The role of serotonin in declarative memory: A systematic review of animal and human research

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\textbf{ABSTRACT}

The serotonergic system is involved in diverse cognitive functions including memory. Of particular importance to daily life are declarative memories that contain information about personal experiences, general facts, and events. Several psychiatric or neurological diseases, such as depression, attention-deficit-hyperactivity disorder (ADHD), and dementia, show alterations in serotonergic signalling and attendant memory disorders. Nevertheless, understanding serotonergic neurotransmission and its influence on memory remained a challenge until today. In this systematic review, we summarize recent psychopharmacological studies in animals and humans from a psychological memory perspective, in consideration of task-specific requirements. This approach has the advantage that comparisons between serotonin (5-HT)-related neurochemical mechanisms and manipulations are each addressing specific mnemonic circuits. We conclude that applications of the same 5-HT-related treatments can differentially affect unrelated tasks of declarative memories. Moreover, the analysis of specific mnemonic phases (e.g., encoding vs. consolidation) reveals opposing impacts of increased or decreased 5-HT tones, with low 5-HT supporting spatial encoding but impairing the consolidation of objects and verbal memories. Promising targets for protein synthesis-dependent consolidation enhancements include 5-HT\textsubscript{2a} receptor agonists and 5-HT\textsubscript{4} receptor antagonists, with the latter being of special interest for the treatment of age-related decline. Further implications are pointed out as base for the development of novel therapeutic targets for memory impairment of neuropsychiatric disorders.

\section{Introduction}

The neurotransmitter 5-HT is involved in a wide variety of brain functions and behaviours. This includes the control of physiological activities, such as sleep, stress response, cardiovascular and endocrine functions, the modulation of reward, emotions, mood, and behaviors such as anger, aggression, appetite, pain, sexuality, as well as neuro-psychological processes like perception, attention, and memory (Bacqué-Cazenave et al., 2020). Indeed, this broad spectrum of contributions and the anatomical fact that 5-HT axons in the central nervous system innervate almost every brain region, led to the claim, that – in terms of brain functions – 5-HT “is at once implicated in virtually everything, but responsible for nothing” (Jacobs and Fornal, 1995).

The specific serotonergic participation in learning and memory was first demonstrated by Eric Kandel in the 1970 s. He demonstrated the decisive contribution of 5-HT to memory formation by increasing the level of cyclic adenosine 3',5'-monophosphate (cAMP) in the sensory neurons of Aplysia (Cedar and Schwartz, 1972). This in turn activates the cAMP-dependent protein kinase, which facilitates synaptic transmission in terms of sensitization (Brunelli et al., 1976) and, after repeated stimulations, induces protein synthesis-dependent long-term potentiation (LTP) of synaptic strength (Schacher et al., 1988). Since then, the participation of 5-HT in memory processes has frequently been subject of research and up until today, the 5-HT system is considered as interesting target in the development of therapeutic applications to treat human memory disorders (Buhot et al., 2000; Chakraborty et al., 2019; Meneses, 2013). In addition, dysregulations of the serotonergic system have been associated with drug addiction and the development of declarative drug memories that maintain addictive behaviors such as drug-seeking behavior. Serotonergic treatments therefore may offer
great potential to addiction treatments via attenuation and extinction of otherwise resistant drug memories (Müller, 2013; Müller and Homberg, 2015).

There already exist some reviews about 5-HT and memory (Meneses, 2015; Perez-Garcia and Meneses, 2008; Zhang and Stackman, 2015a, Van Goethem et al., 2015). Nevertheless, a systematic review with a focus on the serotonergic involvement in the modulation of different phases of declarative memories (encoding, consolidation, retrieval) is lacking to date. This overview will thus be grouped into different types of declarative memories to provide a framework that combines knowledge from cognitive psychology and neuropharmacology. This focus on serotonergic modulation of neuronal circuits required for a specific memory process may provide a basis for deriving new hypotheses that will inspire future research and development of therapeutic targets for disorders of the brain involving memory impairment.

1.1. Anatomy of the serotonergic system

Despite its diverse involvement, the ability to synthesize 5-HT is limited to just a few neurons, these account for less than 0.1% of neurons in the mammalian brain (Okaty et al., 2019). The cell bodies of serotonergic neurons are forming clusters in the brain stem, called raphe nuclei, and their long and fine graded axons are widely branched throughout the central nervous system. Of particular interest in this review are ascending projections stemming from the dorsal raphe (DR; B6 and B7) and the median raphe nuclei (MR; BS and B8).

The rostral DR (B7) mainly projects to the extended amygdala, striatum, cerebral cortex, and substantia nigra, whereas neurons of the caudal DR (B6) innervate the (ventral) hippocampus, locus coeruleus and entorhinal cortex. MR axons are targeting predominantly midline structures, including the septo-hippocampal system, (dorsal) hippocampus, tegmental nucleus, interpeduncular nucleus, hypothalamus, and lateral habenula (Hornung, 2003; Jacobs and Azmitia, 1992; Vertes et al., 1999). Raphe projections are topographically organized and adding the complexity of serotonergic forebrain projections, can be further subdivided based on neuronal density, morphology, co-Transmission of other neurotransmitters, genetic signatures, electrophysiological properties and projection areas (Okaty et al., 2019; Ren et al., 2019). The axonal shapes of 5-HT vary according to function and target regions, with MR arising axons beeing characterized by large beaded varicosities (type M axons) while DR axons are predominantly very fine with small, pleomorphic varicosities (type D axons) (Kosofsky and Molliver, 1987). Type M fibres were shown to form direct synaptic contacts, for example to hippocampal GABAergic interneurons (Papp et al., 1999; Varga et al., 2009) in contrast to type D fibres which mainly innervate cortical regions by volume transmission via extra-synaptic serotonin-containing vesicle release (del Cid-Pellitero and Garzón, 2011).

5-HT receptors (5-HTRs) are classified into seven types, 5-HT1 through 5-HT7. The majority of 5-HTRs are postsynaptic with the exception of 5-HT1A Rs and 5-HT2ARs that additionally function as presynaptic autoreceptors. Except 5-HT3Rs, which are ionotropic, all 5-HTRs are coupled to G-proteins. This remarkable diversity within the 5-HT system enables to carry a variety of information and might represent the morphological substratum of the diverse processes modulated by 5-HT (Zachetti et al., 2020).

1.2. Declarative memories and their underlying substrates and mechanisms

Declarative memory refers to the acquisition and retrieval of facts, events, and episodes allowing the remembered material to be compared and contrasted (Squire, 2004). Representations of declarative memories can be accessed flexibly, enabling logical inferences and generalization of experience. One prominent characterization of declarative memory is that it can be decomposed into episodic and semantic memory, a key distinction offered by Tulving in 1972 (Tulving, 1972). An episodic memory trace usually binds together multiple situational aspects of a unique personal experience, such as the time, place, or the social context. In contrast, semantic memory incorporates memory for generic, context-free knowledge which is acquired over multiple occasions and is therefore partly dissociable from the episodic memory system. However, in terms of the underlying neuronal substrates, these forms of memory are closely related and recruit very similar brain structures during their formation – at least in a healthy brain (Ryan et al., 2008). (See also Duff et al., 2020 for a comprehensive review about the episodic vs. semantic memory interdependence and distinction).

Declarative memories have extensively been studied in cases of human amnesia (Squire and Zola, 1998). Out of this context, this term originally refers to memories that can be consciously and verbally stated. Another line of research investigated mnemonic functions of animals in hippocampal-dependent learning and provided additional insights in fundamental mechanisms of declarative memories across species (Eichenbaum, 2000; Eichenbaum et al., 1992). As some phenomenological aspects of the definition of human declarative memory are not transferable to animal models (e.g. linguistic-based behavioral markers of recollection), a more anatomically and biologically based framework was established to promote translational research. In this framework, a functional organization of the declarative memory system was proposed, that considered the medial temporal lobe as a relational processing system whereas parallel “what,” “where” and “when” information is integrated within the hippocampus to represent events in the spatio-temporal context in which they occurred (Dere et al., 2008; Eichenbaum, 2001). The consolidation of information into a persistent trace relies on the prefrontal cortex areas in addition, which also supports the recombination and transfer of experiences to novel events in service of successful behavior (Preston and Eichenbaum, 2013; Zeithamova et al., 2012). This definition encompasses the domain of spatial memory (Buzsáki, 2002; Eichenbaum and Cohen, 2014; Hasselmo and Stern, 2014), trace conditioning (Connor and Gould, 2016), and contextual fear conditioning (Anagnostaras et al., 2001), since those tasks were shown to critically rely on hippocampal system during memory formation.

In the following, we will first review animal studies investigating spatial memory, object memory, and contextual fear memory, while each section is grouped according to effects of lowering and enhancing 5-HT levels and then summarizes the literature on specific 5-HTRs. Subsequently, we will focus on human studies that employed verbal or visual learning tasks, keeping the same structure for grouping serotonergic manipulations as in the animal section.

2. Method

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Page et al., 2021).

2.1. Study eligibility

For an extensive search of literature, we first defined search-terms describing forms of learning that address declarative memories in humans and mammals. Behavioral tasks assessing declarative memories had to fulfill following criteria: the acquisition and storage of the memory is reliant on brain structures of the medial temporal lobe, and further, encoding, consolidation, and retrieval are critical steps of memory processing (Eichenbaum, 2001). Matching task in humans are verbal or visual tasks including the formation of associations between pairs of stimuli or spatial locations, contextual fear conditioning, and pattern or object recognition. Corresponding tasks in animals are novel object recognition, spatial learning tasks (e.g. reference learning), contextual fear conditioning, trace conditioning.
Two different search terms were used to identify human and animal studies:

1. For human studies, we restricted our search to healthy participants and searched PubMed (all years, 101 results, 21.3.2022) and Embase (all years, 36 results, 21.3.2022) using following search strategy: "((serotonin OR 5-HT OR serotonergic) OR 'declarative memory' OR 'episodic memory' OR 'semantic memory' OR 'verbal memory' OR "verbal learning" OR 'visual memory' OR 'contextual fear conditioning' OR 'spatial memory' OR 'spatial learning' OR 'associative learning' OR 'long-term memory' OR 'pattern recognition' OR 'object recognition')", (placebo OR acute OR challenge OR depletion)) NOT (review) NOT (disease). A filter to select only studies with humans was applied for both databases.

