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Pharmacological Enhancement of Memory and Executive Functioning in Laboratory Animals

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Investigating how different pharmacological compounds may enhance learning, memory, and higher-order cognitive functions in laboratory animals is the first critical step toward the development of cognitive enhancers that may be used to ameliorate impairments in these functions in patients suffering from neuropsychiatric disorders. Rather than focus on one aspect of cognition, or class of drug, in this review we provide a broad overview of how distinct classes of pharmacological compounds may enhance different types of memory and executive functioning, particularly those mediated by the prefrontal cortex. These include recognition memory, attention, working memory, and different components of behavioral flexibility. A key emphasis is placed on comparing and contrasting the effects of certain drugs on different cognitive and mnemonic functions, highlighting methodological issues associated with this type of research, tasks used to investigate these functions, and avenues for future research. Viewed collectively, studies of the neuropharmacological basis of cognition in rodents and non-human primates have identified targets that will hopefully open new avenues for the treatment of cognitive disabilities in persons affected by mental disorders.
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INTRODUCTION

For nearly a century, studies of cognition have shown that certain pharmacological compounds can exert 'pro-cognitive' and/or nootropic effects, improving cognition and memory, respectively, in otherwise normal laboratory animals. Stemming from the original published findings of Lashley (1917), there have been a plethora of studies designed to clarify the mechanisms and specific targets through which drugs may enhance cognition in experimental animals. Elucidation of the particular brain substrates through which drugs may enhance memory and cognition is of basic scientific interest in its own right, as these findings provide important insight into the brain processes underlying representational processes that are used to guide behavior. However, animal research on this topic also provides direct practical benefits that further the discovery of novel compounds, which may lessen the burden of cognitive disability associated with most neurological and psychiatric disorders. Research with animal models represents the first key step in the drug discovery process because of the demonstrable face, as well as construct, validity of many cognitive tests that are used with both animal and human subjects. Historically, the primary thrust of this research has been to develop treatments to improve memory functions in individuals afflicted with diseases that erode declarative memory functions, such as Alzheimer's dementia. More recently, however, it has become apparent that deficits in cognition, reasoning, and executive function are quite common sources of significant functional problems in a range of psychiatric disorders that include, but is not limited to, schizophrenia, bipolar disorder, major depression, attention deficit/hyperactivity disorder, and substance-use disorders (Bolla *et al*, 1998; Barch, 2005; Doyle, 2006; Clark *et al*, 2009). For those individuals affected by these conditions, cognitive impairment appears to be a quantitative indicator of liability for psychiatric disorders, as well as a primary

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mediator of psychosocial impairment. Thus, development of novel treatments to normalize cognitive functioning is of the highest priority in order to enhance the long-term outcome of these individuals.

In this review, we will provide an overview of research on facilitating mnemonic and cognitive processes in animals through pharmacological means. We will initially review some of the research that has concentrated on improving memory functions, as work in this area had its genesis in the study of memory enhancement. We will then discuss more recent data related to improving more complex forms of cognition, with a particular emphasis placed on those processes mediated by the frontal lobes. Specifically, this discussion will focus on three key executive functions that have been shown to be sensitive to pharmacological improvements: (1) the ability to deploy, sustain, focus, shift, and divide attentional resources; (2) working memory, the maintenance and manipulation of information about abstract rules, recent events, goals, and actions; and (3) different types of behavioral flexibility, ranging from simpler (response inhibition, extinction) to more complex (reversal learning, set-shifting) forms. An additional emphasis will be to highlight some of the procedures used to assess these functions in animals, and issues/complications related to this aspect of animal cognition research.

METHODOLOGICAL ISSUES ASSOCIATED WITH RESEARCH ON COGNITIVE ENHANCERS

Normal *vs* Impaired Subjects

If the main aim of animal research on cognitive enhancement is to develop treatments for executive dysfunction associated with certain disease states, one issue to consider when assessing their potential benefit is how these drugs may affect cognition in normal subjects *vs* those with natural or experimentally induced impairments (Floresco *et al*, 2005). There are numerous examples where administration of a variety of compounds can improve different types of memory and cognitive functioning in normal animals. However, the cognition-enhancing effects of other drugs are only observed in subjects exhibiting poor baseline performance or experimentally induced deficits, whereas providing no measurable effects in normal animals. For example, atypical antipsychotics such as sulpiride or clozapine alleviate attentional or working memory impairments that occur following disruptions in the prefrontal cortical function, but these same drugs impair performance when administered to intact control subjects (Murphy *et al*, 1997; Jentsch *et al*, 1997; Passetti *et al*, 2003a, b; Wolff and Leander, 2003; Baviera *et al*, 2008). Another classical example comes from studies with drugs that enhance mesocortical dopamine transmission. D_1 receptor stimulation can have biphasic effects on functions such as working memory, improving functioning in animals when baseline levels of performance are poor, but impairing behavior when baseline performance is good (Granon *et al*, 2000; Chudasama and Robbins, 2004). Thus, although testing the effects of a particular drug on cognition in intact animals may be a useful initial screen for its utility in treating the cognitive deficits associated with a particular disorder, a null effect does not necessarily preclude the possibility that it would have no beneficial action on a perturbed system. Therefore, an item receiving active discussion in the field is whether interventions that will improve cognition in patients with psychiatric or neurological disorders can be successfully identified by psychopharmacological studies in normal animals, or whether these efforts require the generation of an 'impairment model' whose cognitive deficits are being targeted or corrected by the intervention.

Arguments in favor of using normal subjects in drug discovery include: (1) the pathophysiologies of relevance to animal modeling are often not known and are difficult to mimic well when they are known, (2) 'normal' does not equal optimal in as much as natural variation in brain function in normal animals often captures a continuum from high to low abilities and that 'disease' is best thought of the lowest range of these continua, and consequently, (3) normal subjects often exhibit characteristic responses qualitatively identical to the ones that patients with a disorder will make. Arguments against the use of normal animals include: (1) the mean and standard deviation for performance of a cohort of normal subjects may not exhibit sufficient inter-subject variability to easily and robustly detect an improvement ('ceiling effects' are present) and (2) the pathophysiological processes inherent in mental disorders may counteract the ability of a subject to express a pharmacological improvement observed in normal subjects.

Models of impairment come in many forms, ranging from the use of a manipulation to produce impairment (irrespective of the cause) or to the modeling of a specific, theorized disease process. One common type of impairment model that has been employed to test the potential cognitive-enhancing effects of certain drugs is the administration of muscarinic acetylcholine receptor antagonists, which impair a broad range of memory, attention, and executive function-related processes (Safer and Allen, 1971; Greenwald and Davis, 1983; Robbins *et al*, 1997). Whether or not cholinergic dysfunction is linked to the pathophysiology of disorders such as ADHD or schizophrenia, these models may be valuable to elicit impairments that may induce sufficient inter-subject variability to detect drug-induced improvements. Other manipulations are more biologically targeted. For example, in schizophrenia, there is strong empirical evidence linking NMDA hypofunction to the expression of cognitive impairments (Javitt and Zukin, 1991; Jentsch and Roth, 1999; Olney *et al*, 1999). Similarly, acute or chronic stress has long been known to exert detrimental effects on cognition in human beings and may be a contributing factor to impairments associated with numerous psychiatric disorders (Arnsten, 2007; Hains and Arnsten, 2008). Accordingly, a substantial amount of preclinical research focusing on cognitive enhancers has

utilized acute or repeated administration of non-competitive NMDA receptor antagonists or physical or psychological stressors to induce temporary cognitive deficits that theoretically share biological determinants with those found in the idiopathic condition. In addition, as observed in human beings, normal aging in animals has been associated with cognitive dysfunction. Each of these manipulations induces reliable impairments across multiple domains of cognitive functioning, and as such, many of the studies discussed in this review have employed these particular models to assess the cognitive-enhancing effects of different compounds.

