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Review

Pharmacological manipulation of human working memory

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Abstract

Rationale The goal of this paper is to briefly overview human studies that have examined pharmacological agents designed to enhance working memory function, with the idea of providing clues as to promising avenues to follow for the development of drugs likely to enhance working memory and other cognitive processes in individuals with schizophrenia.

Objectives We reviewed the studies that have used pharmacological agents designed to target the dopamine system, the noradrenergic system, the acetycholine system, the serotonin system, and the glycine site on NMDA receptors.

Results There are a large number of studies suggesting that dopamine agents can enhance working memory, though there remain conflicting issues regarding the role that baseline performance plays in modulating the influence of drug and the importance of different dopamine receptors. There is also consistent evidence that cholinesterase inhibitors can enhance working memory function, potentially through improved encoding of the information. There is less consistent evidence that noradrenergic alpha-2 agonists consistently improve working memory in humans, despite the large animal literature suggesting that these agents should have a beneficial effect on memory. As of yet, there is little evidence that agents targeting the glycine site of the NMDA receptor improve working memory, and data to suggest that enhancement of the serotonin system impairs working memory.

Conclusions Compounds geared towards enhancing the dopamine system and the acetycholine system remain promising avenues for the development of pro-cognitive drugs, though further work is clearly needed on developing agents that may more selectively target specific receptors.

Keywords Working memory - Dopamine - Acetylcholine - Serotonin - Glycine - Noradrenergic

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The goal of this article is to briefly overview the current state of knowledge about pharmacological manipulation of working memory in humans. By working memory, I mean the ability to store and manipulate information over short periods of time (Baddeley *1986*), a construct that contains multiple subcomponents. I focus on working memory because of the large body of literature suggesting that individuals with schizophrenia demonstrate deficits in working memory that are associated with disturbances in the function of dorsolateral prefrontal cortex (Barch *2003*). For example, individuals with schizophrenia are impaired on working memory tasks that require them to maintain information over a delay that is sometimes filled with distracting information (Park and Holzman *1992*; Coleman et al. *2002*; Tek et al. *2002*; Lencz et al. *2003*), as well as on tasks that vary the amount of information that needs to be maintained in working memory (Gold et al. *1997*; Callicott et al. *2000*; Barch et al. *2002*). Further, individuals at risk for the development of schizophrenia also show working memory deficits. For example, unaffected relatives of individuals with schizophrenia (i.e. parents, siblings, children) demonstrate deficits on tasks designed to measure working memory

function (Park et al. *1995a*; Callicott et al. *2003*). In addition, individuals who score high on measures of psychosis proneness and individuals diagnosed with schizotypal personality disorder (Barch et al., unpublished data; Park et al. *1995b*; Park and McTigue *1997*; Farmer et al. *2000*; Lenzenweger and Gold *2000*; Roitman et al. *2000*; Mitropoulou et al. *2002*) also display deficits on working memory tasks.

There are a number of different theories and hypotheses as to why working memory might be impaired in individuals with schizophrenia, and the varying mechanisms proposed have different implications for the neurobiological systems involved and the potential pharmacological targets of drug interventions. For example, a prominent hypothesis as to the source of working memory deficits in schizophrenia is that they reflect an impairment in the ability to maintain information over time due to an impairment in dopamine function (either hypofunction or hyperfunction) in prefrontal cortex (Goldman-Rakic *1991*; Arnsten and Goldman-Rakic *1998*). Similarly, my colleagues and I have put forth the hypothesis that impairments in working memory function in schizophrenia reflect a deficit in context processing, again due to impaired dopamine input into prefrontal cortex (Cohen and Servan-Schreiber *1992*; Barch et al. *2001*). Theories such as these suggest that agents that target the dopamine system in prefrontal cortex may be particularly effective at ameliorating working memory deficits in schizophrenia. Additional researchers have suggested that deficits in working memory reflect impairments in central executive functions as opposed to maintenance slave systems, or deficits in the updating and displacement of information in buffer systems (processes some would also consider executive functions) (Goldberg et al. *2003*). Theories such as these may also implicate a deficit in prefrontal cortex function (a region of the brain often associated with a range of executive functions), but could be due to neurotransmitter systems other than dopamine that are also important for intact executive function (e.g. norepinehprine).

