The Roles of Dopamine D1 and D2 Receptors in Working Memory Function

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Abstract
Dopamine has been implicated in the modulation of working memory via its interactions with circuits located in the prefrontal cortex of rodents and non-human primates. However, the role that pathways triggered by dopamine receptor subtypes play in affecting processes of working memory remains unclear. In humans, the evidence for dopaminergic modulation of working memory is controversial and the neurological substrates for dopamine's modulatory effects are not fully understood. This paper will review the major animal and human studies that implicate synaptic dopaminergic transmission in working memory function and will outline a new framework to clarify the specific contribution of dopamine D2 receptors to the performance of this cognitive function. Specifically, it is proposed that activation of hippocampal dopamine D2 receptors by chemical agonists could result in the enhancement of spatial working memory.

Keywords
Working memory, Dopamine, D1 receptor, D2 receptor, Hippocampus, Dorsolateral prefrontal cortex.

Introduction

Working memory is an important cognitive process mediated by circuits involving the prefrontal cortex (PFC) and posterior cortical areas. In patients with schizophrenia, altered synaptic dopaminergic transmission in the dorsolateral PFC is related to deficient working memory (Abi-Dargham, *et al.* 2002). Since this deficit is thought to underlie the extensive cognitive impairment and negative symptoms present in schizophrenia (Green, 1996; Abi-Dargham and Moore, 2003), much research has been devoted in the past couple of decades to determining the neurobiology of working memory. Despite these efforts, however, there are presently no evidence-based treatments available to ameliorate the highly debilitative cognitive symptoms of schizophrenia. The goal of this paper is to review the roles of dopamine D1 and D2 receptors in working memory and to highlight a potential new direction for research in humans that could further improve our understanding of the neurobiological underpinnings of this important cognitive function.

Overview of the Prefrontal Cortex and Working Memory

The prefrontal cortex is a collection of distinct cortical areas located anterior to the frontal eye fields in the frontal lobe. In humans it is larger relative to lower mammals such as monkeys, cats, dogs and squirrels. This anatomical difference is thought to account for some of the pronounced differences in cognitive ability that are observed between species (Squire, *et al.* 2003). The PFC can be separated into three major subdivisions based on general differences in cytoarchitecture and connectivity: ventromedial, ventrolateral and dorsolateral (Fellows, 2004; see Figure 1). The PFC is the substrate for the sophisticated cognitive processing that serves to organize and guide complex behaviour. Specific processes governed by the PFC include decision making, working memory, planning, emotional regulation and reward processing. Collectively, these processes are called executive cognitive functions.

The ventrolateral and dorsolateral areas of the PFC, in unison with posterior cortical areas, such as the posterior parietal cortex, are involved in working memory. While it is widely accepted that these broad cortical areas are critically involved in working memory, there has been less agreement about the precise contributions of each area to this cognitive function. In a seminal paper in 1988, Goldman-Rakic outlined a domain-specific theory of working memory, hypothesizing that the dorsal PFC processes spatial working memory information and the ventral PFC processes non-spatial working memory information. More recently, Petrides (1995, 1996) put forth a process-specific model or two-stage hypothesis of working memory function. In this model, information becomes progressively processed along a pathway leading from the ventral lateral to dorsal lateral PFC. Specifically, the mid-ventral lateral PFC retrieves task-relevant information from posterior cortical association areas and transmits it to the mid-dorsal lateral PFC which is involved in the monitoring of information. Manipulation of task-relevant information, another important facet of working memory, is conducted in the posterior parietal cortex (Champod and Petrides, 2007). Emerging neurophysiological evidence generally supports the domain-specific theory over the process-specific model (for a review, see Tanji and Hoshi, 2008).

Dopamine Receptors

The mesocortical dopamine system projects from the ventral tegmental area of the midbrain to various areas of the PFC, including the orbitofrontal, medial, dorsolateral and cingulate regions (Abi-Dargham and Moore, 2003). Dopamine receptors are found on both pre and post-synaptic neurons (Siegel, *et al.* 2006). There are five different types of dopamine receptors, typically classified into D1-like receptors (D1 and D5) and D2-like receptors (D2, D3 and D4) (Siegel, *et al.* 2006). D1-like receptors cause increases in cyclic AMP concentrations, whereas D2-like receptors cause decreases in cyclic AMP concentrations and calcium channel activity and increases in potassium channel activity (Siegel, *et al.* 2006). The five different dopamine receptors show unique patterns of regional distribution in the human brain (for a review, see Joyce and Meader-Woodruff, 1997; Abi-Dargham and Moore, 2003). D1 receptors are present in high densities in cortical areas, including the PFC, and the striatum. D2 receptors are present in high densities in the striatum, but at very low densities in the PFC. D3 receptors are particularly dense in the ventral striatum while D4 receptors are located in the PFC and hippocampus. D5 receptors are present in the hippocampus and entorhinal cortex.

