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Letter to Editor **Open Access**

Role of selective serotonin reuptake inhibitors for treating memory impairment

Adit Deshmukh

M.B.B.S; M.D. Pharmacology, Hyderabad, India.

Abstract

Memory forms an essential component of cognitive function; therefore, memory impairment can significantly affect a person's quality of life. Serotonin has been implicated as one of the primary neurotransmitters involved in memory. Hence, medication classes such as Selective Serotonin Reuptake Inhibitors (SSRIs) that alter the serotonin levels in the brain have been found to affect memory improvement.

The main areas of the brain involved with memory are the hippocampus, the cerebellum, and the prefrontal cortex. Serotonergic pathways regulate memory in all three areas.

Since the serotonergic system affects memory and learning, SSRIs have been found to improve memory consolidation. SSRIs influence memory in different brain areas through various mechanisms, including neurotrophic actions and 5-HT1A receptors.

There is a huge scope for the discovery and development of novel medications and for repurposing already available classes of drugs to treat memory impairment according to their mechanisms of action, and SSRIs are promising candidates for this. SSRIs have advantages as a medication class, which paves the way for new research lines aimed at exploring their effects on memory in different brain areas.

Keywords: Memory, Selective serotonin reuptake inhibitors, Serotonin

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***Corresponding Author:**

Hyderabad, India.

deet.deshmukh@gmail.com

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Dear Editor,

Psychology defines memory as the faculty of encoding, storing, and retrieving information. It is a neurochemical process that encodes the information as synaptic signals between neurons (1). It is the process of retaining of knowledge over a period for the function of affecting future actions (2). Memory forms an essential component of cognitive function; therefore, memory impairment, observed in various psychiatric disorders, can significantly affect the patient's quality of life. As we shall discuss further, serotonin has been implicated as one of the primary neurotransmitters involved in memory. Hence, medication classes, such as Selective Serotonin Reuptake Inhibitors (SSRIs), which alter the serotonin levels in the brain, have been found to affect memory improvement. This letter aims to briefly review the current knowledge in this area and discuss the future scope of research on these lines.

Memory has been categorized into a few categories based on the type of information processed by that memory. Those types are as follows (3):

- Episodic memory is related to recalling a particular event (or "episode") experienced in the past.
- Semantic memory: It's composed of information such as facts learned in the past, the understanding of different concepts, or the definition of a particular word.
- Procedural memory is involved in the process of learning skills, from the basic ones to those that require considerable practice.
- Prospective memory means remembering an intention from the past to do something in the future.
- Working memory: It specifically involves the temporary storage of information that is being mentally manipulated.

Declarative memory refers to memories of facts and events that can be consciously brought to mind and "declared". It is comprised of episodic and semantic memory (4). Among the different types of memory discussed above, working memory is short-term memory, whereas all other types are categorized into long-term memory.

It has been revealed that specific brain areas are involved in memory. The main areas of the brain involved with memory are the hippocampus, the cerebellum, and the prefrontal cortex. The brain areas involved with different types of memories are mentioned in Table 1 and depicted in Figure 1.

Type of memory
The principal area of the brain involved
Declarative hippocampus and prefrontal cortex (5,6)
Procedural cerebellum (5,7)
Prospective prefrontal cortex (8)
Working prefrontal cortex (9)

Table 1. Principal areas of the brain involved in different types of memory

Type of memory	Principal area of brain involved
Declarative	Hippocampus and prefrontal cortex
Procedural	Cerebellum
Prospective	Prefrontal cortex
Working	Prefrontal cortex