Although no one should ignore the strong arguments made in favor of disease modeling as an approach in the development of cognitive enhancers, there is also substantial evidence that it is not required to achieve a milestone in this effort. One clear example derives from the study of modafinil on inhibitory control processes. This drug improves the ability to stop a response in normal rats (Eagle *et al*, 2007), normal human beings (Turner *et al*, 2003), patients with schizophrenia (Turner *et al*, 2004b), and patients with ADHD (Turner *et al*, 2004a). Another example is the ADHD drug atomoxetine, which enhances inhibitory control in normal rats and monkeys (Robinson *et al*, 2008; Seu *et al*, 2009), in normal human beings (Chamberlain *et al*, 2007b) and in patients with ADHD (Chamberlain *et al*, 2007a). These efforts show the potential for identifying pharmacological enhancement of cognitive functions in normal animals and human beings that subsequently predict their clinical utility.

With that in mind, evidence is quite strong that drug discovery in normal animals is an endorsable strategy. As will be discussed in the following sections, there are many examples of pharmacological enhancement in normal animals that systematically predict these same responses in human beings. Nicotinic receptor agonists, and their effects on performance of tests of vigilance, attention, and working memory are among the clearest examples (Hahn *et al*, 2003; Levin and Rezvani, 2006; Sarter *et al*, 2009). When sufficiently sophisticated tests that challenge animal cognition in relevant ways are used, there can be ample inter-subject variability to detect their effects. That is not to say that every animal exhibits the same response. Indeed, baseline characteristics (stemming from individual variation along the continuum of function) can predict performance enhancement in cognitive tests (Eagle *et al*, 2007). Therefore, if a study is well designed, it uses a sufficiently validated task with appropriately parameterized features and incorporates a sufficiently large number of animals to capture the range of performance, the potential for measuring cognitive enhancement is good.

Enhancing One Function at the Cost of Another

There is considerable overlap between the neural circuitry and neurochemical systems that regulate different processes underlying memory and executive functioning. At the same time, there is ample evidence to suggest dissociable contribution by different circuits to different functions. This leads to the possibility that a particular treatment may enhance some cognitive functions at the expense of others, ameliorating dysfunction in one circuit, whereas at the same time interfering with processes mediated by others. For example, dopaminergic medication for Parkinsonian patients alleviate implicit learning and memory problems related to striatal dysfunction, but may simultaneously cause excessive activation of relatively intact prefrontal dopamine systems leading to deficits of response inhibition, behavioral flexibility, and decision making (Cools *et al*, 2006, 2007; Torta *et al*, 2009). Thus, the potential benefit of a particular treatment in improving one domain of cognition must be weighed relative to the potential for these treatments to interfere with other functions.

With these considerations in mind, we now turn to a review of available data on cognitive enhancement in laboratory animals. Of particular interest are pharmacological interventions that exert the broadest gains on multiple dimensions of cognition and that exert effects in normal subjects and models of impairment.

MODULATION OF LEARNING AND MEMORY

Pharmacological improvements in learning and memory have traditionally been assessed by treating animals before initial training on certain learning task, revealing enhanced performance upon subsequent testing in a drug-free state. This approach, in combination with a variety of discrimination, avoidance and other learning paradigms has proven fruitful in identifying drugs that may improve the formation of new memories. However, interpretation of studies that employ pre-training drug manipulations is complicated, as many drugs that may enhance memory when administered before training may also exert other, non-specific actions on sensory, motor, or motivational processes. For example, by enhancing attention or arousal, a drug may facilitate encoding-related processes. These specific effects are relevant and discussed further below, but are not synonymous with a nootropic effect. These complications in interpretation can be overcome using post-training drug manipulations, whereby subjects remain drug free during initial training and retention testing. The rationale behind this approach stems originally from Hebb's notion that memory formation progresses from labile to more stable forms, a process that may continue after initial exposure to a learning context (McGaugh and Roozendaal, 2009). Observing improved memory upon administering drugs immediately after initial training on a task (but not when drug treatment is delayed for a period after learning) provides a more conclusive demonstration that improvements in memory retention induced by a particular compound are directly attributable to augmentation of memory consolidation.

When discussing how drugs may enhance learning, it is important to emphasize the now well-established notion that there exist multiple learning systems in the brain, each of which may be characterized by fundamentally different rules of operation. Each of these systems addresses a specialized set of functional problems that cannot be solved as readily by the cognitive operations regulated by other systems and are subserved by anatomically distinct brain regions. For example, the hippocampus has long been implicated in learning about the relationship between different stimuli (eg, spatial learning) (Morris *et al*, 1982; Shapiro and Eichenbaum, 1999). Alternatively, acquisition of stimulus–response associations (ie, instrumental or habit learning) is mediated in part by different portions of the dorsal striatum (Packard and Knowlton, 2002). Associative learning about discrete environmental stimuli predictive of either aversive or appetitive reinforcers is critically dependent on different subregions of the amygdala (Ledoux, 2000; Baxter and Murray, 2002). Despite the differences between these systems, not only with respect to the types of information they process, but also to their cellular and neurochemical architecture, a remarkable finding is that certain classes of drugs appear to uniformly enhance learning across these different systems. For example, pre- or post-training administration of stimulant drugs, such as *d*-amphetamine, have been shown to enhance spatial learning (Packard and White, 1989; Brown *et al*, 2000), response learning (Packard and White, 1989), and the acquisition of emotional memories (Hitchcott *et al*, 1997; Wood and Anagnostaras, 2009). An exhaustive list of the types of compounds that can enhance acquisition/consolidation of these different types of memories goes beyond the scope of this review. However, some notable drug classes include those that enhance activity at cholinergic (Packard *et al*, 1990; Salinas *et al*, 1997), glutamatergic (Land and Riccio, 1999; Packard, 1999; Lee *et al*, 2006), and dopaminergic (Packard and White, 1989, 1991; Hitchcott *et al*, 1997) synapses.