2. This search strategy was slightly adapted to obtain equivalent studies for non-human species: ((serotonin OR 5-HT OR serotonergic) ('declarative memory' OR 'episodic memory' OR 'semantic memory' OR 'object recognition' OR 'object memory' OR 'visual memory' OR 'contextual fear conditioning' OR 'trace conditioning' OR 'spatial memory' OR 'spatial learning' OR 'associative learning' OR 'long-term memory')(placebo OR vehicle OR acute OR challenge OR depletion OR deficiency)(animal)) NOT (review) NOT (model of schizophrenia) NOT (model of depression) NOT (model of anxiety) NOT (disease). Like for humans, PubMed (all years, 191 results, 21.3.2022) and Embase (all years, 103 results, 22.3.2022) have been searched. No additional filters were applied. Since for humans the terms "deficiency", "vehicle", and "trace conditioning" did not yield any additional matching results, they were omitted from the search term.

2.3. Inclusion criteria

Studies were identified which matched our definition of declarative memories and then grouped according to population, intervention types, underlying serotonergic mechanisms of actions and form of memory before summarization.

3. Animal studies

3.1. Spatial learning and memory

Spatial learning involves the memorization of landmarks along a route in a cognitive map and their flexible representation during navigation (Tolman, 1948). To evaluate rodent spatial memory, maze learning tasks are widely used. One of the most popular is the Morris water maze (MWM), which assesses hippocampus-dependent reference learning when the animals must search for a hidden platform to escape the maze. It also has a hippocampal independent variant, using a visible platform, that assesses cue learning.

3.1.1. Lowering or depleting 5-HT centrally and globally

Common approaches for lowering central 5-HT include nutritional restrictions and chemical agents. Dietary 5-HT deprivation, for instance, is carried out by substituting nutrition with a drink that contains a mixture of large neutral amino acids but lacks the 5-HT precursor L-tryptophan (TRP). This prevents 5-HT production in brainstem neurons and results in a short-term and reversible reduction of cerebral 5-HT (Hood et al., 2005; Van Donkelaar et al., 2011; Young et al., 1989). Investigations on spatial memory indicated, that acute or chronic (~40 days) nutritional TRP restriction does not affect task performance in the MWM (Lieben et al., 2004; Liu et al., 2013; Uchida et al., 2007) and also not in a radial arm maze (Stancampiano et al., 1997). In line with this, neither the chemical induced attenuation of 5-HT synthesis by the specific and irreversible tryptophan hydroxylase inhibitor p-chlorophenylalanine (PCPA; 300 mg/kg single injection or 400 mg/kg/day×3) nor the serotonergic neurotoxin 5,7-dihydroxytryptamine (5,7-DHT; 150 μg), which selectively destroys 5-HT axons, had any effect on performance in hippocampus-dependent maze learning tasks (Lehmann et al., 2000; Majlessi et al., 2003; Nilsson et al., 1988; Richter-Levin and Segal, 1989). Thus, hippocampal-dependent allocentric spatial memory was not affected across several studies as well as different procedures applied for central 5-HT depletion.
Contrasting results were obtained after repeated 3,4-methylenedioxy-N-methylamphetamine (MDMA) intoxication. Although acutely given MDMA stimulates the release of 5-HT, its repeated administration within a short time frame inhibits 5-HT synthesis and therefore provokes 5-HT depletion (Lyles and Cadet, 2003). Such a regimen (15 mg/kg x 4 doses MDMA in one day) caused deficits in the Cincinnati water maze and, to a lesser extent, long-term impairments in an MWM reversal learning task (Able et al., 2006).  

We briefly mentioned some factors that may account to those contradictory outcomes between MDMA and other 5-HT depletion methods. The Cincinnati water maze, which involves egocentric route-based learning, as well as the MWM reversal learning task are both suggested to rely on the striatum (Braun et al., 2015; Castañé Anna et al., 2010). By contrast, allocentric learning in the MWM reference memory version is assumed to mainly rely on the dorsal hippocampus (Miayoshi et al., 2012; Morris et al., 1982). Able et al. (2006) reported a decrease of dopamine (DA) in the striatum indicating a contribution of dopaminergic interactions in MDMA-induced egocentric spatial memory impairments. A similar pattern was found in adult rodents receiving chronic MDMA treatment during development (Williams et al., 2003). In a further egocentric spatial navigation task, facilitated task acquisition after selective striatal 5-HT depletion (using 5,7 DHT; 25 mg/kg) was observed and this effect was abolished by DA antagonists (SC-23 900 or spiperone) (Anguiano-Rodríguez et al., 2007). This implies that the deterioration in spatial performance may be mediated by a concomitant influence on striatal DA tone following MDMA-induced 5-HT depletion with concomitant learning being more severely affected.

3.1.2. 5-HT depletion in selective regions

Selective depletion of 5-HT from the medial septum (MS)/diagonal band of the brocca or from the hippocampus facilitated spatial task acquisition in the Morris water maze (Gutierrez-Guzman et al., 2011, 2017; Hernández-Pérez et al., 2015). For this, 5,7-DHT was injected into the target region and in addition, hippocampal electroencephalography (EEG) was measured during task performance. Improved spatial task acquisition was accompanied by earlier expression of dominant high frequency theta oscillations during training and increased theta coupling coherence between the MS-hippocampus and the MS-mammillary nuclei. Theta oscillations are critical for spatial cognition, serving the integration of information from separate functional units during mnemonic processes (Korotkova et al., 2018). Accordingly, in a state of low central 5-HT, facilitated communication between task-involved regions could promote information processing. Indeed, spatial encoding was improved, primarily during the initial phase of learning, as expressed in behaviour (Gutierrez-Guzman et al., 2011, 2017). Hippocampal theta involvement was thereby specified for spatial reference memory necessitating the use of cognitive maps, whereas cue learning remained unaffected (Olivera-Cortés et al., 2002).

However, when depleting 5-HT from the supra-mammillary nucleus (SUM), inefficient MWM performance was evident. Hippocampal high-frequency theta was abolished during MWM training and facilitated high-frequency theta oscillations during training and increased theta coupling coherence between the MS-hippocampus and the MS-mammillary nuclei. Theta oscillations are critical for spatial cognition, serving the integration of information from separate functional units during mnemonic processes (Korotkova et al., 2018). Accordingly, in a state of low central 5-HT, facilitated communication between task-involved regions could promote information processing. Indeed, spatial encoding was improved, primarily during the initial phase of learning, as expressed in behaviour (Gutierrez-Guzman et al., 2011, 2017). Hippocampal theta involvement was thereby specified for spatial reference memory necessitating the use of cognitive maps, whereas cue learning remained unaffected (Olivera-Cortés et al., 2002).

Moreover, suppression of theta, regulation of hippocampal ripple oscillations as well as memory consolidation were demonstrated to be crucially modulated by MR 5-HT neuronal activation (Wang et al., 2015).

3.1.3. Enhancement of 5-HT globally

Acutely administered selective serotonin reuptake inhibitors (SSRIs) block 5-HT reuptake and increase its levels in the extracellular space (Walker, 2013). Regarding spatial memory, SSRI administration was robustly associated with performance deteriorations. Acute dosage with citalopram (10 and 20 mg/kg) before MWM training caused spatial reference memory deficits (Mutlu et al., 2011) and pretraining citalopram (5 and 10 mg/kg) impaired long-term retention in the Y-maze test (Bridoux et al., 2013). Further, a dose-dependency in the effects of SSRI on maze-learning was revealed. Accordingly, MWM acquisition and navigation were impaired after pretraining treatment with citalopram (4 and 8 mg/kg), fluoxetine (8 and 16 mg/kg) or alaprocate (7.5 and 20 mg/kg), whereby lower doses had no impact (Majlesi and Noohi, 2002; Riekkinken et al., 1991). The distinction between acute and chronic administration does not seem to be necessarily important, as a consistent effect was still replicated after 4 weeks of fluoxetine (0.7 mg/kg per day) treatment (Ampuero et al., 2013).

3.1.4. 5-HT1A/1B

The 5-HT1A receptor is one of the most studied serotonergic receptors to date (e.g., Glikmann-Johnston et al., 2015). There exists strong evidence for 5-HT1A receptor involvement in spatial memory. When animals had to perform an Atlantis Water maze, pro-cognitive effects during encoding were found after dosing with a selective and silent 5-HT1A antagonist (WAY-101 405; 1, 3, 10 mg/kg) (Hirst et al., 2008). In another study, however, the 5-HT1A antagonists NAD-299 (0.05, 0.15, 0.5 and 1.5 mg/kg) and WAY-100 635 (0.3 and 1 mg/kg) failed to alter MWM performance (Lütten et al., 2005). The selective infusion of 8-OH-DPAT (0.5 µg) into the MS worsened MWM performance (Bertrand et al., 2000) but deficits were reversed by injecting WAY-100 635 at the same site. Interestingly, the variation of the time-points when infusing 8-OH-DPAT into the MS (pre-training, post-training, 2 h after training, before probe-trial) unveils, that 5-HT1A R of the MS contribute to a 5-HT-mediated mechanism involved in encoding and in consolidation, but not retrieval of spatial hippocampal-dependent knowledge. Specifically, 8-OH-DPAT infusion into the MS hindered encoding and the protein synthesis-dependend, late-phase consolidation processes (Koenig et al., 2008). The effect was suggested to be mediated through an 8-OH-DPAT-induced hyperpolarisation of cholinergic and/or GABAergic and/or glutamatergic neurons in the MS-hippocampal neuronal pathway (Bertrand et al., 2000; Koenig et al., 2011).