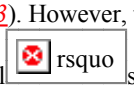
In contrast, other theorists have suggested that deficits in working memory may reflect hypofunction of *N*-methyl-D-aspartate (NMDA) receptors (Umbricht et al. *2000*), which might lead to deficits in the ability to transiently maintain information. Further, it has been suggested that some impairments in the transient maintenance of information may reflect impaired sensory precision due to impairments in NMDA function in temporal cortex (Rabinowicz et al. *2000*), which leads to impaired encoding of information into working memory. However, other researchers have suggested that such sensory impairments may reflect attentional as well as preattentive processes (Bruder et al. *1998*; Lencz et al. *2003*). These hypotheses would implicate agents that regulate NMDA receptor hypofunction as targets for improving working memory function.

To add to the complexity of understanding cognitive function in schizophrenia, working memory is clearly not the only cognitive function impaired in schizophrenia. However, it is likely that some common cognitive mechanisms give rise to deficits among individuals with schizophrenia on working memory tasks as well as cognitive tasks from other domains such as executive function, inhibition, attention and even episodic memory (Barch et al. *2002*, *2003*; Barch *2003*). As such, examining the types of pharmacological agents that have been shown to modulate working memory in both healthy individuals and individuals with schizophrenia may shed light on productive pathways to follow for developing new agents likely to benefit cognitive function in schizophrenia in a variety of domains. In this review, we focus on studies using agents that are primarily agonists of various neurotransmitter systems, studies that are typically designed to examine the beneficial effects of modulating a neurotransmitter system on a cognitive process such as working memory. We do not review the numerous studies that have focused primarily on examining agents (often antagonists) that are thought to impair particular cognitive functions. Studies using cognitive impairing agents clearly have a central place in theorizing and empirical working regarding the role of a particular neurotransmitter system in cognitive processing. However, given space constraints and the focus of the MATRICS project on developing pro-cognitive agents for use in schizophrenia, we wanted to specifically focus on evidence for the ability of different agents to improve cognition, as we thought this would be most useful in terms of identifying potential targets for future drug development.

The studies reviewed below used a wide range of tasks that have been argued to be working memory tasks. However, there may be important variations in the demands upon working memory made by different tasks. For example, some tasks more heavily tap the function of storage buffers (either articulatory rehearsal or the visual-spatial scratchpad) than central executive functions, while others more strongly tap central executive function. To the extent that a neurotransmitter system is more or less important for one versus another component of working memory, studies using tasks that tap different processes within working memory may generate conflicting results. For the most part, these tasks fall into four categories: 1) Span tasks that require individuals to maintain strings of letters or numbers and to repeat them back, either in the same order presented or in reverse order; 2) Delayed match to sample tasks, in which participants are given a cue to remember (spatial location, object, letter, etc.), presented with a delay of some length, and then asked to either reproduce the cue (e.g. point to location), choose between two probe items, or decide whether a presented probe was the same as the cue; 3) ldquo Nback rdquo tasks in which participants are presented with a series of items (letters, words, spatial locations, numbers) and asked either to respond on the current trial with the item presented ldquo *n* rdquo trials back (e.g. two trials), or to decide whether the current item is the same as the item seen ldquo *n* rdquo trials back; and 4) Self-ordered pointing tasks in which participants have to point to a string of items in a random order, requiring them to maintain information about the items previously chosen. We have also included studies that used the Wisconsin Card Sorting task (WCST). The WCST is not a working memory task per se, but has been argued to require working memory and has been used in a significant number of drug studies with individuals who have schizophrenia spectrum disorders. As such, we choose to include studies using the WCST with the recognition that this task is not a classical working memory task and may be even more likely to tap non-working memory processes than the tasks described above.