A large area of work on pharmacological enhancement of *memory* has focused on identifying drugs that improve aspects of long-term declarative memories. One particularly attractive aspect of this research is that this form of memory can be assessed in both human beings and animals, adding to the construct and predictive validity of these tests. Almost all work in laboratory animals has focused on aspects of declarative memory measured by the ability to exhibit recognition, which is thought to represent the general sense of familiarity after exposure to a stimulus. In human beings, monkeys, and rats, recognition memory can be assessed by probing subjects' ability to guide choice behavior between novel and previously -experienced stimuli at test (eg, list learning in human beings, delayed non-match to sample with trial unique stimuli in monkeys, social or novel object recognition in rodents). The focus on recognition memory has stemmed from the original proposal by Tulving (Wheeler *et al*, 1997) that episodic memory (rich memories of personal experiences that can be flexibly recalled) is human specific, as well as from the difficulty of showing similar processes in animals. That said, recent advances showing competency in episodic memory tasks in non-human animals (Clayton and Russell, 2009) supports future research in this area.

In non-human primates, recognition memory is often assessed using procedures where subjects experience a set of stimuli, and later in time, those stimuli are presented in pairs with novel items; the subjects are trained to select the novel item in a pair in order to correctly indicate familiarity and to obtain a reward. Using procedures like this, Aigner and co-workers showed enhanced recognition memory performance after the administration of pro-cholinergic manipulations (acetylcholinesterase inhibitors) or of D-cycloserine—a positive allosteric modulator of the NMDA/glutamate receptor (Aigner and Mishkin, 1986; Matsuoka and Aigner, 1996). The beneficial effects of acetylcholinesterase inhibitors may be mediated in part by the activation of muscarinic receptors, as blockade of these receptors impairs this form of memory in both human beings and animals (Aigner and Mishkin, 1986; Robbins *et al*, 1997), and treatment with muscarinic receptor agonists improves recognition memory in aged rats (Prediger *et al*, 2006). Recent work has suggested that the nootropic effects of acetylcholinesterase inhibitors may also depend upon stimulation of brain nicotinic receptors (Katner *et al*, 2004; Bitner *et al*, 2007). In the case of D-cycloserine, its effects were observed in normal monkeys or in subjects exhibiting memory deficits elicited by NMDA receptor antagonists and/or muscarinic antagonists (Matsuoka and Aigner, 1996). What remains unknown, however, is what aspect of memory was enhanced, as these agents were given before list learning itself. In addition, all agents exhibited complex non-monotonic dose–response curves (inverted-U dose–effect functions), highlighting an often-observed result in studies of cognitive enhancement.

Similar paradigms have been used in rodent models, which are more amenable to routine psychopharmacological testing. Here, subjects are typically exposed to a sample stimulus, and after a delay of minutes to hours, they are presented with that stimulus plus a novel one. Memory is reflected in the tendency of rats to approach the novel stimulus in the pair (Bevins and Besheer, 2006). In most cases, pharmacological treatments are given before the 'test' phase where the animal must retrieve and use the memory to successfully complete the task. As observed in primates, extensive data using these procedures in rats indicate that positive modulation of NMDA- or AMPA-dependent glutamate transmission and nicotinic receptor activation enhances recognition memory in normal and NMDA-antagonist-treated rats/mice (Robbins and Murphy, 2006; Bertaina-Anglade *et al*, 2007; Boulay *et al*, 2008; Smith *et al*, 2009; Woolley *et al*, 2009; Damgaard *et al*, 2010). Similarly, enhancing cholinergic transmission via acetylcholinesterase inhibitors can attenuate deficits in recognition memory in aged rats (Scali *et al*, 1997), and systemic administration of a selective muscarinic M1 agonist also enhance memory

in normal rats (Bradley *et al*, 2010). Likewise, direct or indirect stimulation of nicotinic receptors (both beta-2- and alpha-7-containing) enhances recognition memory in normal rodents or in subjects with pharmacologically-induced impairments (Wishka *et al*, 2006; Boess *et al*, 2007; Pichat *et al*, 2007; Hashimoto *et al*, 2008; Hauser *et al*, 2009; Roncarati *et al*, 2009; Sydserff *et al*, 2009; Noda *et al*, 2010; O'Donnell *et al*, 2010). A key brain region where these drugs may act is the perirhinal cortex, as infusion of glutamate or muscarinic antagonists in this region impairs recognition memory in rodents (Winters *et al*, 2008).

More recent research has revealed several other molecular targets that may exert nootropic effects in these tasks. For example, manipulations of serotonin 5-HT_6 receptors can enhance recognition memory in normal rats, and ameliorate impairments in memory induced by cholinergic or glutamatergic antagonism, aging, or early social isolation (Fone, 2008; Kendall *et al*, 2010). What is particularly intriguing about these studies is that memory enhancements have been observed following either blockade *or* stimulation of these receptors with selective antagonists or agonists. Furthermore, these effects may be mediated in part by the modulation of glutamatergic and cholinergic transmission (Kendall *et al*, 2010). Other promising targets for enhancing recognition memory include H3 histamine receptor antagonists (Kim *et al*, 2004; Southam *et al*, 2009; Giannoni *et al*, 2010), mGluR5 glutamate receptor antagonists (Ballard *et al*, 2005; Liu *et al*, 2008), inhibitors of catecholamine reuptake (Chuhan and Taukulis, 2006; Tzavara *et al*, 2006), and dopamine or norepinephrine receptor agonists (Roozendaal *et al*, 2008; Woolley *et al*, 2008).

As noted above, an issue that often remains to be clarified is how each of these mechanisms contributes to the discrete phases of recognition memory, including encoding during the sample phase, consolidation during the post-sample phase, and retrieval during the test phase. It is possible that some manipulations (eg, gluamatergic) increase encoding and/or consolidation while distinct mechanisms mediate retrieval; the participation of candidate neurotransmitter systems in each of these aspects of memory are not completely well known. Whether or not these compounds exert their beneficial effects by acting on temporal lobe structures such as the perirhinal cortex or other downstream nuclei also remains to be explored. In addition, the ability of agents to target attentional or arousal processes or working memory may also exert effects in recognition memory tests.

Mechanisms of Memory Enhancement

It bears mentioning that classes of drugs that can improve memory formation across different memory systems have also been shown to enhance synaptic plasticity in each of the brain regions that mediate different types of learning. For example, it is well-established that glutamate transmission is critical for increasing synaptic strengths in the hippocampus, as well as the striatum (Kombian and Malenka, 1994) and amygdala (Paré, 2004). Furthermore, cholinergic and dopaminergic transmission has also been shown to play a role in mediating long-term potentiation in each of these regions (Wickens *et al*, 1996; Calabresi *et al*, 1999, Centonze *et al*, 2001; Bissière *et al*, 2003; Park *et al*, 2004). Thus, from a parsimonious view, the ability of these compounds to enhance memory formation may be mediated through an enhancement of the excitability of neurons in a particular brain region that governs a certain type of learning, which in turn may enhance potentiation of synapses that were active during learning.