Animal Studies: How is dopamine involved in working memory?

Studies conducted in rodents and non-human primates suggest that dopamine exerts its modulatory effects on working

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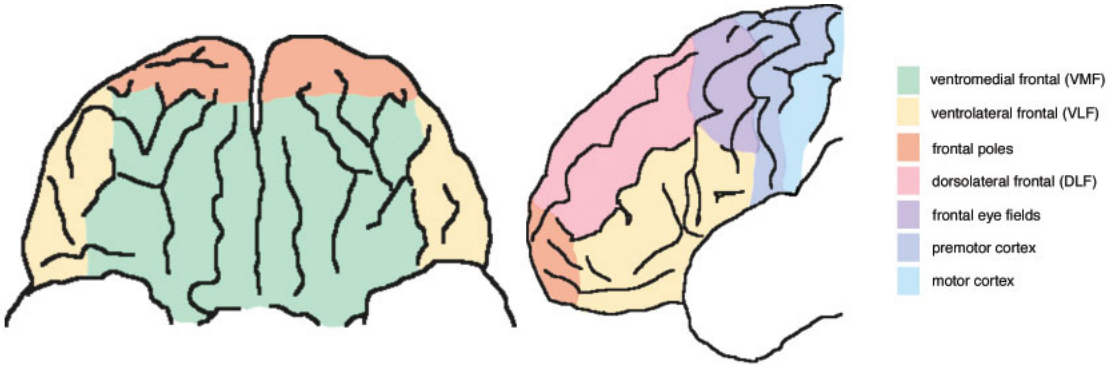

Figure 1: Subdivisions of the prefrontal cortex (PFC).The PFC is composed of all regions anterior to the frontal eye fields, namely the ventromedial, ventrolateral and dorsolateral frontal regions and the frontal poles. Reproduced with permission from Fellows (2004).

memory primarily via the D1 receptor in the PFC. A seminal study by Brozoski, *et al*. (1979) showed that selective depletion of dopamine in the dorsolateral PFC of rhesus monkeys significantly impaired their reaction on a delayed spatial alternation task. In this task, one of two wells was baited with food. After selecting the food, the subject waited over a period of delay ranging from 7 to 60 seconds until the next trial commenced. Then, the subject had to select the well that was not baited in the previous trial, i.e., it had to alternate its selection of wells on successive trials. In the same experiment, Brozoski, *et al.* (1979) also ablated the dorsolateral PFC of one subject and observed a decrease in performance on the delayed spatial alternation task that was similar in magnitude to the dopamine-depleted subjects. Specifically, the performance of both subject types on this task following a 20 second delay fell to between 40% - 60% accuracy after the experimental manipulation compared to between 70% - 100% accuracy prior to the experimental manipulation. Notably, the impairment induced by dopamine depletion was subsequently reversed by administration of levodopa (the immediate precursor to dopamine in the synthetic pathway) or apomorphine (a combined D1 and D2 receptor agonist). However, Brozoski, *et al.* (1979) posited that the location of action for the levodopa-induced reversal of impairment was not confined to the dorsolateral PFC because the drug was administered systemically via an intraperitoneal injection. Nonetheless, this study suggested that dopamine receptors in the PFC could play an important role in the modulation of working memory and spurred further research into the mechanisms underlying this relationship.

Subsequent studies conducted in rodents and non-human primates sought to clarify the behavioral effects of altering synaptic transmission at different dopamine receptors and to determine the cellular mechanisms underlying these effects. The results of several behavioral studies involving pharmacological manipulation of dopaminergic transmission suggested that D1 receptors in the PFC may critically influence performance accuracy on various working memory tasks (Amico, *et al.* 2007; Cai and Arnsten, 1997; Gonzalez-Burgos *et al*., 2005; Henze, *et al.* 2000; Kobori, *et al.* 2006), though D2 receptors can also play a role under some drug and task conditions (Druzin, *et al.* 2000; Karl, *et al.* 2006). Moreover, there may be an optimal range of D1 receptor stimulation in the PFC that underlies this effect, such that working memory performance and synaptic dopamine concentrations in the PFC follow an inverted-U function (Kroner, *et al.* 2007; Vijayraghavan, *et al.* 2007; Williams and Goldman-Rakic, 1995; Zahrt, *et al.* 1997).