Dopamine system

Any discussion of pharmacological manipulation of working memory almost invariably starts with a focus on dopamine agents. This is largely driven by the wealth of studies in non-human primates suggesting that optimal dopamine function is critical for working memory performance (Goldman-Rakic et al. *2000*). For example, working memory function is impaired in non-human primates following 6-hydroxy-dopamine lesions in prefrontal cortex, or administration of dopamine antagonists (Sawaguchi and Goldman-Rakic *1994*). Further, administration of low dose dopamine agonists can improve working memory in monkeys (Williams and Goldman-Rakic *1995*), especially those with impaired performance associated with factors such as advanced age (Arnsten et al. *1994*; Cai and Arnsten *1997*; Castner et al. *2000*). However, we should note that the relationship of dopamine function to working memory integrity is a complex one that many researchers characterize as reflecting an inverted U-shaped curve. In other words, there may be an optimal level of dopamine function necessary for intact working memory performance, with either hypo- or hyperdopaminergic states leading to working memory impairments (Arnsten and Goldman-Rakic *1998*; Castner et al. *2000*). Thus, working memory function in individuals (or animals) whose baseline level of dopamine function is already optimal may be impaired by the administration of dopamine agonists, and may even in some cases be improved by the administration of dopamine antagonists. In contrast, working memory function in individuals or animals with reduced dopamine function in prefrontal cortex (e.g. people with schizophrenia, healthy aging) may show more evidence of improved function with the administration of dopamine agonists.

Although the relationships between dopamine function and cognitive processing are complex, there is growing evidence that the administration of dopamine agonists can improve cognition in humans, including working memory. To start, a number of studies using relatively non-selective agents such as amphetamine and methylphenidate have shown beneficial effects on working memory. Amphetamine is a non-selective dopamine agonist that works by increasing the release of dopamine and blocking its reuptake, while methylphenidate primarily increases the synaptic concentration of dopamine by blocking the dopamine transporter (Seeman and Madras *1998*). Several studies have shown that amphetamine or methylphenidate can improve working memory in healthy individuals, either in terms of accuracy or faster latencies without a loss of accuracy (Barch and Carter, manuscript submitted). For example, Barch and Carter found that healthy individuals had faster RTs on a spatial delayed match to sample task (with no decrease in accuracy) on amphetamine as compared to placebo (Barch and Carter, manuscript submitted). Mintzer and Griffiths found that amphetamine improved performance on a 2Back version of an Nback working memory task in healthy individuals when administered by itself, and also reversed working memory impairments induced by the sedative triazolam (Mintzer and Griffiths *2003*). In addition, several studies have found that amphetamine can ameliorate the deficits in short term/working memory induced by sleep deprivation (e.g. Pigeau et al. *1995*; Magill et al. *2003*). However, the results of other studies have sometimes been complex and the beneficial effects of these drugs may depend on the individual  rsquos baseline level of working memory performance. For example, Mattay found no change in Wisconsin Card Sorting performance in healthy volunteers with amphetamine, but did find increased task-related activity in dorsolateral prefrontal cortex (Mattay et al. *1996*). However, in more recent work, Mattay found that amphetamine improved performance on an Nback working memory task only in those individuals who were relatively poor baseline performers. In contrast, amphetamine impaired performance in individuals with good baseline performance. Interestingly, Mattay also found that the degree of task-related enhancement of dorsolateral prefrontal cortex activity on amphetamine was inversely correlated with degree of task-improvement (Mattay et al. *2000*), such that smaller increases in right prefrontal activity with amphetamine were associated with larger improvements in accuracy. Results such as this have been interpreted as reflecting increased efficiently of prefrontal activity with amphetamine.

On a similar vein, Mattay recently provided evidence that the influence of amphetamine on working memory performance and brain activity is modulated by genetic influences. Several recent studies have shown that individuals with the high activity form of the catechol O-methyltransferase (COMT) gene (the val allele), which is associated with higher catabolism of dopamine in prefrontal regions, have worse working memory performance than individuals with the low activity form (met allele) of the COMT gene (Egan et al. *2001*; Malhotra et al. *2002*). Mattay found that on amphetamine, individuals with the val/val genotype had faster RTs on an Nback working memory task (with no decrease in accuracy) and less dorsolateral prefrontal cortex activity as compared to placebo. In contrast, individuals with the met/met genotype had worse performance on amphetamine as compared to placebo, and increased dorsolateral prefrontal cortex activity, at least at high working memory loads (Mattay et al. *2003*).