Like the different types of learning described above, recognition memory has also been posited to be mediated in part by increases in synaptic strengths, particularly in the perirhinal cortex (Winters *et al*, 2008). However, long-term depression of synaptic plasticity has also been proposed to be a key cellular mechanism that underlies this form of memory. In keeping with this notion, long-term depression in the perirhinal cortex is dependent on both glutamatergic mGluR2 and NMDA receptors, as well as cholinergic muscarinic transmission (Cho *et al*, 2000; Massey *et al*, 2001), and antagonism of each of these receptors impairs recognition memory (Barker *et al*, 2006; Winters *et al*, 2008). Thus, recognition memory may be facilitated by decreases in synaptic strengths that result in decremental neuronal responses evoked by exposure to familiar stimuli, which in turn may result in a contrasting enhancement of neural activity driven by novel stimuli (Brown and Bashir, 2002; Winters *et al*, 2008).

In addition to having direct actions on synaptic plasticity within a particular memory system, certain drugs may enhance consolidation through the modulation of brain systems that are capable of facilitating multiple memory systems, at once. Specifically, it has been proposed that certain drugs may activate the amygdala, which in turn may facilitate memory formation mediated by other brain regions. Thus, pharmacological activation of the amygdala can facilitate the formation of memories processed by other systems (such as hippocampally mediated spatial memories or striatal-mediated habit memories), even though the amygdala does not appear to contribute to the cognitive operations underlying these forms of learning (Packard *et al*, 1994; Packard and Teather, 1998; Hatfield and McGaugh, 1999). Support for this notion comes from the findings that infusions of a variety of drugs directly into the amygdala improve learning mediated by the hippocampus, striatum, as well as recognition memory mediated by the perirhinal cortex (Packard *et al*, 1994; Roozendaal *et al*, 2008). These include *d*-amphetamine (Packard and Teather, 1998) and agents that directly or indirectly activate adrenergic transmission (Wingard and Packard, 2008; Roozendaal *et al*, 2008). Importantly, lesions of the amygdala do not interfere with these forms of learning (McDonald and White, 1993), suggesting that activation of the amygdala may influence neural plasticity in other brain regions either though direct or polysynaptic pathways (McGaugh *et al*, 2002). Given the importance of the

amygdala in emotional processes, it is plausible that this region plays a crucial role in the enhancement of memory elicited by the emotional salience of highly charged events. This notion meshes well with studies of human memory encoding, which have shown that memories associated with heightened emotional states tend to be encoded and retrieved more effectively (Cahill *et al*, 1994; Packard and Cahill, 2001).

Memory Retrieval

The field of drug-induced memory enhancement has focused primarily on augmenting the consolidation of new memories. In comparison, there have been relatively few studies on how drugs may enhance memory *retrieval*. Addressing this question is of particular relevance when it comes to devising novel approaches to ameliorating memory impairments associated with diseases such as Alzheimer's, which is associated with retrograde as well as anterograde amnesia.

Mounting evidence from human imaging and animal studies suggests that different regions of the prefrontal cortex (PFC) play a key role in retrieval of content from long-term memory. In the past 10 years, fMRI studies have showed increased activation of prefrontal networks (in particular, the lateral PFC), during retrieval of different types of memories. These include semantic (Mitchell and Johnson, 2009), episodic (Lee *et al*, 2000) emotional (Buchanan, 2007), and rule-related (Bunge, 2004) memories. These findings are complemented by studies in rodents, wherein subjects acquire information in an intact state and receive reversible inactivation of the medial PFC before memory retrieval. This approach has confirmed that suppression of neural activity in the PFC impairs retrieval of Pavlovian fear memories (Corcoran and Quirk, 2007), spatial memories (Jo *et al*, 2007; Churchwell *et al*, 2010), and temporal order memory (Hannesson *et al*, 2004). These findings would suggest that the development of drugs, which may enhance certain aspects of the prefrontal neural activity, may prove to be a fruitful strategy in designing compounds that may enhance memory retrieval.

As discussed previously, noradrenergic transmission plays a crucial role in memory consolidation, and also appears to play a critical role in the retrieval of contextual fear memories (Murchison *et al*, 2004). Retrieval of these memories is impaired in a selective manner when norepinephrine is genetically deleted, and it is enhanced after the administration of beta adrenoceptor agonists. The ability of beta adrenergic agonists to enhance memory retrieval, and of beta adrenergic antagonists to impair it, appears to depend on effects in both the PFC (Mueller *et al*, 2008) and the hippocampus (Murchison *et al*, 2004).

Dopaminergic mechanisms in the PFC have also been implicated in memory retrieval. For example, in one study (Floresco and Phillips, 2001), rats were well trained on delayed variant of a radial arm maze task, consisting of a training phase and test phase separated by a relatively short delay (30 min). On test day, the delay between training and retrieval phases was increased to 12 h. In control rats, increasing the delay between training and retention testing led to a degradation of a memory trace through normal temporal decay, increasing the number of retrieval phase errors relative to their performance using the shorter delay. However, infusions of a D_1 receptor agonist into the medial PFC before the retrieval phase improved performance relative to controls (Figure 1). Similar enhancements in object recognition memory have been observed following systemic treatment with a D_1 agonist before memory retrieval (Hotte *et al*, 2005). These findings further support the notion that compounds that may augment D_1 receptor activity or its intracellular signaling pathways, particularly in the PFC, may serve as a useful target for facilitating memory retrieval.

PFC AND EXECUTIVE FUNCTIONS

Many real-life problems require coordinated and simultaneous encoding and/or retrieval of different memories across multiple systems and integration of information with representations of recent experiences and abstract rules in order to solve these problems in an efficient manner. The effortful cognitive processes required under these

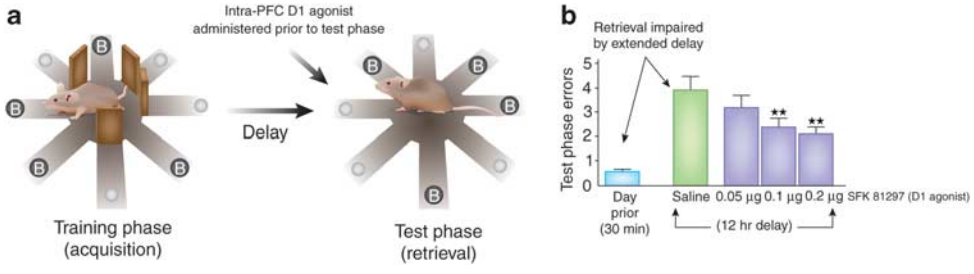

Figure 1. Dopamine D_1 receptor agonists improve memory retrieval. The delayed response variant of the radial-arm maze task (top) consists of a training (acquisition) and a test (retrieval) phase (a). During the training phase, the rat must retrieve four pieces of food from four randomly selected arms, with the four remaining arms blocked. The rat is then removed from the maze for a delay, and then placed back on the maze for the test phase. The arms that were blocked previously are now open and baited. In well-trained rats performing this task, extending the delay from 30 min to 12 h increased the number of retrieval errors in control rats (white and gray bars) (b). However, infusions of the D_1 agonist SKF 81297 directly into the medial PFC before retrieval improved performance, $^*p<0.05$, $^{**}p<0.01$ *vs* saline. Adapted from Floresco and Phillips (2001).

conditions include selective allocation of attentional resources and manipulation of multiple forms of information processed by different memory systems. In addition, novel or unexpected changes in rules or reinforcement contingencies may necessitate the suppression of memories processed by one system, in order to permit learning managed by other systems to optimize behavior. These types of cognitive operations have been termed executive functions and may be defined as a collection of brain processes whose role is to execute and guide patterns of behavior in accordance with internally generated goals or plans. Often, these types of functions are engaged when it is necessary to over-ride responses that may otherwise be automatically elicited by stimuli in the external environment. It is well established that the PFC plays an essential role in mediating a variety of executive functions (Fuster, 2008). Across mammalian species, damage to the frontal lobes leads to impairments on tasks that require different aspects of executive functioning, such as selective attention, working memory, and behavioral flexibility. Furthermore, it is now commonly accepted that to affect overt changes in ongoing behaviour, information processed by the PFC interfaces with the motor and motivational systems via descending connections to the basal ganglia.