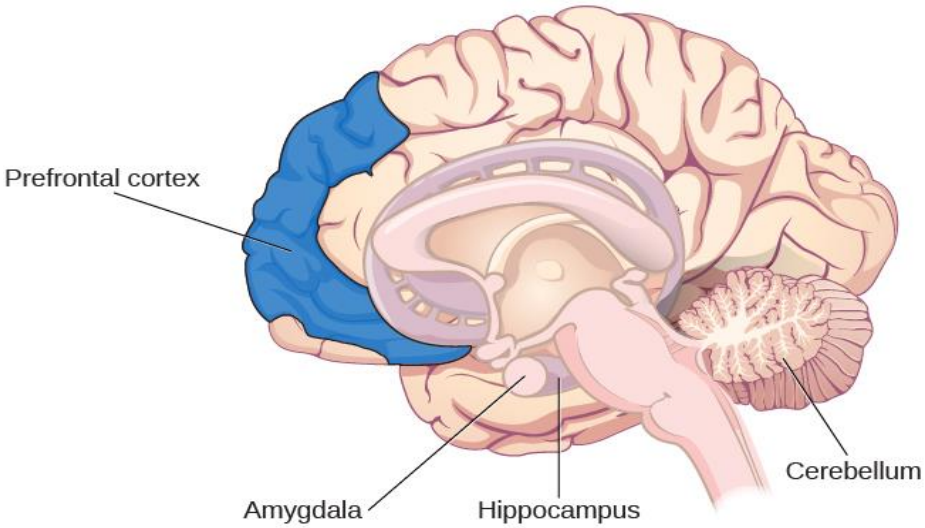

Figure 1. Principal areas of the brain involved in different types of memory

Role of serotonin in the brain areas involved in memory

Hippocampus

The hippocampus has been shown to play a role in memory (10). A region of the hippocampus called CA1 is particularly important in memory. The strength of neuronal communication through the CA1 region is linked to memory formation. Studies have demonstrated that damage to the CA1 region leads to memory impairment.

The hippocampus is heavily influenced by serotonin (among other neurotransmitters) (11). Animal studies have revealed that when serotonin release is increased in the hippocampus, neuronal communication in CA1 becomes stronger, which leads to improved memory. On the contrary, when serotonin release is artificially blocked, memory is impaired.

Thus, these studies have eventually demonstrated that memory formation depends on this serotonergic pathway inside the CA1 region of the hippocampus (12).

Prefrontal cortex

Serotonergic neurons in the prefrontal cortex have been shown to play a role in memory (13), among other functions, including attention and cognitive flexibility. Studies on monkeys have demonstrated that stimulation of serotonergic receptors in the dorsolateral prefrontal cortex modulates the "memory fields" of neurons involved in the working memory (14).

Further studies on primates have clarified the role of serotonin in the OrbitoFrontal Cortex (OFC) neurotransmission, wherein serotonin depletion alters the functioning of OFC (15). Lesion and neuroimaging studies suggest that the OFC supports temporal aspects of episodic memory, a type of declarative memory (16).

Cerebellum

As we discussed earlier, the cerebellum is involved in procedural memory, which requires motor learning (learning to perform a particular task). Studies have proved the role of serotonin in the cerebellum as a regulator of memory (17) and sensorimotor learning (18).

It has been shown that serotonin receptors at a crucial junction in the cerebellar motor learning circuit, namely the PF–PC (Parallel fiber–Purkinje cell) synapse, are directly involved in motor learning, a prerequisite for procedural memory acquisition (18).

After discussing the role of serotonin in memory in different brain areas, we shall discuss the potential effects of SSRIs on memory.

Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs are a class of medications that have revolutionized the treatment of numerous psychiatric disorders. After the introduction of fluoxetine in the United States in the year 1988, SSRIs quickly became a mainstay of treatment for various psychiatric disorders (19). Most commonly used as first-line anti-depressants, SSRIs are the drugs of choice for a multitude of other conditions as well, for which they have FDA-labeled indications. Those conditions are as follows (20):

-Major depressive disorder
-Generalized anxiety disorder
-Bulimia nervosa

-Bipolar depression
-Obsessive-compulsive disorder
-Panic disorder
-Premenstrual dysphoric disorder
-Treatment-resistant depression
-Post-traumatic stress disorder
-Social anxiety disorder

Other off-label uses include but are not limited to binge eating disorder, body dysmorphic disorder, fibromyalgia, etc. (20).

The medications included in this class are fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram, and dapoxetine.