In two classic studies by Sawaguchi and Goldman-Rakic (1991, 1994), monkeys were tested with an oculomotor delayed response task after receiving intra-cerebral injections of either D1 and D2 receptor antagonists or saline control injections. In this task, subjects fixated their gaze on a central spot of a screen and remained fixated on this spot while a visual stimulus was presented somewhere else on the screen, within their peripheral visual field. After a delay period of 1.5 to 6 seconds, the stimulus at the fixation point was turned off, instructing subjects to shift their gaze (make a saccade) to the point on the screen where the visual stimulus was previously located. Compared to injections of saline and D2 receptor antagonists, various D1 receptor antagonists induced a delay and dose-dependent impairment in performance accuracy on the occulomotor delayed response task. Non-specific effects of the antagonists on motor function and visual perception were controlled for by using a separate oculomotor task that required the monkeys to make a sensory-guided saccade rather than a memory-guided saccade. Arnsten, *et al*. (1994) complemented these results by demonstrating that monkeys were impaired on a delayed response task after systemic administration of a D1 receptor antagonist, while their performance improved after systemic administration of a D1 receptor agonist. In each trial of this task, a well was baited with food while the monkey watched. Then, all of the wells (two to four) were covered with plaques. For the delay period (0 to 40 seconds), an opaque screen was lowered. After the delay period, the monkey had to recall which well had been previously baited with food and select it. In another study performed on monkeys, Castner, *et al.* (2000) effectively reversed working memory impairments on a delayed response task by selectively stimulating D1 receptors. Previously, it has been demonstrated that D1 receptors are down-regulated in the PFC of primates after chronic administration of antipsychotic drugs that antagonize D2 receptors (Lidow and Goldman-Rakic, 1994). In order to replicate this effect at the D1 receptor, Castner, *et al.* (2000) chronically administered the potent D2 receptor antagonist haloperidol to monkeys. After a period of one year on this regimen, the monkeys were given a D1 agonist with or without haloperidol and their performance was assessed on a delayed response task. The number of correct responses on this task increased significantly over time in monkeys given the D1 agonist, effectively reversing the performance decline observed during and after long periods of haloperidol administration. Considered together, these studies suggest an important role for D1 receptors in PFC working memory processes.

The modulatory influence of dopamine on working memory is not limited to the dorsolateral region of the PFC. A study conducted by Seamans, *et al*. (1998) showed that dopaminergic modulation of the pre-limbic region of the PFC in the rodent

brain could also affect spatial working memory performance. They used delayed and non-delayed versions of the spatial win-shift task to assess spatial working memory after injection of D1 or D2 antagonists via a cannula into the pre-limbic region of rodents. In this task, the animal is placed in an eight-armed maze (spatial aspect). In a training session, the animal obtains food in four out of eight arms of the maze, while the other four out of eight arms are blocked by barriers. In the delayed version, the animal is placed back in the maze after a delay of 30 minutes and must now locate food in the four out of eight arms that were previously blocked. In the non-delayed version, the animal must immediately locate the food in the same manner as described above. After obtaining food in one arm of a maze, the animal must switch to a different arm to obtain another piece of food (win-shift aspect). Half of the arms are baited with food, while the other half are empty. After infusions of a D1 receptor antagonist into the pre-limbic region of the PFC, rodents were significantly impaired in the delayed version of the spatial win-shift task, but not in the non-delayed version. Interestingly, injection of a D2 receptor antagonist did not affect performance of this task relative to the baseline. These results further support the theory that D1 receptors have a greater influence on the functioning of working memory in the PFC than D2 receptors.