The PFC is susceptible to modulation by a diversity of neurochemical influences, each of which contributes to this brain region's functional integrity in a distinct manner. In addition to glutamate and GABA arising from afferent input and intrinsic neurons, the PFC receives innervation from all of the major ascending neuromodulatory pathways, including dopamine, serotonin (5-HT), noradrenaline, acetylcholine, histamine, etc. This arrangement, combined with the multiple receptor subtypes for each of these transmitters and their intracellular signaling pathways that are expressed in PFC neurons provide for multiple targets for pharmacological modulation that may enhance functioning of prefrontal networks and improve executive functioning. With this in mind, the remainder of this review will highlight some of the recent work in experimental animals that has showed pharmacological improvement in different types of executive functioning mediated by the PFC and its subcortical afferents.

PHARMACOLOGICAL ENHANCEMENT OF ATTENTION

Pharmacological modulation of the ability to deploy, sustain, focus, shift, and divide attentional resources is of significant relevance to a number of neuropsychiatric disorders in which cognitive deficits hinge, at least in part, upon deficits in the top–down control of attention (eg, ADHD, schizophrenia, autism, etc). Given the broad relevance of controlled attentional processing to a host of other cognitive mechanisms, it is widely believed that deficits in attention contribute to problems with other mnemonic and executive functions. Accordingly, it is possible that pharmacological enhancements in attention will exert broad gains to other domains of cognition.

Most high-merit pre-clinical research on attention has focused on the performance of choice or simple reaction time tasks that place demands on various aspects of attentional control. For example, in classical signal detection tasks, subjects are trained to sustain focused attention on a potential stimulus over a temporally unpredictable period. In most versions, rats watch a light bulb for a visual stimulus for a variable period of time; at some point during their waiting, two levers will be presented to the subjects. If they saw a stimulus presented during the waiting period, they press a pre-designated 'stimulus' lever; if no stimulus was observed during the waiting period, they press a pre-designated 'no stimulus' lever. The power of this approach is the ability to apply signal detection theory analyses to the resulting data and to characterize performance in very specific ways (eg, decreased misses *vs* fewer false alarms, etc). On the other hand, multiple-choice serial reaction time tasks (CSRTT) measure the ability of subjects to monitor multiple possible spatial locations for the presentation of a visual stimulus (presented on a fixed or variable time schedule) and to respond accurately to that location when the stimulus occurs (Figure 2). Although the former procedures measure the ability to sustain focused attention, the latter depends on the ability to sustain either a divided or scanning attention strategy. Importantly, both also depend a great deal on executive control of attention and behavior in order to optimize responding.

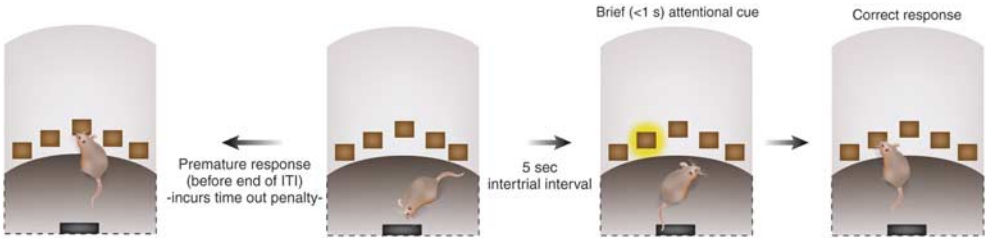

Figure 2. Diagram of the 5-choice serial reaction time tasks (CSRTT) that can be used to assess both attentional function and response inhibition ('waiting'). The rat begins each trial with a nose poke in the food magazine located on the opposite wall of the chamber to the response apertures. Following a 5-s inter-trial interval, a brief light appears in one of the apertures and the rat must make a nose poke response in that hole to receive reward. Premature responses, which may be used as an index of response inhibition, are recorded when a response occurs during the inter-trial interval before the light signal. Adapted from Eagle and Baunez (2010).

Cholinergic neurons, particularly those that innervate the PFC, clearly play a role in attentional performance. For example, lesions of the basal forebrain cholinergic system, or cholinergic deafferentation in the PFC, impair attentional performance (Muir *et al*, 1994; McGaughy *et al*, 2002), and these effects are attenuated by the administration of acetylcholinesterase inhibitors (Muir *et al*, 1992, 1995; Balducci *et al*, 2003). Impairments in attentional accuracy induced by cholinergic lesions may be due, in part, to reduced muscarinic transmission, as systemic blockade of these receptors with scopolamine impairs performance on the 5-CSRTT (Mirza and Stolerman, 2000). However, a large body of work shows that systemic administration of nicotinic receptor agonists (including nicotine itself) produces their clearest and most robust performance enhancements in signal detection or choice reaction time tasks. Specifically, acute treatment with nicotine increases choice accuracy and speeds response times in both tests (Mirza and Stolerman, 1998; Stolerman *et al*, 2000; Hahn *et al*, 2002a, b, 2003; Rezvani *et al*, 2002, 2005; Bizarro and Stolerman, 2003; Rezvani and Levin, 2003, 2004; Bizarro *et al*, 2004; Young *et al*, 2004; Hahn and Stolerman, 2005; Hoyle *et al*, 2006; Levin *et al*, 2006; Dillon *et al*, 2009). These effects are sustained with chronic nicotine treatment (Hahn and Stolerman, 2002; Rezvani *et al*, 2006, 2008; Semenova *et al*, 2007; Amitai and Markou, 2009). Subsequent studies with subunit-specific nicotinic receptor agonists seems to indicate that both low-affinity alpha-7-containing (Grottick and Higgins, 2000; Grottick *et al*, 2001, 2003) and high-affinity beta-2-containing nicotinic receptors are involved in these effects (McGaughy *et al*, 1999; Young *et al*, 2004, 2007; Hoyle *et al*, 2006; Rezvani *et al*, 2009; Howe *et al*, 2010; Mohler *et al*, 2010). The precise psychological basis of these effects has not been clearly defined, but the broad effects of nicotinic agonists in attentional tasks have been theoretically linked to an increase in the speed of processing that facilitates choice or simple reaction time performance (Mancuso *et al*, 2001). In contrast, acetylcholinesterase inhibitors or muscarinic receptor agonists do not share the effect of nicotinic agonists on attention in normal animals (Kirkby *et al*, 1996; Mirza and Stolerman, 2000). Note that M1 muscarinic receptor agonists have been reported to enhance recognition memory (Bradley *et al*, 2010), suggesting that the nootropic effects of these compounds are unlikely to be related to enhancements in attentional processes.