Studies with methylphenidate have also had somewhat complex results. Mehta and colleagues found that methylphenidate improved spatial self-ordered pointing in healthy adults, accompanied by a reduction in task-related activity in dorsolateral prefrontal cortex (Mehta et al. *2000*). Eliott et al. found that methylphenidate improved performance on a spatial span task and spatial self-ordered pointing in healthy adults, but only if participants received the drug in the first session (Elliott et al. *1997*). However, a more recent study from Robbins group found that methylphenidate did not improve either spatial span performance or spatial self-ordered pointing in older healthy adults (Turner et al. *2003*). The influence of methylphenidate on working memory has also been examined in individuals with attention deficit hyperactivity disorder. De Sonneville and colleagues found the methylphenidate improved performance on a visual memory search task, though this effect was interpreted as reflecting an improvement in response organization rather than working memory per se (de Sonneville et al. *1994*). Berman also found that methylphenidate improved performance on a visual memory search task for accuracy, though they found that reaction times were slower at higher loads with methylphenidate (Berman et al. *1999*).

In sum, the studies using amphetamine and methylphenidate have shown some evidence of improvement in working memory, though there is some suggestion that improvement seems to be greater for those individuals who have relatively worse baseline performance. Although several

of these agents are not selective for dopamine, and these drugs influence neurotransmitter systems other than the dopamine system, such results are generally consistent with the hypothesis that administration of dopamine agonists can improve working memory.

A number of other studies have employed agents that are more selective for the dopamine system, such as bromocriptine, a D_2 agonist. These studies have demonstrated an improvement in spatial delayed match to sample performance on bromocriptine, though perhaps more so at lower doses (1.25 mg) than at higher doses (2.5 mg) (Luciana et al. *1992*, *1995*, *1998*; Luciana and Collins *1997*; Mehta et al. *2001*). Such evidence for dose dependent effects of bromocriptine may reflect the fact that higher doses are more likely to cause sedation, nausea, etc. and thus cause participants to drop out of the study. Interestingly, the one study that examined object as well as spatial delayed match to sample performance (Luciana and Collins *1997*) with bromocriptine found that this drug enhanced spatial but not object working memory. The interpretation of this result is that is may be consistent with the non-human primate evidence suggesting that different regions of prefrontal cortex represent different kinds of information in working memory (e.g. dorsal prefrontal cortex for spatial information, ventral prefrontal cortex for object), and that dopamine function may be more important for spatial information (Goldman-Rakic *1995*, *1996*). However, such segregation is less clear in humans (D rsquo Esposito et al. *1998*), and more work is clearly needed to examine this issue and to more definitively establish whether there is truly a dissociation between the effects of dopamine agonist on spatial versus object working memory.

There is also one study with bromocriptine that suggested that individuals with lower working memory span (as measured by the reading span task) show more of a cognitive benefit on the Wisconsin Card Sorting Task from bromocriptine than do individuals with higher working memory spans (Kimberg et al. *1997*). However, a more recent study by Kimberg found the opposite result for the Wisconsin Card Sorting Task (individuals with a higher span showed more benefit) despite using the same drug and dosage (2.5 mg), and no influence of drug on an Nback working memory task (Kimberg et al. *2001*).