Consequences of persistent alterations in 5-HT1A expression were investigated in transgenic mouse models. 5HT1A KO mice exhibited spatial memory impairments but intriguingly, this was only obtained in tasks requiring the integrity of hippocampal functions (Sarnyai et al., 2000). As contributing factors, the absence of 5-HT1A autoreceptors was identified (Wolff et al., 2004) and/or long-term developmental plastic adaptions such as altered hippocampal CA1 GABAergic transmission (Sarnyai et al., 2000) were suggested. Spatial performance of 5-HT1A KO seems to be age-dependent, since deficits were obvious in young adult (3 months) but not older (22 months) 5HT1A KO mice. This is possibly attributable to an age associated compensation of reduced cholinergic activity by the 5-HT1A KO mutation (Wolff et al., 2004). Likewise, elevations of hippocampal acetylcholine after acute dosage of WAY-101 405 (10 mg/kg) have been reported (Hirst et al., 2008).

1. MDMA studies with mice are omitted in this review given that MDMA is mainly neurotoxic for the dopamine system instead of the 5-HT system in mice, which is in contrast to other species (Logan et al., 1988).
Overexpression of 5-HT1AR did not affect spatial learning. 8-OH-DPAT (0.3 mg/kg) administration in transgenic mice, however, resulted in a higher sensitivity for MWM task failures. Those might be mediated by the surplus of postsynaptic heteroreceptors in projection areas of 5-HT neurons such as the hippocampus and outer cortical layers (Bert et al., 2009).

There are only two studies on 5-HT1Rs and their role in spatial memory. Both investigations observed improved long-term performance in 5-HT1R KO mice which was specifically evident in the hippocampus-dependent reference version of the MWM, but not in the cue-guided visual version (Buhot et al., 2003; Malleret et al., 1999). This effect was stronger at increased task complexity and even persisted with older age. Those findings indicate pro-cognitive influences of 5-HT1R genetic deletion on spatial memory and even a protective effect on age-related hippocampal-dependent memory decline.

3.1.5. 5-HT2AR
Activation of 5-HT2AR was associated with impaired spatial memory encoding and retrieval. Acute dosing with the 5-HT2AR agonist TCB-2 (1 mg/kg) before the probe trial delayed the initiation of spatial search behavior, which is required to escape the MWM in the reference version, without affecting cue memory. In addition, those findings were accompanied by diminished long-term stability of hippocampal CA1 place fields especially for the novel environment, but not for pre-existing place cell firing maps. Those effects were prevented by the 5-HT2AR antagonist MDL 11 939 (0.5 mg/kg) (Zhang et al., 2017). Similar findings were obtained using the 5-HT2AR agonistic action psilocin, which impaired encoding in the Carousel maze (1 and 4 mg/kg) and retrieval in the MWM (4 mg/kg) after previous drugfree acquisition (Rambousek et al., 2014). Blockade of hippocampal CA1 5HT2ARs by ritanserin (4 μg) improved learning in spatial version of MWM. According to the authors, ritanserin might act on GABA interneurons and disinhbit cholinergic transmission and/or prevent 5-HT induced inhibition on CA1 pyramidals neurons (Naghdi and Harooni, 2005). In line with this finding, no navigational deficits were found in 5-HT2AR KO mice in several spatial memory tasks (Morici et al., 2015).

3.1.6. 5-HT4R
The blockade of hippocampal CA1 pyramidal neuron 5HT4Rs by granisetron (0.25 μg) caused impairments in the MWM (Naghdi and Harooni, 2005). Another investigation, however, found spatial navigation being improved after application of the 5-HT4R antagonist ondansetron (doses between 100 and 1000 μg/kg) (Staubli and Xu, 1995).

3.1.7. 5-HT5R
There is one investigation on 5-HT5R signalling providing evidence for a bidirectional impact on memory formation. Accordingly, the agonist BMW8 (30 mg/kg) enhanced plasticity on the Schaffer collaterals and improved performance in an MWM. The specific antagonist GR125487 (10 mg/kg), on the other hand, impaired synaptic potentiation and in consequence, spatial memory was attenuated (Teixeira et al., 2018).

3.1.8. 5-HT7R
5-HT7R antagonists produced beneficial effects on spatial learning (Da Silva Costa et al., 2008; SB-27 104 610 mg/kg; Rogers and Hagan, 2001; SB-271 046-A or SB-357 134-A, 10 mg/kg). Acute dosage prolonged the retention MWM reference memory (Rogers and Hagan, 2001) and further, improved acquisition and consolidation of spatial recognition in the Y-maze in young adult mice. In addition, 5-HT7R antagonism counteracted age-related consolidation deficits of spatial recognition memory in older mice (18–21 months) (Da Silva Costa et al., 2008; Foley et al., 2004). In another examination, Long-Evans rats (2 years old) were tested in a clinical trial-like design. For this, a “patient population” was created by increasing the difficulty of the task step-by-step. In this, sub-chronic treatment (13 days) with the 5-HT7R antagonist RO-4 368 554 (3 mg/kg per day) did not yield any effects on spatial cognition (Gyertyán et al., 2020). Nevertheless, another investigation pinpointed the cognition-enhancing effects of the 5-HT7R antagonist (SB-27 104 610 or 20 mg/kg per day for 40 days) on the acquisition and recall of a spatial learning task following chronic drug administration in a population of aged rats (Foley et al., 2004). Together, 5-HT7R antagonists might still be an interesting target for cognitive enhancement and memory improvement especially in some age-related dysfunctions.

3.1.9. 5-HT3R
In 5-HT3R KO mice, long-term memory formation, memory consolidation, and memory retrieval of a Barnes maze were unaffected, suggesting that this receptor is not critical for spatial memory in general. However, 5-HT3R KO mice were less efficient in accommodating to changes in spatial arrangement as evident in reversal learning. When changing the location of the escape hole, 5-HT3R KO mice displayed perseverative behavior. Therefore, a role for the 5-HT3R in the adjustment of neuronal networks to changes in environments was suggested. In line with this, the ability to perform a switch from a striatal-dependent egocentric cognitive strategy towards a hippocampus-dependent allocentric cognitive strategy while solving a spatial task was reduced (Roberts et al., 2004; Sarkisyan and Hedlund, 2009).

3.2. Summary
In general, global lowering of 5-HT levels did not affect spatial learning except when using MDMA as depleting agent. Sub-chronic MDMA administration might particularly affect spatial tasks whose performance is additionally modulated by the striatal DA tonus. Global enhancement of 5-HT by SSRIs worsened spatial performance. Interestingly, the serotonergic tonus in the SUM might be important for memory consolidation. By contrast, high levels of 5-HT in the MS hampered encoding/consolidation but low levels supported encoding. MS 5-HT levels were additionally related to increases in theta frequency and coherence suggesting a role for 5-HT as hippocampal theta modulator. Studies investigating specific receptors revealed mostly conflicting results, but acute administration of 5-HT3R antagonists might improve spatial learning performance.

3.3. Object recognition
Novel object recognition is usually assessed by letting the animal deeply explore two objects (sample session) and afterwards, replacing one object with a new object (test session). Rodents have a natural proclivity to explore novel, non-threatening objects and therefore, the time spent exploring the new object in comparison to the old object is considered as valid measurement for novelty recognition (Cohen and Stackman, 2015). Although the hippocampus and amygdala were once thought to be critical contributors to object recognition memory, recent systematic studies have revealed the greater importance of temporal cortical areas, with particular emphasis on perirhinal cortex. While the hippocampus clearly contributes to the performance of object recognition tasks under certain, as yet not fully understood conditions, it does not appear to be required for the familiarity-based recognition of object information per se (Winters et al., 2008).

3.3.1. Lowering or depleting 5-HT globally
In contrast to in spatial learning, global cerebral serotonin deficiency was quite consistently related to object recognition impairments. A bunch of evidence using acute TRP depletion observed object recognition impairments, that have been evident 2 – 6 h after the first treatment (Jans et al., 2007, 2009, 2010; Lieben et al., 2004, 2005a; Olivier et al., 2008; Rutten et al., 2007; van Donkelaar et al., 2008). Similar findings were obtained after 21 days of a TRP-free diet (Jenkins et al., 2010). In addition, TRP depletion decreased 5-HT levels in brain structures that
incorporate a crucial role in memory, such as the hippocampus and the frontal cortex (Jans et al., 2007; Jenkins et al., 2010; Olivier et al., 2008). The observed effects of TRP depletion were even more pronounced in rodents with pre-existing abnormal 5-HT function (Olivier et al., 2008). Importantly, sex and estrous cycle phase were demonstrated to influence the behavioral response to TRP depletion whereby females in pro-estrus/estrous exhibited the strongest object recognition deficits after acute TRP depletion (Jans et al., 2007). Notably, a possible strain dependence of animals in TRP effects was suggested as well (Jans et al., 2010).

Those findings were not obtained in two examinations using other chemical agents for cerebral 5-HT depletion. One study applied a subcutaneous p-chloroamphetamine (PCA) regimen (5 mg/kg) and tested animals in an object recognition task one week later. Object recognition remained intact, even though SEKT binding in the hippocampus and perirhinal cortex was decreased in depleted animals (Belcher et al., 2005). In another investigation repeated MDMA treatment (15 mg/kg x 4 doses in one day) produced substantial reductions of 5-HT and 5-HIAA concentrations in the whole brain including the hippocampus and the prefrontal cortex. Nonetheless, object recognition performance was not impaired (Able et al., 2006). By contrast, (Morley et al., 2001) compared a high dose MDMA regimen (4 × 5 mg/kg, over 4 h on each of 2 consecutive days) with a moderate dose regime of MDMA (1 × 5 mg/kg on each of 2 consecutive days). Animals were then tested in a novel object recognition task 14 weeks after drug administration. After 15 min retention, deficits were evident in the high dose group. The authors of this study considered neurotoxic effects due to the high MDMA dosage as an explanatory factor.