Monoaminergic systems have defined roles in the modulation of attentional performance (Robbins, 2002). Selective neurotoxic depletions of monoamine transmitters in frontostriatal circuits, coupled with behavioral pharmacological studies—often involving site-specific intra-cranial infusions, have primarily implicated catecholamine systems in attentional performance. With respect to noradrenaline, forebrain depletions of this catecholamine do not impair baseline performance in simple attentional tasks, but do impede performance under taxing conditions (distraction, unpredictable event rate) (Carli *et al*, 1983; Milstein *et al*, 2007). At the receptor level, lower doses of alpha-1 or alpha-2 receptor agonists can enhance attentional performance (Puumala *et al*, 1997; O'Neill *et al*, 2000). Despite a wealth of data implicating dopaminergic systems in working memory (see the following section), much less is known about the nature of its role in attention. Systemic administration of D_1 agonists impairs CSRTT performance (Passetti *et al*, 2003a). However, direct intra-prefrontal application of the same agonist improves performance in poor-performing rats (Granon *et al*, 2000). Similarly, infusions of a low dose of the D_1 agonist SKF38939 into the nucleus accumbens also improved attentional accuracy in normal rats, whereas higher doses tended to increase perseverative responding (Pezze *et al*, 2007). In a similar vein, impairments in 5-CSRTT performance induced by repeated amphetamine treatments have also been reported to be ameliorated by intra-PFC infusions of a D_1 agonist (Fletcher *et al*, 2007b). These latter findings suggest that there is a non-linear function relating D_1 receptor stimulation to attentional performance—a relationship that may be explained by the levels of baseline dopamine transmission at these receptors, as well as baseline variations in performance. Thus, even though systemic treatment with D_1 agonists may impair attentional performance in normal rats, the possibility remains that similar treatments may improve these functions in perturbed animals.

Although the effects of catecholamine receptor agonists on attention is somewhat equivocal, studies using stimulant and non-stimulant agents that interfere with catecholamine reuptake (methylphenidate, atomoxetine) or elicit the release of monoamine transmitters (amphetamine, caffeine) can improve attentional performance, although their effects also appear to depend on task conditions and baseline performance (Grilly *et al*, 1989; Grilly, 2000; Grottick and Higgins, 2002; Bizarro *et al*, 2004; Blondeau and Dellu-Hagedorn, 2007; Higgins *et al*, 2007; Robinson *et al*, 2008; Navarra *et al*, 2008b; Newman *et al*, 2008; Robinson *et al*, 2008; Jentsch *et al*, 2009). For example, a recent study showed highly selective effects of noradrenaline reuptake blockade on attention, facilitating performance under conditions where top–down control of attentional resources was favored, whereas impairing performance when stimulus-driven responding was emphasized (Jentsch *et al*, 2009). As noradrenaline reuptake inhibitors increase both extracellular dopamine and noradrenaline levels in the PFC (Bymaster *et al*, 2002), it is not yet possible to ascribe their effects on attention to one catecholamine transmitter. Overall, these results encourage continued attempts to characterize the precise role for brain monoamine receptor subtypes as targets for attentional enhancement.

In contrast to the above-mentioned findings, depletion of serotonin in the forebrain fails to affect attentional accuracy, although it does increase anticipatory impulsive responding (Harrison *et al*, 1997). Furthermore, neither 5-HT_{2A} agonists nor antagonists affect indices of attentional performance (choice accuracy) but do alter impulsive responding (Ruotsalainen *et al*, 1997; Koskinen and Sirvio,

2001; Higgins *et al*, 2003; Passetti *et al*, 2003b; Winstanley *et al*, 2004b; Carli *et al*, 2006; Fletcher *et al*, 2007a; Quarta *et al*, 2007). Although not having any measurable effects on attention on their own, 5-HT_{2A} receptor antagonists are reportedly able to mitigate deficits in CSRTT performance elicited by intra-PFC blockade of NMDA receptors (Carli *et al*, 2006; Pozzi *et al*, 2010), highlighting one example of the potentially disparate results when comparing drug effects in normal *vs* pathological systems. Intra-PFC infusion of the 5-HT_{1A} agonist 8-OH-DPAT has been reported to improve attentional accuracy in both normal rats (Winstanley *et al*, 2003) and ameliorate impairments induced by PFC NMDA receptor blockade (Carli *et al*, 2006). However, systemic treatment with 8-OH-DPAT reduces attentional accuracy assessed with the 5-CSRTT (Carli and Samanin, 2000). Collectively, these data indicate that targeting forebrain serotonin system may not be the most suitable strategy for enhancing attentional functions.

The histaminergic neurotransmitter system is also emerging as an important candidate. Histamine is a wake- and arousal-promoting neurotransmitter, and the wake-promoting agent, modafinil, releases histamine (among other actions) in the brain. Notably, modafinil also shows the potential to enhance attentional performance in rodents under certain circumstances (Waters *et al*, 2005). The connection between modafinil, histamine, and attention is further supported by the observation that H3 receptor antagonists (which increase brain histamine output since H3 is the autoreceptor for histamine) also improve attentional performance in choice reaction time tasks (Ligneau *et al*, 1998). In a similar vein, another wake-promoting transmitter, orexin, has also been reported to enhance attention when administered directly into the PFC, in a manner similar to nicotine (Lambe *et al*, 2005). These data urge focus on other than just monoamine systems in the development of attention-enhancing drugs.

Beyond the neuromodulatory transmitters, there has been an emergent interest in AMPAkines that positively modulate ionotropic glutamate receptors, metabotropic glutamate receptors, or subunit-specific GABA modulators for effecting cognitive enhancement in psychiatric disorders. Of these, metabotropic glutamate receptors have been implicated as enhancers of attentional performance in animals whose performance was impaired by treatment with NMDA receptor antagonists (Greco *et al*, 2005), but clearly, more systematic work in this area is required.

PHARMACOLOGICAL ENHANCEMENT OF WORKING MEMORY

As discussed previously, there are multiple memory systems in the brain that mediate important aspects of adaptive behavior. The term 'working memory' refers to a set of limited-capacity representational processes by which information about abstract rules, recent stimulus events, expected goals, and planned actions are maintained and manipulated in real time to affect on-going behavior (Baddeley and Hitch, 1974; Goldman-Rakic, 1987; Fuster, 2008; Baddeley, 2010). In that sense, it cannot be viewed as a unitary process, and indeed, cognitive psychological accounts of working memory involve a multi-component system (Baddeley and Hitch, 1974). That being said, studies in laboratory animals mostly assess the ability to use this system to rapidly encode, temporarily maintain, and utilize information in tasks that are heavy in pro-active interference in order to require the use of a limited capacity, efficiently updatable memory system. These include the so-called delayed response tasks (Fuster and Alexander, 1971; Goldman *et al*, 1971; Curtis and D'Esposito, 2004), in which the content being stored is either visuospatial or object oriented (spatial delayed alternation/response; delayed match/non-match to position; delayed match/non-match to sample).