While D1 receptors may contribute significantly to the dopaminergic modulation of working memory, recent studies posit that dopamine also exerts its effects through other receptors. Von Huben, *et al*. (2006) found evidence for D2 receptor modulation of working memory in monkeys after systemic administration of raclopride (a D2 antagonist) and SCH23390 (a D1 antagonist). In this study, accuracy on a self-ordered spatial search task was significantly decreased in monkeys administered raclopride compared to those administered SCH23390. In this task, two, three or four coloured rectangles were presented randomly in different locations on a dark screen. The subject had to select each of the coloured rectangles once, without reselecting any of the coloured rectangles. It is important to note, however, that the negative linear association observed between D1 agonist administration and accuracy on the self-ordered spatial search task was not statistically significant. Although this contradicts other statistically-substantiated studies that demonstrate a preferential modulatory effect of D1 receptor agents over D2 receptor agents when administered systemically (Arnsten, *et al*. 1994; Castner, *et al*. 2000), it does raise questions concerning relative influences of D1 and D2 receptors.

Human Studies: Are D2 receptors less important than D1 receptors for working memory?

Studies in humans involving the selective modulation of D1 and D2 receptors also exhibit a spectrum of results. Several papers have demonstrated facilitation of working memory following administration of D2 receptor agonists (Kimberg, *et al*. 1997, 2001; Luciana, *et al*. 1992, 1998; Luciana and Collins, 1997) while others show impairment of working memory after administration of D2 receptor antagonists (Luciana and Collins, 1997; Mehta, *et al*. 2004). In addition, some studies have reported no effect of D2 receptor modulation on working memory (Kimberg, *et al*. 2001; Muller, *et al*. 1998). Ellis, *et al*. (2005) also published data suggesting that combined stimulation of D1 and D2 receptors in dopamine-depleted participants results in an impairment of working memory. Thus, the relative contributions of D1 and D2 receptors to working memory function in humans remains unclear.

Work by Muller, *et al*. (1998) suggests that D2 receptors may play a less significant role than D1 receptors in modulating working memory in humans. In this study, a pharmacological subtraction paradigm was used to compare the relative contributions of D1 and D2 receptors on working memory since a chemical agonist with specificity for D1 receptors in humans has yet to be discovered. Participants were tested on two separate days after administration of comparable doses of pergolide (a mixed D1 and D2 receptor agonist) or bromocriptine (a D2 agonist). It is a "subtraction paradigm" because the effect of stimulating D1 receptors is examined indirectly by subtracting the effect of a mixed D1 and D2 receptor agonist (pergolide) from the effect of a D2 agonist (bromocriptine). Working memory was tested using a visuospatial delayed matching task in which participants had to remember the location of seven points on a screen, over a delay period of 2, 8 or 16 seconds, and then determine if a newly presented pattern matched the previously viewed pattern. The results showed that working memory performance was improved by administration of pergolide, but not bromocriptine. Since the drugs were administered at comparable doses in an attempt to provide a similar level of D2 receptor stimulation, the authors concluded that only D1 receptor stimulation was responsible for the observed performance enhancement on the working memory task. Conceivably, it is possible that stimulation of both D1 and D2 receptors resulted in working memory improvement because of a common action on a downstream molecule. In the case of the D2 receptor stimulation alone, this downstream molecule may not have been adequately affected. However, this is not a likely explanation for the observed effect in the study by Muller, *et al*.(1998), given that D1 and D2 receptors generally have different effects on downstream molecules, such as cyclic AMP (Siegel, *et al*. 2006).

While it is likely that D1 receptors also prominently modulate working memory in humans, evidence has emerged that suggests D2 receptors could play a specialized role in facilitating spatial aspects of working memory. In a series of studies using the D2 receptor agonist bromocriptine in healthy human volunteers, Luciana, *et al*. (1992, 1997, 1998) observed ameliorated performance on a visuospatial delayed response task and no effect on the visuospatial non-delayed response task or other tasks assessing attention, arousal, and motor and perceptual functioning. At the beginning of each trial of the visuospatial delayed response task, the participant initially fixated their eyes on a central point of a computer screen. A black circle subsequently appeared somewhere on the screen in their peripheral vision. After a delay period of 500, 4000 or 8000 milliseconds, participants were prompted to touch the screen with a pen to indicate where the black circle was situated prior to the delay. In the visuospatial non-delayed response task, however, participants selected the location of the black circle immediately after it was presented instead of after a delay period. Specifically, Luciana and Collins (1997) showed that the D2 antagonist haloperidol impaired performance on this task more severely when subjects were asked to indicate the location of the circle after a short delay compared to those who were asked to recall the location of the circle immediately. Moreover, it was observed in the same study that antagonism and agonism of the D2 receptor modulated performance of memory tasks requiring spatial coordination but did not alter performance of working memory tasks lacking a spatial component. Thus, it is possible that D2 receptors could play a specialized role in controlling the spatial components of working memory.