Object recognition was also impaired in a hypo-serotonergic mouse model (Pet1KO) at delayed recalls (90 min and 2 h). Measurements of field excitatory postsynaptic potential (fEPSP) at Schaffer collaterals during task performance revealed exaggerated LTP mechanisms in Pet1KO mice compared to a control group. Increases in fEPSP amplitudes were observed directly after training and were even strikingly larger after 5 h. To note, no alterations in hippocampal theta or gamma oscillations were found in this study. Further, novel object recognition deficits have been restored by increasing global 5-HT levels through genetic inhibition during task performance (Fernandez et al., 2017).

A whole, a bunch of evidence reliably related acute lowering of 5-HT levels by TRP depletion, but not more direct 5-HT depletion methods, to object recognition impairments. We will briefly mention some possible reasons for the discrepancies reported beyond depletion regimens. In this strain specific variations might play a role. For example, Able et al. (2006) and Belcher et al. (2005) used Sprague-Dawley rats for their examinations. In contrast to other strains (e.g. Morley et al., 2001), Sprague-Dawley rats have been found to be less vulnerable to 5-HT associated object recognition deficits (Jans et al., 2007). Moreover, Able et al. (2006) used a rather short retention time (1 h), compared to other studies (e.g. Lieben et al., 2004, 2005b [4 h, 24 h]; Rutten et al., 2007 [3 h]; Jans et al., 2009 [2 h, 4 h, 6 h]). This pinpointed a role of 5-HT specifically in late phase consolidation processes.

### 3.3.2. Enhancement of 5-HT globally

In line with the experimental findings on spatial learning, the acute increase of central 5-HT tones by SSRI treatment resulted in worse object recognition performance. In this regard, fluoxetine (10 mg/kg) was demonstrated to increase the extracellular 5-HT concentrations, e.g. in the medial prefrontal cortex (mPFC), and impaired performance of mice in the object recognition 24 h post-administration (Castañé et al., 2015; Flores-Burgess et al., 2019).

### 3.3.3. 5-HT1A/1B<sup>R</sup>

A role of 5-HT<sub>1A</sub>/R<sub>1B</sub> in object recognition was pointed out. In this regard, the treatment with 5-HT<sub>1A</sub>R antagonists (WAY-101 405: 1.0–10 mg/kg or WAY-100 635: 1.0 mg/kg) prolonged memory span in object recognition up to 48 h (Hirst et al., 2008; Pitsikas et al., 2003). These promoting effects were observed regardless of the time of administration, which took place either before the acquisition, storage, or retrieval. Accordingly, 5-HT<sub>1A</sub>R antagonists likely restore time-related object recognition deficits overall and not specific to memory phases (Pitsikas et al., 2003). To determine the unique contribution of 5-HT<sub>1A</sub> autoreceptors and heteroreceptors on object recognition, Van Goethem et al. (2015) used ‘biased agonists’ which preferentially activate only one of these subtypes. They challenged mechanisms of hippocampal pattern separation with an object-in-context recognition version of object recognition. The results described a bell-shaped dose response curve for both agents. Activation of postsynaptic 5-HT<sub>1A</sub> heteroreceptors (with F15599) positively affected object recognition at a midrange dose (0.04 mg/kg), whereas higher and lower doses tended to impair performance. Activation of 5-HT<sub>1A</sub> autoreceptors in raphé (with F13714) impaired object recognition at concentrations of 0.0025 or 0.01 mg/kg, with no effects at other doses. Together, those findings indicate that object recognition performance might benefit from activation of 5-HT<sub>1A</sub> heteroreceptors (Van Goethem et al., 2015). On the contrary, the genetic deletion of 5-HT<sub>1B</sub>Rs did not change object recognition performance (Malleret et al., 1999).

### 3.3.4. 5-HT<sub>2A/2C</sub>R

Systemic 5-HT<sub>2A</sub>/2C activation (TCB-2; 1.0 mg/kg) enhanced the consolidation of object memory. The strongest impact on object recognition performance was reported when the agent was given directly after object memory acquisition. Pre-treatment with a 5-HT<sub>2A</sub> antagonist (MDL 11 939) diminished this effect. Since memory consolidation in its initial stages is thought to start right after learning, this finding suggests that TCB-2 likely strengthened the nascent object memory (Stackman et al., 2013). In line with this, activation of 5-HT<sub>2A</sub>R was associated with increases of extracellular glutamate efflux and facilitated induction of synaptic plasticity (Zhang et al., 2016).

The ability to remember the spatial context or the temporal order of objects was demonstrated to rely more heavily on the hippocampus than the usually applied simple object recognition procedure (Balderas et al., 2008; Forwood et al., 2005). To challenge hippocampal functions as such, animals were trained to remember object-in-context combination or the temporal-order-of objects, that necessitate the recollection of conjunctive ‘what’ or ‘when’ and ‘which context’ representations at test. Specific and retrieval associated deficits for object-in-context recognition were found after the selective blockade of 5-HT<sub>2A</sub>Rs (MDL 11 939) in the mPFC (Bekinschtein et al., 2013) and the same findings were obtained in 5-HT<sub>2A</sub>R KO mice (Barre et al., 2016; Morici et al., 2015), whereas the conventionally applied object recognition procedure remained unimpaired (see also Castané et al., 2015). Their role in retrieval-related deficits was supposed to be mediated by imbalances of 5-HT concentrations in the mPFC. A detrimental excess of 5-HT is likely due to increased 5-HT<sub>2A</sub>R activation, as observed in the absence of 5-HT<sub>2A</sub>R signalling (Castané et al., 2015; Morici et al., 2015).

Prefrontal-hippocampal circuit are essential for the encoding and retrieval of declarative memories, and the specific role of 5-HT<sub>2A</sub>Rs herein was further pinpointed. Bekinschtein et al. (2013) injected rats either ipsilateral, contralateral, or bilateral with the 5-HT<sub>2A</sub>R antagonist MDL 11 939 in the mPFC and/or muscimol in the hippocampus. They found that both, the 5-HT<sub>2A</sub>Rs in the mPFC and 5-HT<sub>2A</sub>R activity in the
hippocampus are necessary for the correct solution of the object-in-context task. In addition, contralateral infusion of both agents resulted in performance deficits, whereas ipsilateral infusions, which leave the more dominant interactions between the mPFC and the hippocampus intact (Churchwell and Kesner, 2011), had no impact. Crucially, the restoration of object-in-context recognition performance in 5-HT\textsubscript{2A}R KO mice was possible using a viral gene-delivery approach. After the re-expression of 5-HT\textsubscript{2A}Rs at presynaptic sites in the medi-odorsal thalamus, no more differences to wild-type mice have been evident (Barre et al., 2016). Morici et al. (2015) demonstrated a role for mPFC 5-HT\textsubscript{2A}Rs in the selection of the correct memory trace during retrieval. Together, these findings strikingly suggest a necessary engagement of 5-HT\textsubscript{2A}Rs in prefrontal-hippocampal circuits, incorporating a role specific to the retrieval of contextual elements in episodic memories.

Pro-cognitive effects in object recognition were also demonstrated after selective blockade of 5-HT\textsubscript{2A}Rs. Specifically, SB 242 084 (0.63, 2.5 and 10 mg/kg) prolonged object recognition memory duration up to 24 h (Bertaina-Anglade et al., 2011).

3.3.5. 5-HT\textsubscript{4}R

Systemic activation of 5-HT\textsubscript{4}R yielded beneficial effects on object memory. In general, 5-HT\textsubscript{4}R agonists have been shown to improve acquisition and consolidation in several mnemonic domains (e.g. Hagena and Manahan-Vaughan, 2017), which also applies to object recognition tasks. Acute and sub-chronic activation (14 days) of the 5-HT\textsubscript{4}R with the partial agonist RS-67 333 extended memory traces in the novel object recognition task. This was suggested to result from a functional interaction between the cholinergic and serotonergic system, which is mediated by the nucleus basalis magnocellularis (NBM). Regarding this, the local intra-NBM infusion of RS-67 333 enhanced the acquisition and the consolidation of place recognition memory but did not affect recall. These effects were reversed by pre-treatment with the selective 5-HT\textsubscript{4}R antagonist RS-39 604 (Orsetti et al., 2003; Quiedeville et al., 2015).

3.3.6. 5-HT\textsubscript{7}R

Evidence of 5-HT\textsubscript{7}R on object recognition revealed mixed results, but quite a bunch of studies reported prolongations of object memory after treatments with 5-HT\textsubscript{7}R ligands. Acute dosage with 5-HT\textsubscript{7}R antagonists (Ro 04–6790 and SB-271 046; both: 10 mg/kg) shortly before, or directly after the object recognition sample session, improved object memory acquisition and/or consolidation and prolonged the duration of the memory (up to 4 h). No effects were evident when the administration took place before the test session (Kendall et al., 2011; King et al., 2004, 2009). Similar findings where obtained after 14 days sub-chronic antagonistic treatments (Mitchell et al., 2009; Ro4368554 [5 mg/kg]; Quiedeville et al., 2015; SB-271 046 [10 mg/kg]). In addition, Ro4368554 (3 mg/kg or 10 mg/kg) was able to reverse object recognition retention deficits within 1 h delay in a serotonergic deficiency model (TRP-restriction regimen) (Lieben et al., 2005a). Those beneficial effects on object recognition were suggested to be mediated via MR innervated brain regions. Accordingly, the selective lesioning of the MR – but not the DR – completely abolished the effects of a 5-HT\textsubscript{7}R antagonist (Ro 04–679 010 mg/kg) (King et al., 2009). However, it is worth mentioning that together, the abovementioned enhancing effects on retention were rather short-lived and absent with longer inter-trial intervals (up to 24 h) (Gyertyan et al., 2026; Lieben et al., 2005b) or non-evident within a very short inter-trial time interval (1 min) (Woolley et al., 2003).