Cholinergic systems have a long-studied and important role in working memory enhancement. Although acetylcholinesterase inhibitors can reduce the impairing effects of a cholinergic receptor antagonist, of normal aging or of basal forebrain damage, they do not improve working memory in normal, young animals (Dawson and Iversen, 1993; Jakala *et al*, 1993; Barnes *et al*, 2000; Bontempi *et al*, 2003; Tsukada *et al*, 2004; Lindner *et al*, 2006; Marighetto *et al*, 2008a; Cutuli *et al*, 2009). At the same time, nicotinic receptor agonists targeting either the high-affinity, beta-2/4-containing or low-affinity, alpha-7-containing subtypes can improve working memory performance in otherwise normal rodents and monkeys (Bontempi *et al*, 2001, 2003; Spinelli *et al*, 2006; Bitner *et al*, 2007; Buccafusco *et al*, 2007; Tietje *et al*, 2008). As attentional processes play a crucial role in the encoding phases of working memory, as well as the resistance to distraction-related disruptions in retention (Zanto and Gazzaley, 2009), it is possible that these reported benefits of nicotinic receptor agonists on working memory are related to their attention-enhancing effects.

A very large literature relates the catecholamine neuromodulatory systems to aspects of working memory retention. Increases in frontal cortical catecholamine levels, produced by stimulant drugs, improve working memory in normal, young animals and human beings (Mehta *et al*, 2000; Aultman and Moghaddam, 2001; Arnsten and Dudley, 2005; Arnsten, 2006; Berridge *et al*, 2006). The beneficial effects of methylphenidate on working memory have been proposed to be mediated by increased activity at both dopamine D_1 and noradrenergic alpha-2 receptors (Arnsten and Dudley, 2005). However, dopamine D_1 agonists given to healthy young subjects do not improve working memory *per se*, whereas alpha-2 agonists do (Franowicz and Arnsten, 1998, 1999; Franowicz *et al*, 2002; Chudasama and Robbins, 2004; Arnsten and Li, 2005), suggesting that the latter action is more crucial. In addition, alpha-2 agonists are highly effective at improving working memory performance in animals treated with NMDA receptor antagonists to simulate aspects of cognitive impairment in psychoses (Jentsch and Anzivino, 2004; Marrs *et al*, 2005). In addition,

improvements produced by D_1 or alpha-2 agonists are larger in animals with experimentally reduced prefrontal cortical catecholamine levels or transmitter depletion associated with normal aging (Brozoski *et al*, 1979; Arnsten and Goldman-Rakic, 1985a, b, 1990; Arnsten *et al*, 1988, 1995, 1994; Ramos *et al*, 2006; Buccafusco *et al*, 2009).

Despite the very clear evidence that catecholamines are involved in working memory performance, serotonin plays little, if any role (Ruotsalainen *et al*, 1997; Robbins and Roberts, 2007), resembling a similar dissociation between indolamine and catecholamine transmitter systems in the modulation of attention. This being said, there is one report of 5-HT_{2A} antagonists improving delayed match to position performance (Terry *et al*, 2005). Nevertheless, even though 5-HT compounds may not improve working memory in normal animals, the possibility remains that manipulations of this system may have some benefit in reversing impairments in this function induced by certain deficit models. This has yet to be tested systematically, and remains a key avenue for further research.

Excitatory amino-acid neurotransmitters also represent an interesting target for working memory enhancement. Recent data indicate that positive allosteric modulators of AMPA receptors can enhance working memory performance in normal or sleep-deprived animals, as well as in aged rodents (Hampson *et al*, 1998a, b; Porrino *et al*, 2005; Marighetto *et al*, 2008b). There is a great deal of evidence, as well, that working memory is dependent on metabotropic glutamate receptor function. Notably, blockade of mGlur1 receptors has been show to enhance performance in working memory tasks, whereas mGlurR2/3 agonists and mGluR5 antagonists impair it (Aultman and Moghaddam, 2001; Homayoun *et al*, 2004; Spinelli *et al*, 2005; Homayoun and Moghaddam, 2006; Sukhotina *et al*, 2008). Alternatively, mGluR2/3 agonists are known to enhance working memory performance in animals with pharmacologically reduced NMDA receptor function (Moghaddam and Adams, 1998; Moghaddam, 2004).

PHARMACOLOGICAL ENHANCEMENT OF BEHAVIORAL FLEXIBILITY

Behavioral flexibility, like working memory, is not a unitary phenomenon, but rather, may be viewed as a hierarchical set of processes that are subserved by anatomically distinct cortical and subcortical regions. For example, response inhibition may be viewed as a fundamental form of executive control, requiring relatively rapid inhibition of a pre-potent action in response to internal and external cues (Eagle *et al*, 2008a). Extinction learning entails a more gradual suppression of a conditioned response upon repeated non-reinforced presentations of a stimulus previously associated with reward or punishment. Reversal learning is another form of flexibility that can occur when an organism discriminates between two or more stimuli, only one of which is initially associated with reward, but then requiring a switch to another stimulus–reinforcement association within a particular stimulus dimension. On the other hand, set-shifting is a more complex process that entails shifts between strategies, rules, or attentional sets, requiring that attention be paid to multiple aspects of complex environmental stimuli. In these latter two forms of flexibility, successful performance requires both the suppression of a previously -learned response, rule, or strategy and the direction of attention to a previously irrelevant stimulus or stimulus dimension.

Response Inhibition

Although all forms of behavioral flexibility require some form of response inhibition, in its most fundamental form, this process deals with relatively rapid inhibitory control over on-going behavior. Even though suppression of motor output may seem to be a relatively simple construct, recent studies in rats have revealed dissociable neural circuitry and neurochemical modulation of different types of action suppression. For example, in CSRTT, animals must wait until a signal is given to initiate a response, as making a premature response triggers a time-out penalty (Figure 2). Other situations may require actively inhibiting a prepotent action in response to external 'stop' cues, which can be assessed with a stop-signal reaction time task (Eagle *et al*, 2008a) (Figure 3a). In this task, rats are most often required to press one lever and then rapidly respond on another to obtain reward; however, on a minority of trials, a cue signals animals to stop responding on the second lever in order to obtain reinforcement. Lesion studies have revealed that 'waiting' (as in the CSRTT) *vs* 'stopping' (as in stop-signal tasks) may be controlled by different prefrontal circuits. Lesions of the ventromedial, but not orbital PFC, increase premature responding on the CSRTT (Chudasama *et al*, 2003), whereas orbitofrontal, but not medial PFC lesions, slow stop-signal performance (Eagle *et al*, 2008b).