Hippocampal D2 Receptors: A potential substrate for the facilitation of spatial working memory?

The juxtaposition of studies by Luciana, *et al*. (1992, 1997, 1998) and Muller, *et al.* (1998) serves to highlight the continuing controversy surrounding the involvement of D2 receptors in working memory. Various explanations have been offered to account for these contradictory results, including differences in the working memory tasks used across studies (Von Huben, *et al.* 2006), D2 receptor involvement in the focusing of attention via a striatal mechanism (Mehta, *et al.* 2004), D2 receptor facilitation of goal-directed behaviour (Luciana, *et al.* 1992) and D2 receptor contributions to the alteration of PFC inputs (Abi-Dargham, *et al.* 2003). None of these possible explanations can be discarded because all studies in humans, and some studies in animals, have used systemic administration as a means of targeting drugs to dopamine receptors, resulting in indiscriminate distribution of these drugs to the entire brain. Still, these theories do not adequately account for the selective facilitation of spatial working memory by drugs modulating D2 receptors observed in both monkey and human studies (Luciana, *et al.* 1992, 1997, 1998; Mehta, *et al.* 2004; Von Huben, *et al.* 2006). While animal studies overwhelmingly suggest that D1 receptors rather than D2 receptors critically modulate working memory processes subserved by the PFC, findings from human studies suggest that D2 receptors outside the PFC could potentially contribute to this cognitive process. Based on this proposition, and emerging evidence from animal studies and recent human neuroimaging and post-mortem studies, an alternative framework for the influence of D2 receptors outside of the PFC on working memory function will be outlined.

Post-mortem studies in humans have shown the precise anatomical location and relative distribution of D2 receptors in the brain. Using radioactively labeled D2 receptor agonist [3H]CV 205-502 and the D2 receptor antagonist [3H]Spiroperidol to label D2 receptors in post-mortem human brain tissue slices, Camps, *et al*. (1989) found moderate densities of D2 receptors in areas CA1 and CA3 of the hippocampus. Kohler, *et al*. (1991) used the radioactive D2 receptor ligand 125I-NCQ 298 and found that the highest densities of D2 receptors in the human brain tissue samples were located in the outer layers of the presubiculum and hilus of the dentate gyrus, in the hippocampus. Comparatively, Cortes, *et al*. (1989) showed that high densities of D1 receptors were located primarily in the striatum, while intermediate densities were located in the cerebral cortex, amygdala, mammillary bodies and area CA1 of the hippocampus of post-mortem human brain tissue slices. It can be inferred from these anatomical findings that moderate levels of D2 receptors are present in different regions of the hippocampus and directly adjacent brain tissue as well. Additionally, higher densities of D1 receptors relative to D2 receptors were found in the PFC. This evidence supports the proposition that D2 receptor modulating agents could exert their effects on spatial working memory outside of the PFC, specifically in the hippocampus.

Previous findings in animals have similarly suggested that dopaminergic transmission plays an important role in the function of normal spatial working memory (Beatty and Rush, 1983; Oades, 1981; Bushnell and Levin, 1993; Kim and Levin, 1996; Korz and Frey, 2007; Lopes Aguiar, *et al.* 2008; Simon, *et al.* 1986; Wilkerson and Levin, 1999; Wisman, *et al.* 2008), most likely through a pathway located in the hippocampus. In two separate studies with rats, Packard and White (1989, 1991) found that the D2 receptor agonist LY 171555 facilitated spatial working memory performance as assessed by the win-shift paradigm. Although it was found that intra-hippocampal injection of the D1 agonist SKF-38393 also facilitated spatial working memory performance in rats (Packard and White, 1991), this could have been due to the different drug administration methods used in the two studies. In the first study (Packard and White, 1989), rats received subcutaneous injections of each drug into the systemic circulation, while in the second study (Packard and White, 1991), rats received direct injections into the dorsal hippocampus. Previous research has indicated that the effect of D2 receptor modulation on spatial working memory is more robust when experimental manipulations target the ventral hippocampus specifically, rather than in combination with other areas (Wilkerson and Levin, 1999). This could account for the increased facilitation of spatial working memory that was observed after subcutaneous injection of a D2 receptor agonist compared to direct injections into the dorsal hippocampus.