At first glance, it might be paradoxical, that agonistic ligands such as E-6801 (5 or 10 mg/kg) and EMD-386 088 (10 mg/kg) were shown to enhance object recognition memory as well. This was true, even when given together with sub-effective dose of the 5-HT\textsubscript{4}R antagonist SB-271 046. The closer inspection on this phenomenon revealed distinct contributions of agonistic and antagonistic agents to object recognition. One plausible explanation is, that agonists directly amplify the action of 5-HT\textsubscript{4}Rs on glutamatergic and/or cholinergic neurones whereas antagonists attenuate active serotonergic input to upstream inhibitory GABAergic neurones, which in turn disinhibit glutamate and/or acetylcholine release. Thus, both agents may elevate glutamate and/or acetylcholine release and augment object memory albeit via distinct mechanisms of action (Kendall et al., 2011).

3.3.7. 5-HT\textsubscript{6}R

A role in novelty detection for 5-HT\textsubscript{6}Rs was indicated. Accordingly, both pharmacological blockade (SB-269 970; 10–15 mg/kg) and genetic inactivation resulted in a lack of behavioral response to novel objects and novel environments without altering habituation behavior. In addition, the tendency to actively seek novelty was inversely correlated with 5-HT\textsubscript{6}R gene expression in pivotal areas for information trafficking, such as thalamo-cortical projection areas and the dorsal hippocampus (Ballaz et al., 2007; Sarkanen and Hedlund, 2009). On the other hand, 5-HT\textsubscript{6}R activation LP-211 (0.25 mg kg-1) improved the consolidation of chamber-shape memories after the sample session. This was evident in the subsequent novelty-preference test where ameliorated chamber recognition memory was observed that persisted up to 24 h (Beaudet et al., 2017).

3.4. Summary

Global 5-HT lowering or elevation impaired object memory, except in two studies where MDMA or PCA, respectively, was administered to achieve central depletion. 5-HT\textsubscript{4}R and 5-HT\textsubscript{2C}R antagonists prolonged the memory of the object unspecific to any memory phase. 5-HT\textsubscript{2A}R, 5-HT\textsubscript{4}R and possibly 5-HT\textsubscript{R} agonists as well as 5-HT\textsubscript{4}R ligands enhanced its acquisition and/or consolidation. Concordantly, blockade of 5-HT\textsubscript{2A}Rs worsened object memory and underlined the involvement of 5-HT\textsubscript{2A}Rs in hippocampal - prefrontal circuits as modulators of synaptic plasticity and memory consolidation.

3.5. Contextual fear conditioning

Contextual fear conditioning can be described as a type of associative learning that involves a strong emotional arousal due to the sudden application of a painful stimulus in a specific spatial context. Contextual fear conditioning accounts for an episodic-like memory in its extended definition, since successful learning and retrieval can be inferred from behavioral expressions referring to the content (what), place (where), and temporal context (sequence of events) (Pause et al., 2013). It requires the normal function of the hippocampus, where the contextual element is stored, and the amygdala. Cued fear conditioning instead builds an associative memory between a tone and fear, it requires normal function of the amygdala only (Kim and Fanselow, 1992). While the former is dependent on a specific context (place) as a conditioned stimulus for fear induction, the latter is context-independent in the sense that the cuing stimulus triggers fear behaviour no matter where it is perceived.

3.5.1. Lowering or depleting 5-HT globally

Some studies obtained contextual fear conditioning impairments after acute central 5-HT depletion that were evident in reduced freezing behavior of rodents at the test session. It was thereby irrelevant, whether 5,7-DHT (25 mg/kg) (Matsumoto et al., 2004) or TRP dietary restriction (Uchida et al., 2007) was applied as depleting compound. Contextual fear conditioning deficits were apparent 2 h, 24 h, and 3 weeks after acquisition. No behavioral alterations have been obtained during training and 30 min afterwards at the first test session, indicating that 5-HT deficiency did not affect contextual fear conditioning acquisition or baseline anxiety levels. Crucially, animals did also not differ in a cued fear conditioning paradigm, where – as mentioned above - the hippocampal-dependent processing of the contextual component is lacking (Uchida et al., 2007). Taken together, those findings suggest that
acute central 5-HT deficiency might impair the hippocampal-dependent, but not
the amygdala-dependent, processes that are involved in the consolidation of contextual fear memory.

Contrasting results were obtained in mice with a constitutive lack of central 5-HT. Such mice were generated, for example, by a region-specific conditional KO of the transcription factor Lmx1B and consequently, those mice are lacking essentially all central 5-HT neurons and 5-HT levels are decreased to a level of <10%. Another approach is the targeted inactivation of the neuronal tryptophan hydroxylase-2 (Tph2) gene. Such Tph2 null mutant (Tph2−/−) mice lack the capability to synthesize 5-HT specifically in the brain (Gutknecht et al., 2009). Both variants of genetic manipulations in mice provoked greatly enhanced contextual fear memory. Tph2−/− mice displayed a faster acquisition of conditioned fear, as well as enhanced contextual representation of the fear memory, but normal functional extinction of the context (Gutknecht et al., 2015; Waider et al., 2019). In conditional KO mice, exaggerated contextual fear memory was diminished after injecting 5-HT into the lateral ventricles or by administration of the 5-HT1A agonist 8-OH-DPAT (Dai et al., 2008). The examination of immediate-early gene expression (c-Fos imaging) and electrophysiological recordings in the dorsal hippocampus (dHip) of Tph2−/− mice emphasized that lifelong 5-HT deficiency renders the dHip hyperexcitable in fear conditioning (Waider et al., 2019). These observations are in accordance with the finding of exaggerated LTP at Schaffer Collaterals after high-frequency stimulation in the 5-HT deficient Pet1KO mouse model (Fernandez et al., 2017). In this sense, exaggerated context-dependent fear memory likely involves dysfunctional raphe-hippocampal 5-HT innervation, which may result in the failure of 5-HT receptor-mediated inhibition of hippocampal circuitry. Of note, female Tph2−/− mice, in contrast to males, displayed increased stress vulnerability and depression-like behavior, suggesting additional sex-hormone-dependent interactions between female and male behavioral responses to central 5-HT deficiency (Gutknecht et al., 2015). In sum, the abovementioned results support the view of a direct relationship between 5-HT levels and contextual fear memory. However, whereas in the case of a chronic 5-HT deficit since birth, contextual fear memory was exaggerated, the opposite was true in case of an acutely induced deficit by 5-HT depletion, which specifically deteriorated the storage of the contextual element in the hippocampus. Yet, under both conditions, cued fear conditioning remained unaffected (Fernandez et al., 2017; Uchida et al., 2007), this was also true when using 5,7-DHT for central 5-HT deficiency induction (Romano et al., 2006).

3.5.2. Enhancement of 5-HT globally

Acute or chronic SSRI treatment before contextual fear conditioning training revealed mixed behavioral responses. Escitalopram 1 mg/kg (but not 0.5 and 5 mg/kg) given 30 min before training increased freezing time in the retention test 24 h after acquisition. However, when escitalopram 1 mg/kg (but not 0.5 and 5 mg/kg) was administered the next day after acquisition, 30 min before the test session, reduced freezing time was evident. To elucidate the effect on memory consolidation, escitalopram (5 mg/kg; but not 0.5 and 1 mg/kg) was given immediately after the acquisition phase which induced augmentation of freezing at the retention test held on next day. Of note, escitalopram did not affect baseline freezing behavior at any dose tested. This demonstrates that contextual fear conditioning is affected differently and dose-sensitively by central 5-HT tone depending on the mnemonic phase (Montezinho et al., 2010). Moreover, investigation showed that acute, sub-chronically (21 days; 7 mg/kg; 18 doses) after having been subjected to contextual fear conditioning. Contextual fear conditioning acquisition (over 3 days) took place in a box with the contextual element being represented by a specific odor and using eyelid-shocks as an unconditioned stimulus. Following three weeks of fluoxetine treatment (7 mg/kg), they were re-exposed to the conditioning context. In this investigation, SSRI treatment failed to abolish conditioned freezing to contextual stimuli. However, fluoxetine treatment restored electrophysiological baseline activity of fimbria-CA3 synaptic efficacy and furthermore, when animals where re-exposed to the fear context after successful extinction training, fear learning potentiation was suppressed. This finding suggests a protective effect of fluoxetine on conditioned fear and stress-induced disturbances of hippocampal plasticity (Spennato et al., 2008).

3.5.3. 5-HT1A/1B

During stressful conditions, protective functions of endogenous 5-HT were shown, by decreasing the firing activity of hippocampal CA1 pyramidal neurons (McEwen and Magarinos, 1997). The 5-HT1A antagonists WAY-100 635 (0.2 mg/kg) and WAY-100 135 (5 mg/kg) abolished the decrease in firing frequency during conditioning, yet without affecting contextual conditioning-induced freezing behavior at retrieval (Tada et al., 2004). Congruently, the selective intra-hippocampal activation of postsynaptic 5-HT1A receptors by injection of flecainoxan (3 µg) reduced the expression of conditioned fear (Li et al., 2006). Moreover, the MR – hippocampal pathway was associated with reduced fear responses evoked by contextual but not acoustic sensory stimuli. This finding was obtained after selective 8-OH-DPAT microinjection into the MR (1 µg/0.5 µl saline), which underlines the involvement of 5-HT1A receptors during the process of memory formation of conditioning fear associated with aversive contexts (Avanzi and Brandán, 2001).

The one investigation on 5-HT1A KO mice revealed no alterations of contextual fear conditioning compared to wild-type controls (Mallaret et al., 1999).