Although of a number of the human studies have used bromocriptine, a D_2 agonist, the non-human primate literature has focused much more on the role that D_1 receptors play in working memory. For example, a growing amount of evidence suggests that D_1 receptor function may be particularly crucial for the integrity of working memory in non-human primates (Williams and Goldman-Rakic *1995*; Castner et al. *2000*; Goldman-Rakic et al. *2000*), and recent computational modeling work on the role of dopamine in prefrontal cortex has also emphasized the importance of D_1 receptors (Durstewitz et al. *1999*, *2000*). For a recent review of the computational modeling work on dopamine function in prefrontal cortex, see Cohen (*2002*). Unfortunately, however, there are no selective D_1 agonists available for use in humans. As such, to look at the role of D_1 receptors in human working memory, researchers have attempted to use what has been referred to as a pharmacological subtraction design. This has involved comparing a drug such as pergolide (a mixed D_1 and D_2 agonist) to a drug such as bromocriptine (D_2), with the logic that beneficial effects found with pergolide and not bromocriptine might reflect actions at D_1 receptors. For example, Muller compared pergolide to bromocriptine using a visual delayed match to sample task (16 s), and found that pergolide, but not 2.5 mg bromocriptine, led to improved performance (Muller et al. *1998*). More recently, Kimberg found that pergolide improved spatial and object delayed match to sample performance, but only in high as compared to low memory span participants (Kimberg and D rsquo Esposito *2003*). In contrast, however, Bartholomeusz compared 2.5 mg bromocriptine to 0.05 mg pergolide, and found that neither drug influenced performance on an object Nback working memory task (Bartholomeusz et al. *2003*). As such, there is a small amount of preliminary evidence that pergolide may be more effective than bromocriptine (at least 2.5 mg doses) at improving working memory, but clearly more research is needed to examine the role of D_1 receptors in human working memory.

Additional evidence for the importance of dopamine in working memory comes from studies of individuals with diseases that impair the dopamine system, such as Parkinson rsquo s disease. A number of studies suggest that unmedicated individuals with Parkinson rsquo s have deficits in working memory (Owen et al. *1997*). Further, a growing number of studies suggest that the administration of levodopa to individuals with Parkinson rsquo s disease can improve working memory (Lange et al. *1992*; Malpalani et al. *1994*; Fournet et al. *2000*; Costa et al. *2003*). For example, Costa found that levodopa improved both spatial and object delayed match to sample performance in individuals with Parkinson rsquo s disease, both for accuracy and reaction times (Costa et al. *2003*). Mattay examined the influence of levodopa on both behavioral performance and brain activity during an Nback working memory task. They found a tendency for Parkinson rsquo s patients to do better on the Nback working memory task on levodopa, though this effect was not statistically significantly. In addition, they found less activity in prefrontal cortex regions when the individuals were on levodopa as compared to off (Mattay et al. *2002*). Further, for some of the prefrontal regions, a reduction in activity on levodopa correlated with improved performance. Again, such a result has been interpreted as suggesting that dopamine-enhancing agents can lead to more efficient prefrontal cortex activity during working memory tasks.

A few studies have also directly examined the influence of dopamine agonist on working memory in schizophrenia. In early research,

Weinberger rsquo s group administered apomorphine to medication withdrawn individuals with schizophrenia and examined behavioral performance and brain activity during the Wisconsin Card Sorting Task (Daniel et al. *1989*). They found no significant change in performance with apomorphine, but did find a significant task-related increased in blood flow in dorsolateral prefrontal cortex (Daniel et al. *1989*). Weinberger rsquo s group has also examined the influence of administering low dose amphetamine to stably medicated individuals with schizophrenia taking haldol. The logic of such an approach is that cognition might be improved with schizophrenia with the co-administration of haloperidol and amphetamine because treatment with a typical antipsychotic blocks D_2 receptors in subcortical regions, preventing a negative impact of a dopamine agonists of positive symptoms, leaving D_1 receptors in regions such as prefrontal cortex free to benefit for enhanced cholinergic transmission (Goldberg et al. *1991*).

