts three main outcomes observed in previous studies: non-significant
501 changes, decreased performance, and increased performance, marked by arrows in black, red,
502 and green, respectively. Behavioral effects were produced through various experimental
503 interventions. These included acute tryptophan depletion (ATD), neurotoxic lesions induced by
504 5,7-dihydroxytryptamine (5,7-DHT), serotonin depletion caused by inhibiting tryptophan
505 hydroxylase with Para-chlorophenylalanine (PCPA), genetic manipulations such as knockouts of
506 the serotonin transporter (5-HTT) or serotonin 1A receptor (5-HT1A) genes, as well as
507 administration of serotonin precursors like 5-hydroxytryptophan (5-HTP) and tryptophan (TRP).
508 Key studies are cited for each outcome, providing an overview of the role of serotonin in spatial
509 memory.

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

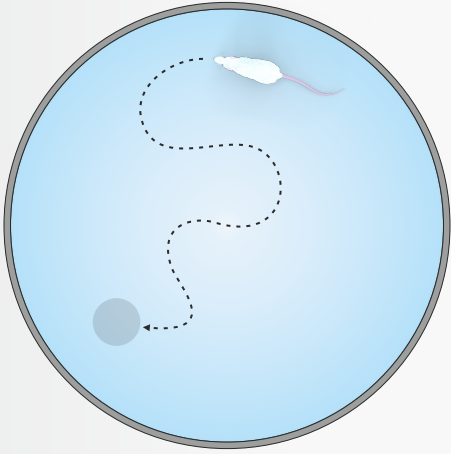
Effects of global serotonin level changes on spatial memory tasks in rodents

↔ non-significant changes

↓ decreased performance

↑ improved performance

Morris water maze



↔

ATD: Lieben et al., 2004; Liu et al., 2013; Stancampiano et al., 1997; Uchida et al., 2007.

5,7-DHT: Lehmann et al., 2000; Majlessi et al., 2003; Nilsson et al., 1988.

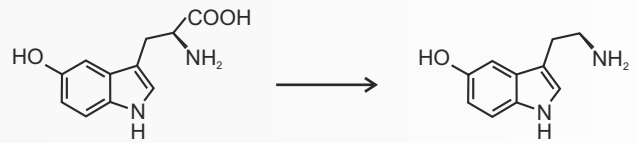
PCPA: Beiko et al., 1997; Dringenberg and Zalan, 1999; Harder et al., 1996; Jäkälä et al., 1993; Richter-Levin and Segal, 1989; Riekkinen et al., 1993, 1992.

↓

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

↑

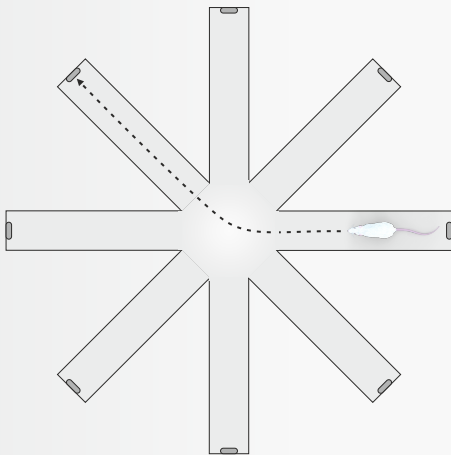
5-HTP in old rats: Levkovitz et al., 1994



5-Hydroxytryptophan (5-HTP)

Serotonin (5-HT)

Radial arm maze

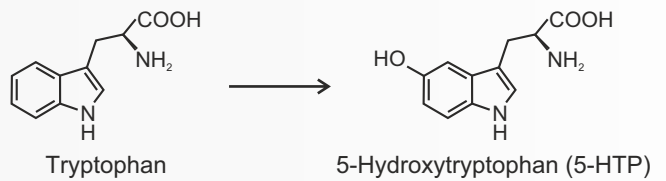


↔

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

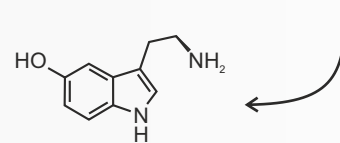
↑

Tryptophan: Haider et al., 2006



Tryptophan

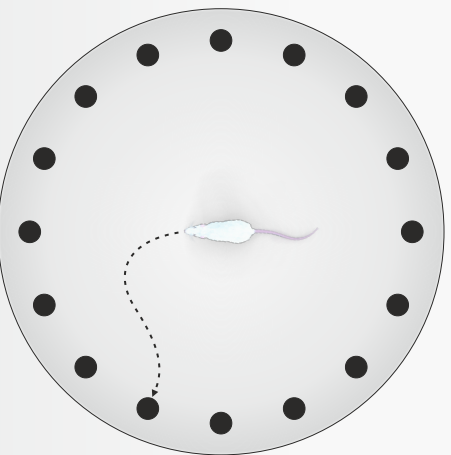
5-Hydroxytryptophan (5-HTP)



Serotonin (5-HT)