3.5.4. 5-HT2A

Stimulation of 5HT2A receptors was found to facilitate consolidation and extinction of fear memories in a trace fear conditioning task. Trace fear conditioning demands the CS and the US to be associated over a stimulus-free interval known as the “trace” and are thereby thought to be functionally and morphologically incorporated by hippocampal neurons. It was found that post-conditioning activation of 5-HT2A receptors by TCB-2 (1 mg/kg) enhanced consolidation of the fear memory, whereas post-conditioning blockade of 5-HT2A receptors by MDL 11 939 (0.5 mg/kg) yielded a tendency towards less freezing. Both ligands had no effects when administered right before encoding or retrieval (Stackman et al., 2013). 5-HT2A receptor activation facilitated consolidation in fear condition, was further shown in cued and Pavlovian eyelid conditioning, indicating that 5-HT2A receptor activation is not specifically related to the contextual element but to associative learning (Romano et al., 2006). In addition, dosing animals with TCB-2 (1.0 mg/kg) before training facilitated the extinction of the non-hippocampus-dependent cued delay fear memory and by contrast, MDL 11 939 (0.5 mg/kg) delayed the recovery of freezing in mice (Stackman et al., 2013). Taken together, reported studies indicate a rather general role for 5-HT2A receptors in memory consolidation and extinction. Nonetheless, it is conceivable that 5-HT2A receptor activation facilitates hippocampal glutamate transmission (Zhang and Stackman, 2015b), thereby promoting the information transmission and retention in mnemonic circuits in support of consolidation including the hippocampus, lateral amygdala and mPFC.

3.5.5. 5-HT7

In 5-HT7R KO mice, a specific impairment of contextual fear conditioning was found, sparing other forms of learning such as spatial learning, cued and operant conditioning (Roberts et al., 2004). The dissociation between contextual-based learning and the cued fear conditioning indicates, that more complex integrative learning mechanism involving contextual processing, may rely on 5-HT7 receptors. Dissociations between spatial learning and contextual fear conditioning have been previously reported (Cho et al., 1998; Clark et al., 2008). This complementing finding of Roberts et al. (2004) might indicate a deficit in place learning that is distinct from spatial processing and navigation, with 5-HT7 receptors playing a role.
3.6. Summary

Central or hippocampal 5-HT elevations may protect against hypersensitivity to contextual fear learning in cases of innate 5-HT deficiency by reducing pyramidal cell firing in the CA1 region. 5-HT sensitivity to contextual fear learning in cases of innate 5-HT deficiency by 3.6. Summary

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Specifically, activation of 5-HT receptors or inhibition of 5-HT receptors appears to facilitate contextual memory processes in a cortico-limbic circuit.

3.7. 5-HT and interactions with other neurotransmitters

Interactions between 5-HT and the cholinergic system have often been addressed. The potential of serotonergic agents to change levels of cholinergic transmission is of great interest for research on novel therapeutic targets treating disorders such as age-related cognitive decline or dementia (Lancot et al., 2001).

It was demonstrated, that the combined cholinergic and serotonergic denervation of the forebrain in rodents produces severe spatial memory impairments, whereas 5-HT depletion alone had no effect (Lehmann et al., 2000; Nilsson et al., 1988; Richter-Levin and Segal, 1989; Richter-Levin et al., 1994). Further, the administration of the SSRI alprazole (20 mg/kg) together with scopolamine (0.8 mg/kg) or the combination of 8-OH-DPAT and scopolamine at subthreshold doses (30 μg/kg and 100 μg/kg, respectively) likewise induced a far greater place navigation deficit than scopolamine alone (Riekkinen et al., 1995, 1991). This entails, that changes in central 5-HT levels are capable to magnify the functional defects induced by cholinergic blockade, leading to a severe failure of spatial performance.

On the other hand, scopolamine induced deficits in contextual fear conditioning and object recognition tasks where reversing by pretraining administration of 5-HT1A antagonists (WAY-101 405 [1 mg/kg]; Ro4368554 [10 mg/kg or 30 mg/kg]; WAY 100 635 [1 mg/kg]; Ro 04–6790 [10 or 30 mg/kg]) (Hirst et al., 2008; Lieben et al., 2005a; b; Pitsikas et al., 2003; Woolley et al., 2003). The memory improving effects were thereby associated with increases in hippocampal acetylcholine levels (Hirst et al., 2008). A possible underlying mechanism of action could involve opposite interactions between 5-HT1A receptors and scopolamine at the level of pyramidal hippocampal neurons. Accordingly, the blockade of hyperpolarizing actions by endogenous 5-HT may compensate the loss of cholinergic input, favouring the action of other excitatory neurotransmitters on pyramidal cells (Carli et al., 1997; Pitsikas et al., 2003).

In a similar vein, scopolamine induced object recognition deficits were counteracted by 5-HT1A ligands. The agonistic compound E-6801 (2.5 or 5 mg/kg) alone or in combination with subthreshold doses of the agonistic compounds EMD386088, as well as the agonistic compound Ro4368554 (3 mg/kg or 10 mg/kg) restored object recognition performance (Kendall et al., 2011; Woolley et al., 2003). Furthermore, the acute and prolonged (21-day) administration of both, the selective 5-HT1A agonist WAY-181 187 (1 and 3 mg/kg) and the agonist SB-745 427 (3 mg/kg) prevented memory impairments and alterations in BDNF signaling induced by MK-801 in rats (Rychtyk et al., 2019).

4. Human studies

4.1. Verbal learning and memory

Verbal learning tests in humans usually consist of a list of words that has to be memorized by the subject being tested. During the learning phase, words are presented verbally or visually and immediately retrieved afterwards, a procedure that is repeated several times (5 times in general). This is followed by delayed recall procedures including the recognition of words from a list. Delayed recalls are performed after the presentation of an interference list (without recognition), after 2 h delay and after 24 h delay (to assess protein-dependent long-term memory). The most popular tests following this procedure are the Rey Auditory Verbal Learning Test (RAVLT) and the California Verbal Learning Test (Strauss et al., 2006).

4.1.1. Lowering 5-HT globally

TRP depletion as a pharmacological 5-HT deficiency model in humans, commonly results in impairments of declarative memory. In verbal learning tests, the effects were most prominent at delayed recall, with fewer words recollected after TRP depletion (Amin et al., 2006; Borghans et al., 2017; Harrison et al., 2004; Klaassen et al., 1999; McAllister-Williams et al., 2002; Riedel et al., 1999a, 1999b; Sambeth et al., 2007, 2009; Schmitt et al., 2000). There are only two studies, which at least partly, failed to replicate this finding (Evers et al., 2005; Hughes et al., 2003). In another examination on verbal memory, whereas prose paragraph had to be recalled, no verbal memory deficits have been observed after using chronic fenfluramine (20 mg PO/day) application for 5-HT depletion (Meador et al., 2008).

In contrast to verbal learning, immediate verbal recall was mostly either unaffected (Harrison et al., 2004; Klaassen et al., 1999; Riedel et al., 1999a, 1999b; Schmitt et al., 2000), or only females were found to be impaired (Borghans et al., 2017; Helmbold et al., 2013; Mace et al., 2008; Sambeth et al., 2007). The specific greater vulnerability of females to the effects of TRP restriction likely involves interactions with estrogen. Evidence for this was provided by estrogen treatments in menopausal woman, which led to augmented verbal memory performance (Amin et al., 2006) and increased 5-HT turnover (Lippert et al., 1996). Moreover, recovered depressed participants receiving a low-dose TRP diet were more vulnerable to deteriorations in cognitive function. In this study, impairments were specific to verbal short-term memory deficits, without showing changes in word encoding, long-term memory, and subjective mood (Hayward et al., 2005).

Regarding specific memory phases, a TRP depletion-related consolidation impairment was pointed out. Consolidation is a process involving several stages (McGaugh, 2000), and in relation to TRP depletion, mostly immediate consolidation, which begins as early as during encoding up to 30 min after acquisition, was reduced (Harrison et al., 2004; Riedel et al., 1999a, 1999b; van der Veen et al., 2006). EEG measurements during a verbal learning task revealed alterations of the N400 event-related potential component after acute TRP depletion, which is consistent to consolidation deficits (Borghans et al., 2017). No event-related potential changes were found at retrieval (McAllister-Williams et al., 2002). One study, applying task-based fMRI after TRP depletion, observed attenuated neuronal activity in the right hippocampus during encoding of a visual-verbal memory task. No brain activity differences in comparison to a control group were detectable during retrieval (van der Veen et al., 2006).

Effects of TRP depletion on word recognition were less consistent. Recognition deficits were reported to be most pronounced after some hours delay (Riedel et al., 1999a, 1999b; Rubinsztein et al., 2001; Sambeth et al., 2007; Schmitt et al., 2000; van der Veen et al., 2006). Evers et al. (2005) found increased reaction times in delayed visual word recognition, however, other examinations failed to find differences in comparison to control conditions (Borghans et al., 2017; Harrison et al., 2004; Helmbold et al., 2013; Klaassen et al., 1999; Sambeth et al., 2009). Interestingly, the cognitive effects of TRP depletion were differentially affected by genotypes at the 5-HTTLPR polymorphism (ss vs. ll genotype). Regarding this, the ss genotypes showed deficits in an affective verbal directed forgetting task after TRP depletion, in contrast to the ll genotype group (Roiser et al., 2007).

4.1.2. Enhancement of 5-HT globally

Acute treatment with SSRIs, which causes a global increase in the serotonergic tonus, had fairly inconsistent effects on verbal learning across studies. Citalopram (10 mg IV) was found to improve long-term recall and recognition in the RAVLT in female volunteers, without
affecting immediate recall 15 min earlier. This finding is consistent with studies suggesting reduced memory consolidation after TRP depletion, thus indicating reciprocal effects of low and high 5-HT levels in long-term memory processes in humans (Harmer et al., 2002). Yet, other studies did not find group differences in verbal memory after acute citalopram ingestion (20 mg oral) (Sambeth et al., 2015; Wingen et al., 2007) or by contrast, they observed impaired verbal memory performance (Heckman et al., 2019a). Chronic escitalopram treatment (10–20 mg/day) for 15 days did not affect visual-verbal memory, which was tested on several days during this period (Wingen et al., 2006).