Of importance, administering amphetamine to these medicated individuals with schizophrenia improved Wisconsin Card Sort task performance and enhanced task-related brain activity in dorsolateral prefrontal cortex (Daniel et al. *1991*; Goldberg et al. *1991*). In more recent work, Barch and Carter examined a similar approach in individuals with schizophrenia, comparing placebo to low dose amphetamine in stably medicated individuals with schizophrenia (Barch and Carter, manuscript submitted). These researchers found that amphetamine significantly improved spatial delayed match to sample performance in individuals with schizophrenia, in terms of both accuracy and latency. However, performance was improved both in conditions with a delay and without a delay, suggesting that the potential mechanism of improvement might be through enhanced encoding of information into working memory, rather than improved storage or maintenance per se. On a related note, Siever rsquo s group has found that amphetamine can improve both Wisconsin Card Sorting performance and spatial delayed match to sample performance in individuals with schizotypal personality disorder, a disorder thought to share liability to schizophrenia (Siegel et al. *1996*; Kirrane et al. *2000*). Further, converging evidence for the importance of dopamine for working memory function in schizophrenia comes from research examining the availability of dopamine receptors in prefrontal cortex in schizophrenia. Abi-Dargham has reported that increased D_1 receptor availability in DLPFC was associated with working memory impairment in schizophrenia. These researchers have argued that increased D_1 receptor availability in schizophrenia may reflect compensatory upregulation secondary to chronic deficiency in D_1 receptor stimulation by dopamine (Abi-Dargham et al. *2002*).

In sum, the existing literature on the influence of dopamine enhancing agents on working memory provides reasonable support for the hypothesis that augmenting dopamine function can improve working memory. Further, there is evidence that enhancing dopamine function in schizophrenia can improve working memory, though this is most clear for individuals who are on stable doses of antipsychotic medication. In unmedicated individuals with schizophrenia, the administration of amphetamine can worsen some psychotic symptoms (Van Kammen et al. *1982*; Levy et al. *1993*). As such, simple administration of dopamine agonist to individuals with schizophrenia is clearly not the optimal pathway for enhancing cognition. In addition, further work is needed to determine the role that different dopamine receptors play in working memory, potentially through the development of new agents that more selectively target specific receptors such as D_1 or D_4.

Noradrenergic system

Although dopaminergic agents have clearly received the most attention in relationship to modulation of working memory in both healthy individual and individuals with schizophrenia, modulation of other neurotransmitter systems may also have a positive impact on working memory. For example, Amy Arnsten and colleagues have spearheaded a growing animal literature that suggests that noradrenergic alpha-2 agonists can help improve working memory in nonhuman primates, particularly in aged animals (Arnsten and Goldman-Rakic *1995*, *1998*; Arnsten et al. *1998*). Further, Arnsten and colleagues have suggested that one potential mechanism by which alpha-2 agonists might improve working memory (or protect it from interference) is potentially by decreasing distractibility (Arnsten and Contant *1992*). Spurred by the positive results in non-human primates, a number of researchers have examined the influence of alpha-2 agonists on working memory in human. However, the results in humans have been much more mixed than in the non-human primate models.

Coull and colleagues found that clonidine, an alpha-2 agonist, improved spatial self-ordered pointing in healthy adults, but only after participants were practiced on the task and only at a 2.5 mgr g/kg dose, and not a 1.5 mgr g/kg dose (Coull et al. *1995b*). In contrast, Coull found that a 1.5 mgr g/kg dose of clonidine impaired performance on an object self-ordered pointing task, again in participants who were practiced on the task (Coull et al. *1995b*). In contrast, Jakala has shown than clonidine at both low doses (0.5 mgr g/kg, 2 mgr g/kg) and higher doses (5 mgr g/kg) impaired both spatial delayed match to sample and self-ordered pointing performance in healthy adults, either by increasing errors or by slowing responding (Jakala et al. *1999a*, *1999b*). Similarly, Coull found that clonidine (both 1.5 mgr g/kg