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MOST WIEDZY



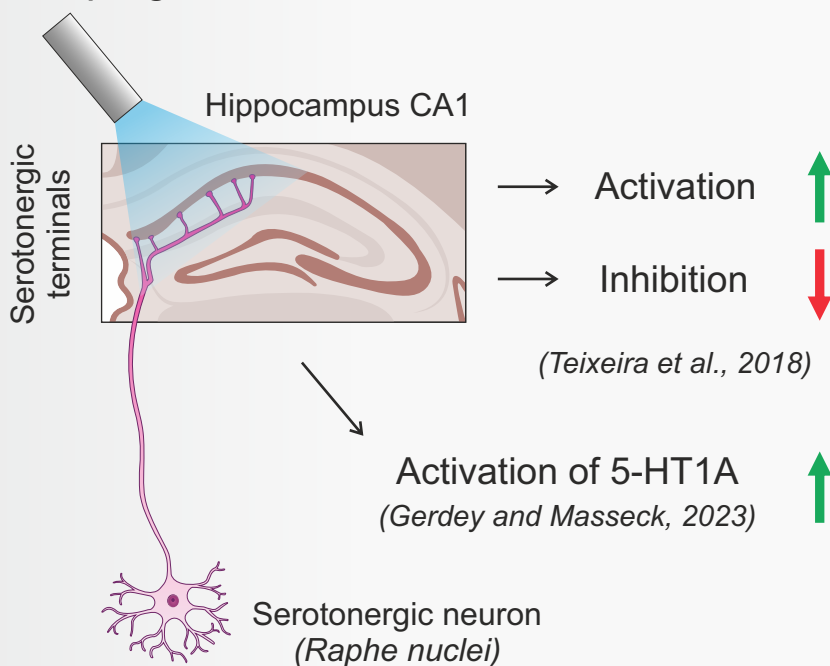
↔

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

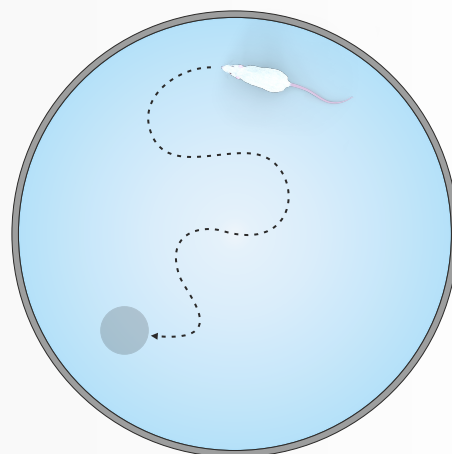


A

Optogenetic stimulation



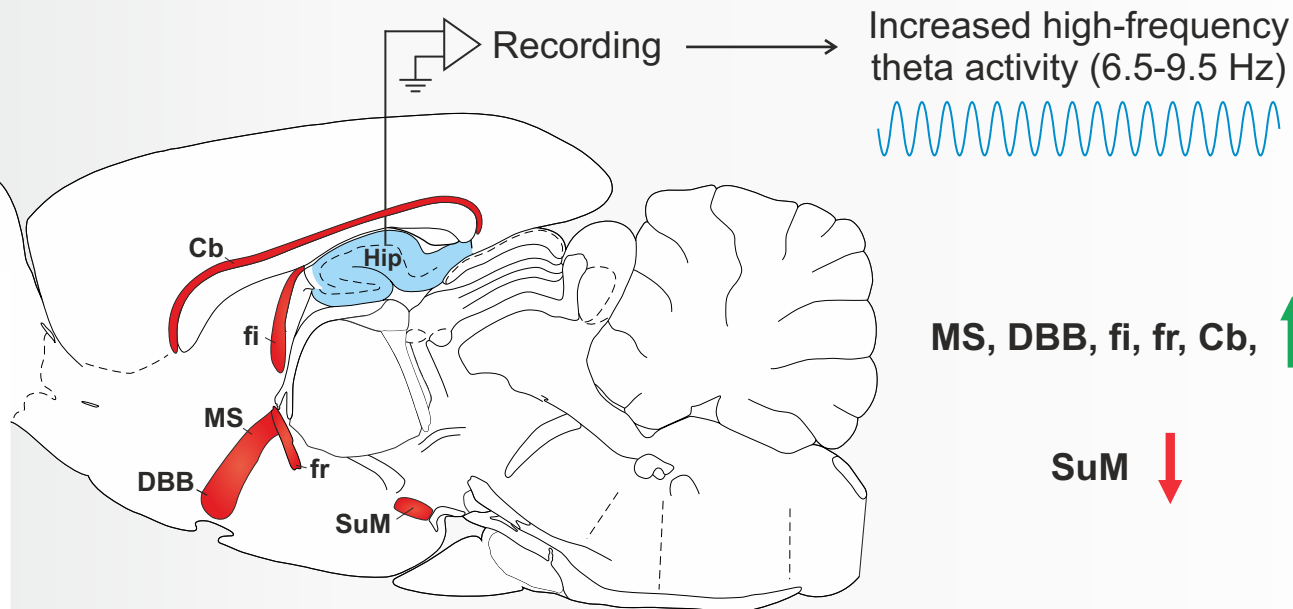
Morris water maze



↑ improved performance

↓ decreased performance

Local 5,7-DHT serotonergic lesions



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