Recent human neuroimaging studies further support the proposition that D2 receptors in the hippocampus could modulate cognitive functions subserved by the PFC. For example, Takahashi, *et al.* (2007, 2008) found a positive correlation between performance on tasks assessing memory, verbal fluency and executive cognitive function and D2 receptor binding in the hippocampus. The authors suggest that D2 receptors in the hippocampus influence memory functions subserved by this structure as well as other cognitive functions executed in the PFC. It should be noted, however, that the task used in these studies to assess "frontal lobe function" (the Wisconsin Card Sorting Task) does not explicitly test working memory function. Additionally, the authors highlight several specific neurochemical and neurophysiological processes initiated by D2 receptors in the hippocampus and suggest that they are at least partly responsible for influencing the dopamine receptor-cognitive function relationships demonstrated in their studies. These findings suggest that hippocampal D2 receptors influence circuits between this structure and the PFC and this could have an effect on executive cognitive functions, including working memory. The present framework extends this notion by suggesting a specific construct that is modulated by D2 receptors in the hippocampus, namely spatial working memory.

Smialowski and Bijak (1989) proposed that facilitation of spatial working memory is a direct result of changes to levels of excitatory and inhibitory stimulation and to long-term potentiation of hippocampal CA1 neurons. This hypothesis was derived from electrophysiological studies with rat hippocampal tissue slices that demonstrated a modulatory effect of D2 receptor agonists and antagonists on the firing rates of CA1 pyramidal neurons. Specifically, it was shown that D2 receptor agonists and antagonists caused increases and decreases, respectively, in CA1 hippocampal neuron firing rates in the rat brain. Conversely, they found that agonist-activation of the D1 receptor in the same hippocampal slices decreased the rate of CA1 neuronal firing. These results suggest that stimulation of D2 receptors in the hippocampus facilitates excitation of CA1 pyramidal neurons, while D1 receptor stimulation elicits the opposite response. A more recent study by Hammad and Wagner (2006) suggests that drugs that stimulate the D2-like family of receptors could increase the firing rates of CA1 pyramidal neurons by decreasing the effects of their local inhibitory signals. Other studies have also demonstrated that activation of D2 receptors in CA1 neurons of the hippocampus increases effects associated with long term potentiation (Swant and Wagner, 2006; Thompson, *et al.* 2005). While these findings point to a direct role for hippocampal D2 receptors in modulating spatial working memory functions, it is possible that these are indirect effects that are actually due to the increased acetylcholine release associated with D2 receptor stimulation (Imperato, *et al.* 1993; Umegaki, *et*

al. 2001). Nonetheless, extrapolating these findings to humans suggests that hippocampal D2 receptor activation by chemical agonists is at least partly responsible for the facilitation of spatial working memory seen in humans.

Conclusion

More work is needed to specify the nature of the relationship between hippocampal D2 receptors and components of working memory in humans. Specifically, future neuroimaging studies need to determine if hippocampal D2 receptor binding correlates with performance on tasks that explicitly test spatial and non-spatial working memory, such as the visuospatial delayed response task and the n-back task, respectively. If, contrary to expectations, a dissociation between these two constructs is not observed, it will be necessary to conduct subsequent functional and receptor neuroimaging studies in humans with tasks that separate working memory into putative component processes, such as retrieval, monitoring and manipulation. This would provide insight into the specific role that D2 receptors play in affecting specific component processes related to working memory. Additionally, the development of a clinically-viable D1 agonist would allow for a direct comparison of its effects on working memory to those initiated by a D2 agonist, such as bromocriptine. This approach could be used in unison with functional and receptor neuroimaging designs to enhance our understanding of the respective contributions of these receptor subtypes to working memory in humans. Furthermore, it will be necessary to elucidate the specific neurochemical and neurophysiological mechanisms that underpin the suspected relationship between hippocampal D2 receptors and spatial working memory.

Most research into the effect of modulating synaptic dopamine transmission on working memory has focused on the roles of D1 and D2 receptors in the PFC. While evidence in rodents and non-human primates has overwhelmingly pointed to D1 receptors as the most important receptors in the modulation of PFC-associated working memory functions, evidence from studies in humans is less conclusive. This paper has reviewed the major findings in the animal and human literature and has proposed a framework that implicates synaptic dopamine transmission at hippocampal D2 receptors in the modulation of spatial working memory. A fuller understanding of the neurochemical and neurophysiological mechanisms that underlie working memory could one day lead to clinically-relevant advances in the treatment of the debilitating cognitive impairments associated with neuropsychiatric diseases such as schizophrenia.

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