and 2.5 mgr g/kg doses) impaired performance on a rapid visual information processing task with a working memory component in healthy adults (Coull et al. *1995a*). Jakala has also examined the impact of guanfacine, another alpha-2 agonist, on spatial working memory in healthy adults, again with mixed results. In one study, Guanfacine did not have any influenced on delayed matched to sample performance (either a 7 or 29 mgr g/kg) dose (Jakala et al. *1999b*). However, in a second study, a 29 mgr g/kg dose of guanfacine reduced errors on a self-ordered pointing task with a higher number of boxes, though a 7 mgr g/kg dose had no impact on the same task (Jakala et al. *1999a*). In patients with schizophrenia, Fields and colleagues found that longer-term administration of clonidine (target does of 0.8 mg/day) improved both working memory (as indexed by the Wechsler Memory Quotient) and episodic memory (as indexed by logical memory, visual memory, and paired associates performance) (Fields et al. *1988*). However, Friedman and colleagues did not find that guanfacine significantly enhanced spatial delayed match to sample performance in individuals with schizophrenia, at least in their primary analyses. Nonetheless, in non-parametric analyses restricted to individuals with schizophrenia taking risperidone, there were hints that guanfacine improved spatial working memory at a 5-s delay (the effects were less apparent at a 15-s delay) (Friedman et al. *2001*).

In general, the results of studies examining the influence of alpha-2 agonists on working memory in humans have not been nearly as positive as the results of studies in non-human primates with similar agents. It is not entirely clear what accounts for this discrepancy. However, one intriguing possibility relates to the fact that many of the non-human primate studies have been conducted in aged monkeys, a sample thought to have impairments in noradrenergic function due to age-related changes. As such, it is possible that alpha-2 agonists are more beneficial in improving working memory when the noradrenergic system is impaired in some way or even when working memory is impaired through any mechanism, and that alpha-2 agonists are less helpful, and even harmful, in individuals with intact noradrenergic function. Given that the majority of the studies reviewed above were conducted with healthy young adults who presumably have intact noradrenergic function, such a hypothesis would help explain the lack of positive results with alpha-2 agonists. Work by Newcomer provides some support consistent with this hypothesis (Newcomer et al. *1998*). These researchers found that guanabenz (an alpha-2 agonist used as an antihypertensive) had no influence on working memory when administered by itself, but that it was able to reverse the working memory impaired induced by administration of ketamine (Newcomer et al. *1998*). If it is true that alpha-2 agonists are more likely to improve working memory in individuals with impaired noradrenergic function, then it is possible that continued work with alpha-2 agonist in individuals with schizophrenia will reveal more positive effects if individuals with schizophrenia have impaired noradrenergic function.

Acetylcholine system

Several studies have also examined whether cholinergic agents might have an impact on working memory. Although cholinergic systems have been predominantly studied in relationship to their influence on episodic or long term memory, there is a growing recognition that encoding mechanisms important for episodic memory are also critical for working memory (Barch et al. *2002*). As such, agents that enhance cholinergic function might have a positive impact on working memory through enhancement of encoding into working memory. Consistent with this hypothesis, Furey and colleagues have shown that the cholinesterase inhibitor physostigmine can improve face delayed match to sample performance and reduce working memory task-related prefrontal cortex activity (Furey et al. *1997*, *2000b*). More specifically, Furey found that increased activity in medial occipital visual cortex was correlated with decreased reaction times on the working memory task, while *decreased* activity in prefrontal and temporal regions was correlated with decreased reaction times. In further work, Furey et al. found that physostigmine lead to a significantly enhancement of brain activity in extrastriate brain regions during stimulus presentation (Furey et al. *2000a*, *2000b*). They have interpreted this visual cortex activity enhancement as consistent with the idea that physostigmine may improve working memory and reduce prefrontal activity by leading to better encoding of visual information, which reduces the load on working memory performance (Furey et al. *2000b*). Interestingly, in very recent work, Siever rsquo s group has found that in individuals with schizotypal personality disorder, a short infusion of physostigmine tended to improve errors on a visual spatial working memory task with long delays (20–30 s), though not with a shorter delay (10 s) (Kirrane et al. *2001*).