Acute administration of the serotonin and noradrenaline releaser MDMA causes a strong increase of extracellular 5-HT and noradrenaline levels by promoting non-exocytotic release of these neurotransmitters from storage vesicles (Rothman et al., 2001). Acute MDMA worsens verbal memory during the intoxication phase at immediate and delayed recall (Haijen et al., 2018; Kuypers et al., 2013, 2016; Kuypers and Ramaekers, 2005). The effects were strongest when MDMA was given before encoding, but also present when MDMA was given before retrieval (Doss et al., 2017). Verbal memory recognition scores were not affected by acute MDMA intoxication (Kuypers et al., 2013; Kuypers and Ramaekers, 2005; Van Wel et al., 2011), yet deficits have been obtained in a pictorial recognition task (Kuypers et al., 2013). Some research points towards a specific role of 5-HT 

### 5. Visuo-spatial learning and memory

#### 5.1. Lowering 5-HT globally

A simple spatial learning task involved the pictorial presentation of a house with nine windows, yet only four of those windows had a light turned on. The memory for the positions of those illuminated windows after a short delay was not different between an TRP depletion group and controls, indicating no visuo-spatial learning alterations. To note, reducing dopamine availability resulted in short-term memory impairments in the same task (Harrison et al., 2004). Furthermore, no influence of TRP depletion was found on spatial pattern – location recognition or in visuo-spatial learning tests from neurocognitive assessments (Amin et al., 2006; Evers et al., 2005; Hughes et al., 2003; Mace et al., 2008; Park et al., 1994; Rubinsztein et al., 2001; Scarnà et al., 2005). In an object relocation task, ten objects were presented shortly to participants in a square frame. Afterwards, the positions of the objects were marked, and the objects had to be assigned to their previous positions. In this specific task, TRP depletion was found cause performance deficits in delayed recall taking place 4 h later. However, for the same task, there was a separate condition, demanding the placement of a set of new objects in their original position as accurately as possible, without pre-marked dots. Interestingly, the TRP depletion group’s performance was superior to controls in placing objects to their exact coordinate position. According to the authors, the assignment of objects to a relative position likely incorporates a verbal component, as opposed to the remembrance of the more precise, metrical position of an object whereas the metrical displacement to the correct position is measured (Sambeth et al., 2009). Similarly, TRP depletion was found to augment spatial pattern recognition (Scarnà et al., 2005).

#### 5.1.1. Enhancement of 5-HT globally

Acute administration of the SSRI citalopram (20 mg) did not affect spatial memory or visuo-spatial recognition, neither in a spatial test based on object relocation, nor in a continuous pattern recognition test (Heckman et al., 2019b; Park et al., 1994; Sambeth et al., 2015). In accordance, no effects on memory outcomes, white matter plasticity (measured by diffusion tensor imaging), or structural changes (T1-weighted MRI data) were found after chronic escitalopram treatment for 3 weeks (10 mg/day) during a visual face – object associate relearning task (Vanieck et al., 2022). However, functional activation changes while relearning were found from the right insula to both the anterior cingulate and right angular gyrus in the same sample (Reed et al., 2022). In contrast to these previous studies, the combined treatment of citalopram (20 mg) together with anodal transcranial direct current stimulation, entailed beneficial effects on short-term memory in an object-location recognition task. This applied to both, younger and older adults (Prehn et al., 2016).

Acute MDMA induced pronounced impairments of visuo-spatial memory. Neither pretreatment with the 5-HT 

#### 5.2. Summary

Interestingly, spatial memory for accurate placements might even slightly benefit from 5-HT deficiency induced by TRP depletion. This contrasts with the apparent impairments in verbal memory using the 5-5-HT 

### 4.2. Summary

Central 5-HT deficits mainly impaired delayed recall in verbal learning tasks, suggesting poor consolidation. But also, studies that induced overstimulation of the 5-HT system through SSRI, 5-HT

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5-HT 

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same psychopharmacological manipulation.

6. General discussion

6.1. Low global 5-HT

In the majority of studies, TRP depletion induced deficits in human verbal memory or object recognition in animals while sparing spatial memory. Across species, females were more vulnerable to TRP depletion-induced deficits, especially before ovulation when estrogen levels are rising. To mention at this point are findings that document a higher 5-HT synthesis overall in males than in females, which could relate to the abovementioned finding (Chugani and Muzik, 2000). In addition, conditions associated with less efficient 5-HT functions, such as psychiatric disorders in humans or their mimicry in genetically modified animals, enhanced the effect of TRP depletion (Alhaj et al., 2012; Merens et al., 2008). TRP depletion was further associated with slight increases in attentional processes and perceptual processing (Schmitt et al., 2000), whereas dopamine depletion primarily affected spatial working memory (Harrison et al., 2004). Concerning human studies a contribution of lowered mood which negatively affects memory performance has been discussed, but in most of the studies showing memory effects after TRP depletion, mood was not altered (Ruhé et al., 2007).

Evidence stands that partially segregated networks are recruited for spatial navigation and object memories even though they all do account as medial temporal lobe dependent memories (Chao et al., 2016; Hales et al., 2014; Rauchs et al., 2008). Most interestingly, according to the findings reviewed here, cognitive subroutines underlying spatial navigation, object memories, and storage of the contextual element in contextual fear conditioning, seem to be differentially affected by central 5-HT deficiency. This suggests dissociable processes underlying storage of objects and contexts as opposed to the formation of cognitive maps during allocentric navigation. Research on such topics remained sparse to date, especially with regard to 5-HT. The retrosplenial cortex and the MS are critically involved in spatial navigation (Kubik et al., 2012), yet storage of objects relies on extrahippocampal structures such as the parahippocampal cortex in particular (Burwell et al., 2004; Miranda and Bekinschtein, 2018). Considering this, further research might take up findings describing different molecular mechanisms in the respective brain regions that process and store different types of information (Mitchnick et al., 2015; Natale et al., 2020), and relate them to the 5-HT

### Table 1
Main effects animal studies. Superscript arrow symbols refer to directions of effects found in the respective studies. ↑: memory improvement. ↓: memory deterioration. →: no effect.

| Substances | Effect | Substances | Effect | Substances | Effect | Substances | Effect | Authors spatial learning | Authors object recognition | Authors contextual fear conditioning |
|------------|--------|------------|--------|------------|--------|------------|--------|--------------------------|-------------------------------|-----------------------------------|
| TRP depletion | ↓ | Tryptophan depletion | ↓ | Tryptophan depletion | ↓ | Lieben 2004; Liu 2013; Starkampiano 1997; Uchida 2007 | |
| PCPA | ↑ | PCA | ↓ | 5-HT | ↓ | Richter-Levin 1989; Lehmans 2000; Majlessi 2003; Nilsson 1988 |
| MDMA (selective) | ↓ | MDMA (selective) | ↑[↑][↑] | PET1KO | ↓ | Aise 2006 |
| Citalopram | ↓ | Citalopram | ↓ | Fluoxetine | ↑ | Bridgda 2013; Majlessi 2002; Muzli 2011 |
| Fluoxetine | ↓ | Fluoxetine | ↑ | Amaaro 2013; Majlessi 2002 | |
| Sertraline | ↓ | Sertraline | ↑ | Riekkinen 1991 |
| Ko 5-HTa | ↑ | Ko 5-HTa | ↓ | Bertrand 2000; Haider 2012; Koenig 2008, 2011; Lutgen 2005; Haider 2012 | |
| Ko 5-HTc | ↑ | Ko 5-HTc | ↓ | Hirt 2008; Liotgen 2005; Sanyal 2000; Wolff 2004 | |
| Ko 5-HTd | ↑ | Ko 5-HTd | ↓ | Hirt 2008; Pittsakas 2003; Tac 2004 |
| Ko 5-HTe | ↑ | Ko 5-HTe | ↓ | Hirt 2008; Pittsakas 2003 | |
| Ko 5-HTf | ↑ | Ko 5-HTf | ↓ | Hirt 2008; Pittsakas 2003; Tac 2004 |
| Ko 5-HTg | ↑ | Ko 5-HTg | ↓ | Hirt 2008; Pittsakas 2003; Tac 2004 |
| Ko 5-HTh | ↑ | Ko 5-HTh | ↓ | Hirt 2008; Pittsakas 2003; Tac 2004 |
| Ko 5-HTi | ↑ | Ko 5-HTi | ↓ | Hirt 2008; Pittsakas 2003; Tac 2004 |
| Ko 5-HTj | ↑ | Ko 5-HTj | ↓ | Hirt 2008; Pittsakas 2003; Tac 2004 |
| Ko 5-HTk | ↑ | Ko 5-HTk | ↓ | Hirt 2008; Pittsakas 2003; Tac 2004 |
| Ko 5-HTl | ↑ | Ko 5-HTl | ↓ | Hirt 2008; Pittsakas 2003; Tac 2004 |
| Ko 5-HTm | ↑ | Ko 5-HTm | ↓ | Hirt 2008; Pittsakas 2003; Tac 2004 |
| Ko 5-HTn | ↑ | Ko 5-HTn | ↓ | Hirt 2008; Pittsakas 2003; Tac 2004 |
| Ko 5-HTo | ↑ | Ko 5-HTo | ↓ | Hirt 2008; Pittsakas 2003; Tac 2004 |
| Ko 5-HTp | ↑ | Ko 5-HTp | ↓ | Hirt 2008; Pittsakas 2003; Tac 2004 |
| Ko 5-HTq | ↑ | Ko 5-HTq | ↓ | Hirt 2008; Pittsakas 2003; Tac 2004 |
| Ko 5-HTr | ↑ | Ko 5-HTr | ↓ | Hirt 2008; Pittsakas 2003; Tac 2004 |
| Ko 5-HTs | ↑ | Ko 5-HTs | ↓ | Hirt 2008; Pittsakas 2003; Tac 2004 |
| Ko 5-HTt | ↑ | Ko 5-HTt | ↓ | Hirt 2008; Pittsakas 2003; Tac 2004 |
| Ko 5-HTu | ↑ | Ko 5-HTu | ↓ | Hirt 2008; Pittsakas 2003; Tac 2004 |
| Ko 5-HTv | ↑ | Ko 5-HTv | ↓ | Hirt 2008; Pittsakas 2003; Tac 2004 |
| Ko 5-HTw | ↑ | Ko 5-HTw | ↓ | Hirt 2008; Pittsakas 2003; Tac 2004 |
| Ko 5-HTx | ↑ | Ko 5-HTx | ↓ | Hirt 2008; Pittsakas 2003; Tac 2004 |
| Ko 5-HTy | ↑ | Ko 5-HTy | ↓ | Hirt 2008; Pittsakas 2003; Tac 2004 |
| Ko 5-HTz | ↑ | Ko 5-HTz | ↓ | Hirt 2008; Pittsakas 2003; Tac 2004 |