Mechanism of action

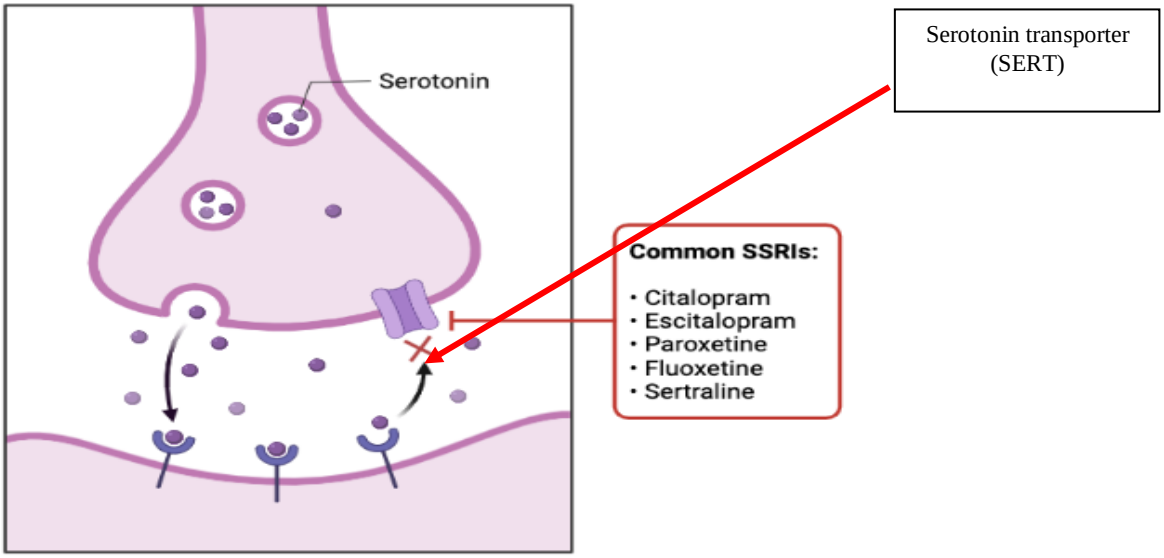

Figure 2. Mechanism of action of SSRIs

As depicted in Figure 2, SSRIs inhibit the serotonin transporter (SERT) at the presynaptic axon terminal in the brain. By inhibiting SERT, an increased amount of serotonin remains in the synaptic cleft and can stimulate the post-synaptic receptors for an extended period.

The basis for this mechanism lies in the monoamine hypothesis, which states that a deficiency of serotonin in the brain synapses is the cause of various psychiatric disorders (enlisted earlier). Therefore, when the increased amount of serotonin acts on post-synaptic receptors for a prolonged period due to the action of SSRIs, the symptoms of the underlying psychiatric disorder diminish (20).

Role of SSRIs in memory improvement

Since the serotonergic system affects memory and learning, memory consolidation is improved by SSRIs in various studies. Among the different molecular pathways involved in neuronal organization and adaptation processes, the serotonergic neurotransmitter system influences neuronal circuit formation (neurotrophic action) by regulating neuroplastic processes at the synaptic level. SSRIs stimulate protein synthesis of two major proteins, viz; Cyclic Adenosine MonoPhosphate (cAMP) response element binding protein (CREB) and Brain-Derived Neurotrophic Factors (BDNF), which are responsible for synaptic formation and, consequently, for memory.

Recently, research has also discovered that SSRIs achieve their neurotrophic actions by binding to neurotrophic growth factor receptors. Moreover, it has been revealed that SSRIs enhance the synthesis of synaptic cell adhesion molecules and thus lead to balanced neurotransmission, further strengthening the memory processes (21).

Chronic administration of SSRIs in humans has been demonstrated to increase the neurogenesis of the hippocampus by the mechanisms discussed above, leading to improved memory and learning abilities (22). Another mechanism by which SSRIs have been shown to influence memory is by acting via hippocampal 5-HT1A receptors (23). Long-term treatment with SSRIs has been shown to increase the 5-HT1A receptor-mediated hippocampal transmission (24). This 5-HT1A-mediated pathway influences the activity of glutamatergic, cholinergic, and possibly GABAergic neurons in the cerebral cortex,

hippocampus, and septohippocampal projection, thereby affecting declarative and non-declarative memory functions (25).

Regarding the prefrontal cortex, the SSRI treatment has increased the grey matter volume of the DLPFC (26), a crucial region in working memory (27).

Similarly, in the case of the effect of SSRIs on the cerebellum, treatment with SSRIs for at least 8 weeks has been shown to increase the cerebellar volume (28).

The above discussion points towards SSRIs' significant role in improving memory through different mechanisms.

Future perspectives

Memory impairment has become increasingly prevalent in the past few decades. It can be age-related in the elderly population or can present as one of the symptoms of psychiatric disorders such as Alzheimer's dementia, schizophrenia, Post-Traumatic Stress Disorder (PTSD), and bipolar disorder (29). There are a few classes of medications used currently to manage this memory impairment. However, the improvement in memory produced by these medications is limited. Therefore, there is a huge scope for the discovery and development of novel medications and the repurposing of already available classes of drugs for treating memory impairment according to their mechanisms of action, and SSRIs are promising candidates for the same (30).

SSRIs have advantages as a medication class. First of all, they have been used for various psychiatric disorders for many years now. Therefore, the fundamental pharmacological data regarding all the individual drugs of that class, such as pharmacokinetics, pharmacodynamics, and adverse reactions profiles, are already available, unlike the completely novel drug candidates that are under development.

Secondly, SSRIs have little or no effect on other neurotransmitters, such as dopamine or norepinephrine. Therefore, they have fewer side effects compared to different classes of antidepressants, which makes SSRIs a preferred option for treatment (19,20).

Conclusion

Considering these favorable aspects of SSRIs, there is room for research on the effects of these medications on memory. As discussed above, the mechanisms by which they influence learning and memory in general and in the hippocampus are somewhat known. However, we do not have sufficient data to demonstrate if their neurotrophic effect on the prefrontal cortex and cerebellum can be translated to memory improvement. This might pave the way for new research lines to explore the impact of SSRIs on memory in different brain areas.

Conflict of Interest

The author reports no conflict of interest.

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