Serotonin system

Two additional studies have examined the influence of serotonergic manipulations on working memory. Luciana has shown that fenfluramine, a serotonin agonist, impairs delayed spatial memory (Luciana et al. *1998*), and that tryptophan (a precursor to serotonin) loading impairs digit span backwards and affective working memory (Luciana et al. *2001*). Such results do not suggest that serotonergic enhancement will be an effective means of enhancing working memory, though clearly more work examining both agonists and antagonists of the system are needed. Lastly, the growing research on the role of NMDA receptor hypo-function in the pathophysiology of schizophrenia has lead to interest in agents that may counteract or compensate for such NMDA receptor dysfunction. For example, several studies in individuals with schizophrenia have examined

whether D-cycloserine, a partial agonist of the glycine site of NMDA receptors, can improve cognition when added to standard antipsychotic treatment in patients with primary negative symptoms. However, at least two studies have shown no change in digit span and/or Sternberg item recognition performance in individuals with schizophrenia treated with D-cycloserine (Goff et al. *1999*; Evins et al. *2002*).

In sum, the existing literature in humans on pharmacological agents that can enhance working memory function provides the most support for the idea that modulating the function of the dopamine system and the cholinergic system can improve working memory in humans. However, clearly more research is needed on compounds that can influence both of these systems. For example, we still know relatively little about which specific dopamine receptors are most important in humans for modulating working memory or other cognitive processes, and there is a clear need for the development of compounds that can more selectively target specific receptor subtypes. Further, even with the compounds that are somewhat more selective for the dopamine system, we do not yet understand the exact mechanisms by which any of these agents are having their positive influence on working memory. Their effects could be mediated by influences on the dopamine system itself, or downstream effects on other neurotransmitter systems, and understanding the precise mechanisms will presumably help with the development compounds even more effective at improving cognitive function.

The data on the positive influence of a cholinesterase inhibitor on working memory is also particularly intriguing, and seems a promising avenue for future research. Further, there is some evidence that adjunctive treatment with the cholinesterase inhibitor donepezil can improve visual and verbal episodic memory in schizophrenia (Buchanan et al. *2003*), though at least one other study did not report a positive influence of donepezil on cognitive function in schizophrenia (Friedman et al. *2002*). However, the inclusion criteria for this study were very strict, requiring individuals to perform two standard deviations below the mean on the California Verbal Learning Test. As such, the extreme level of impairment present in the individuals who were included in the study may have precluded identifying a level of improvement that might be obtained with less impaired individuals. Thus, it would be interesting to examine the influence of cholinesterase inhibitors on working memory in schizophrenia, do determine if such agents can improve working memory, either instead of or in addition to episodic memory function. The literature on noradrenergic agents in humans is much more mixed, with relatively little support for the hypothesis that alpha-2 agonists consistently improve working memory in humans. However, as noted above, it is possible that continued work with alpha-2 agonists in individuals with presumed impairments in noradrenergic function may reveal more positive benefits for working memory function. In addition, there is some evidence that alpha-2 agonist may improve other aspects of cognitive function in humans, such as sustained or selective attention in individuals with attention deficit hyperactivity disorder (Taylor and Russo *2001*). As such, further research on the influence of alpha-2 agonist on human cognition is clearly warranted.

We should also note that despite the promising avenues suggested by some of the studies described above, the results of some studies might not necessarily be applicable to guiding the development of drugs that improve cognition in individuals with disorders such as schizophrenia. The majority of the studies described above were conducted with healthy individuals who presumably do not have impairments in the neurotransmitter systems relevant to working memory function. However, it is possible that many of the agents used in studies with healthy individuals would not necessarily operate in the same way in individuals who have some sort of compromise in one or more neurotransmitter systems. As discussed earlier in the section on dopamine, many researchers accept the idea that the relationship between dopamine function and working memory follows an inverted U-shaped curve. If so, then one would clearly expect different results from the administration of dopamine agonists versus antagonists in individuals whose baseline state of dopamine function are at very different points on this curve. Further, it is probably true that individuals with schizophrenia suffer from abnormalities in multiple neurotransmitter systems, and that there may be interactions among these systems that also lead to differential responses to agents that target one or more of the systems. Thus, although studies in healthy individuals and animals can identify promising pathways for further drug development, we must also focus drug development efforts on mechanisms that may be uniquely beneficial for individuals with impairments in one or more neurotransmitter systems.

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