### Table 2
Table 2. Main effects animal studies. Superscript arrow symbols refer to directions of effects found in the respective studies. ↑: memory improvement. ↓: memory deterioration. →: no effect.

### Table 3
Table 3. Main effects animal studies. Superscript arrow symbols refer to directions of effects found in the respective studies. ↑: memory improvement. ↓: memory deterioration. →: no effect.
system. A further interesting topic to pursue are theta wave changes found to occur after modulating 5-HT levels. For example, Kragel et al. (2020) suggested that encoding and retrieval happens at different phases of hippocampal theta oscillations, an observation which may provide indications why a lower central 5-HT tone supported encoding under some conditions (e.g. spatial learning).

In addition, another intriguing issue to be addressed is the fact that 5-HT might differently influence distinct forms of synaptic plasticity. In this respect, it was found that various forms of LTP contribute to different aspects of memory storage with theta frequency and CaMKII-dependent LTP being particularly necessary for spatial navigation (Bach et al., 1995; Rotenberg et al., 1996). This was indicated by the observation, that CaMKII mutant mice exhibit a selective loss of hippocampal LTP in the range of the theta frequency and displayed impairments in spatial memory but not in contextual memory storage (Bach et al., 1995; Silva et al., 1992).

Some other mechanism of actions underlying TRP depletion than merely serotoninergic ones have been suggested (see van Donkelaar et al., 2010 for an extensive review). One of the most debated is the possible interaction between TRP depletion and the enzyme nitric oxide synthase (NOS). Yet, NOS inhibitors have been demonstrated to severely impair both, spatial learning and object recognition (Bhattacharyya and Powell, 2002; Burgess et al., 2011; Kalechstein et al., 2007; Quednow et al., 2006).

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Table 2

| Humans | Substances | Domain | Effect |
|--------|------------|--------|--------|
| Low 5-HT | Trp depletion | Insom. recall | ↓ [3] ; ↑ [27] |
|        |            | Dei. recall | ↓ [8] ; ↑ [27] |
|        | Fenfluramine | Dei. recall | ↑ [1] |
|        | Trp depletion | Recogn. | ↓ [3] ; ↑ [31] |
| High 5-HT | Citralopram | Recall / Recogn. | ↑ [3] ; ↑ [37] ; ↓ [17] |
|        | Acute MDMA | Insom. / Dei. recall / Recogn. | ↓ [5] ; ↓ [1] |
| S-HTA | Agonist | Agonist | ↓ [2] |
| S-HTA | Agonist | Recall / Recogn. | ↑ [2] |
| S-HTT | Agonist | Recall | ↑ [1] |

modulates the output in dorsal and ventral hippocampus in opposite directions, causing cell firing attenuation in the dorsal and facilitation in the ventral segment (Mlinar and Corradetti, 2018). In response to aversive stimuli, 5-HT level of dorsal hippocampus increases, serving protective functions (Almada et al., 2013; Dai et al., 2008) and likely counteract the consolidation of the contextual component in stressful memories (Graeff et al., 1996; Maren et al., 2013). At the same time, ventral hippocampal facilitation likely boosts the signal to its downstream targets, such the amygdala, that are involved in emotional regulation (Mlinar and Corradetti, 2018; Ohmura et al., 2010; Twining et al., 2020). The failure in retrieving fear-related contextual memory occurs by not activating the subsequent fear circuit that induces freezing behavior (Tada et al., 2004). Such a modulation was lacking in chronically 5-HT deficient mice (Waider et al., 2019). Since innate anxiety behaviors were reduced in chronic-5-HT deficient animals (Dai et al., 2008; Mosienko et al., 2014), albeit inconsistently (Gutknecht et al., 2015), exaggerated contextual fear conditioning is plausibly a consequence of altered synaptic plasticity and circuitry in the hippocampus resulting from lifelong 5-HT deficiency, and rather not due to a more anxious phenotype. Abovementioned considerations pinpoint the MR as crucial in fear-conditioning and this might further be a highly relevant basis for exploring differences in terms of raphé nuclei and material-specific consolidation (Lieben et al., 2006; Lin et al., 2021; Netto et al., 2002).

6.2. High global 5-HT

Spatial navigation and object memories were both impaired after either acute SSRI or acute MDMA treatment in animals, yet mixed effects were obtained for contextual fear conditioning. Acute SSRI administration in humans yielded inconsistent results so far. The global elevations in extracellular 5-HT concentrations trigger non-specific increases in the activity of autoreceptors and heteroreceptors, which impede efficient information processing (Fuller, 1995). Hence, resulting memory alterations might involve complex interactions and currently, it is not known which receptors are indeed involved in the reduced memory performance after elevation of 5-HT and whether different phases of memory are affected differently (Fig. 1).
6.3. 5-HT receptors

For all forms of declarative memories investigated, proconvective effects of 5-HT1A R antagonists were demonstrated, while 5-HT1A R agonists as well as changes in their expression profile yielded mixed results. Improving effects on memory are likely mediated via stimulation of postsynaptic receptors, yet overstimulation of the serotonergic system might produce the opposite suggesting that associated pro-cognitive effects may follow a bell-shaped function. There is further evidence indicating that more efficient pattern separation in hippocampal CA1 is accountable for improved memory due to increased inhibitory serotonergic tone (Fernandez et al., 2017). 5-HT1A R interact with the cholinergic and glutamatergic system and thus, might serve the treatment of age-related cognitive disorders. Up until today, however, cognition improving effects of 5-HT1A R partial agonists applied for treating schizophrenia-related cognitive impairments in humans (e.g. buspirone and tandospirone) has not been unambiguously demonstrated yet (Buoli and Altamura, 2015).

Acute blockade of 5-HT2A R impairment of objects in context and reduced the conditioned response in contextual fear conditioning, yet contrastingly, improved spatial reference memory retrieval. Further investigations revealed that 5-HT2A R in the mPFC play an important role in controlling contextual retrieval of concurrent memories by selecting the correct memory trace and suppressing competitors in complex tasks. In rodents – but not in humans – 5-HT2A R activation enhanced consolidation of object memory and contextual fear memory as well as the reconsolidation of object memories in the perirhinal cortex, especially when administered directly after learning, while pre-training activation facilitated extinction of fear memories. In spatial learning, however, agonistic ligands produced impairments. Accordingly, effects of 5-HT2A R on declarative memories could differ across mnemonic modalities. There is also an impairing side effect of hallucinogenic agents on spatial navigation that merits consideration (Zhang et al., 2017). Further studies with regard to possible cognition-enhancing effects of 5-HT2A R antagonists could certainly be beneficial (Bertaina-Anglade et al., 2011).

Although the effects of 5-HT2A R antagonism on spatial learning were inconclusive in healthy animal populations, it may represent a potential treatment for cholinergic dysfunction (Passani and Blandina, 1998).

Pre-proconvective effects on acquisition and/or consolidation were also induced by 5-HT2A R agonists and on the other hand, impairments were observed when blocking this receptor. Positive effects also occurred in humans, as evidenced by increased precision in recall and recognition of verbal memory, conceiving 5-HT2A R agonists as a potential target for the treatment of cognitive deficits (Murphy et al., 2020b).

5-HT2A R constitute a further promising therapeutic objective particularly for the prevention of age-related deficits due to its interactions with the cholinergic system. Interestingly, both agonistic and antagonistic ligands enhanced declarative memories in a similar vein, yet via distinct neuronal mechanism of action (Kendall et al., 2011).

5-HT-R were of special relevance for the detection of novelty in object recognition without having direct behavioral impacts in spatial learning. Interestingly, KO models provided an example of dissociations between egocentric and allocentric spatial learning strategies. Specific deficits in contextual learning were uncovered, seemingly involving a cognitive subroutine that is less important for egocentric spatial-navigational processes with 5-HT-Rs playing a role (Sarkisyan and Hedlund, 2009).

7. Conclusion

Taken together, the findings reviewed here indicate that acutely lowered brain 5-HT tones most likely impairs protein synthesis-dependent consolidation in humans and rodents. Considering task-related cognitive processes unveils material-specific for object-related and verbal memory content being particularly affected. By contrast, spatial navigation might even benefit from low serotonergic tone in support of encoding. Central and non-specific pharmacologically induced 5-HT elevations may be beneficial for consolidation in some cases, but further studies are clearly needed for clarification. 5-HT1A R antagonists, 5-HT2A R agonists, and 5-HT4 R ligands might comprise promising targets for declarative memory impairments.

Conflict of interest

The authors declare no conflict of interest.

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