Psychopharmacological studies have revealed further dissociations in the neurochemical modulation of these two forms of response inhibition. In contrast to the relative lack of involvement in attention or working memory, 5-HT transmission appears to be of particular importance in mediating 'waiting', and may act as a brake in the control of impulsive responses (Winstanley *et al*, 2004a; Eagle and Baunez, 2010). This effect appears to be mediated via actions on 5-HT_{2C} receptors, as stimulation of these receptors with WAY-163909 or blockade of these receptors with SB242084 decreases and increases premature responses, respectively (Winstanley *et al*, 2004b; Navarra *et al*, 2008a). However, blockade of 5-HT_{2A} receptors with M100907 also reduced premature responding (Winstanley *et al*, 2004b), suggesting that this subtype may normally antagonize the effects of 5-HT_{2C} receptor activation on waiting. In contrast, global depletion of 5-HT, or increasing transmitter release via blockade of 5-HT reuptake with citalopram, does not affect stop-signal performance (Bari *et al*, 2009).

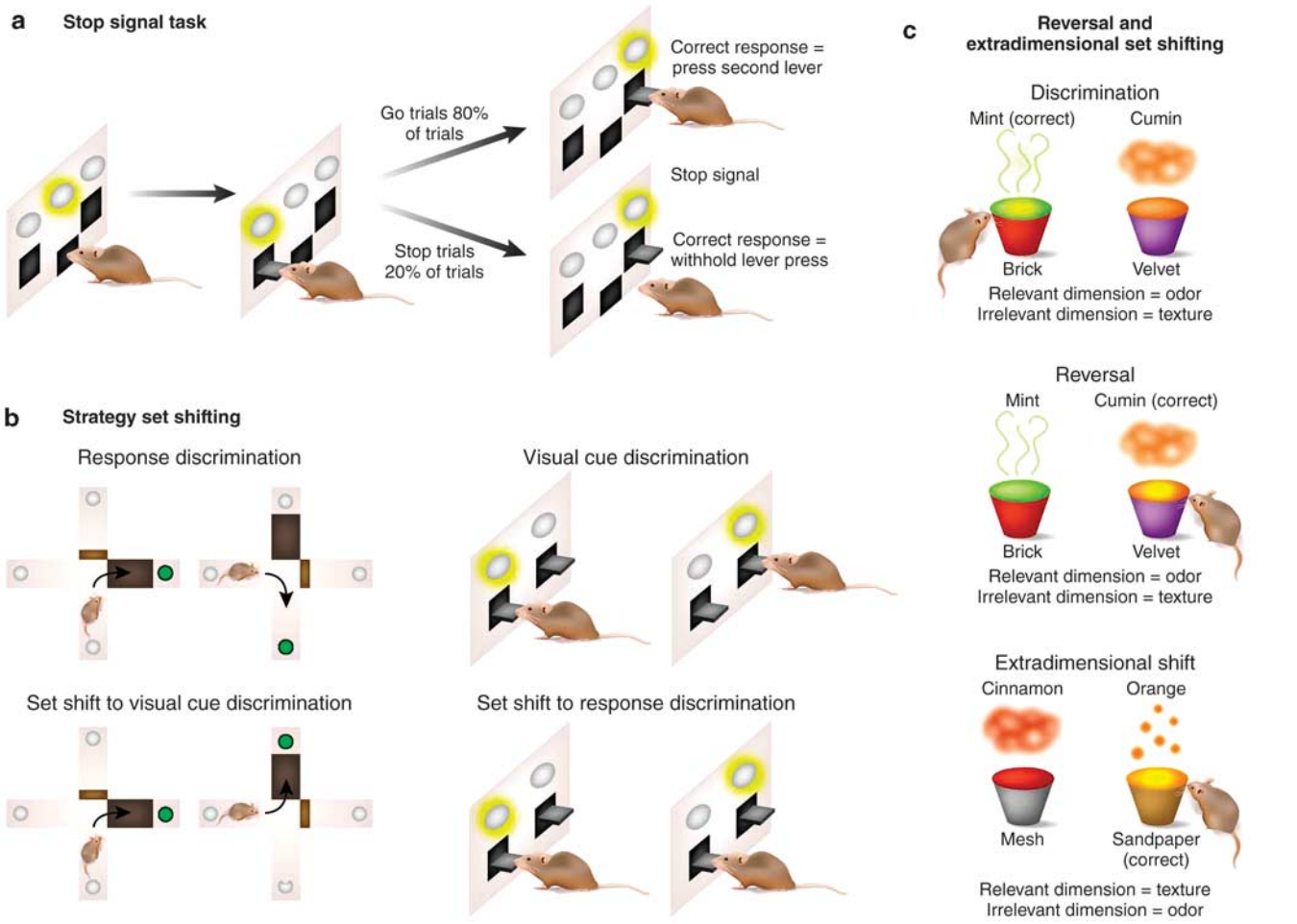

Figure 3. Diagrams of procedures used to assess different aspects of behavioral flexibility. (a) In the stop-signal task, rats begin each trial with a nose poke in the central food magazine. The go-phase trial begins with a left lever press and then the rat must move quickly to press the right lever to complete the 'go' response. On 20% of trials, a stop-signal tone during the go-phase signals that the rat must inhibit the right lever press. Adapted from Eagle and Baunez (2010). (b) Strategy set-shifting tasks have been conducted on either a cross-maze (left) or operant chambers (right). On the maze, rats are initially trained to make a 90° right turn to receive food reinforcement. A visual cue is randomly placed in one of the choice arms on each trial, but do not reliably predict the location of food. During the set-shift, the rat is now required to use a visual-cue discrimination strategy, entering the arm with the visual cue, requiring either a right or left turn. Thus, the rat must shift from the old strategy and approach the previously irrelevant cue in order to obtain reinforcement. In the operant chamber, rats are initially trained on a visual-cue discrimination (upper panel), being required to always press the lever that had a stimulus light illuminated above it. For the set-shift to a response discrimination (lower panel), rats are trained to always press one of the levers (eg, left), regardless of the position of the cue light. (c) In the extradimensional shifting task, rats initially dig for food in one of two bowls that can be discriminated on the basis of odor, texture, or other attributes, with only one stimulus dimension being relevant initially (eg, odor, left). During reversal learning, the same stimuli are used, but the bowl that was previously un-reinforced now contains food (middle). During the critical extradimensional shift, new bowls are presented, and now the rat must discriminate based on the texture that surrounds the bowl, but not the odor (right).

Noradrenergic systems appears to be a more promising target for improving this aspect of response inhibition, as treatment with the selective noradrenergic uptake blocker atomoxetine improved stop-signal performance (Robinson *et al*, 2008). Atomoxetine also reduced impulsive premature responding in the 5-CSRTT (Robinson *et al*, 2008, Navarra *et al*, 2008b), suggesting that selectively enhancing noradrenergic transmission may enhance multiple types of response inhibition. However, the specific receptor subtypes and neural regions, which increased noradrenergic transmission, may be facilitating this form of flexibility remains to be elucidated. Furthermore, whether or not these treatments may normalize deficits in response inhibition in animal models of impaired inhibitory control remains under-explored.

Extinction

It is now generally accepted that the suppression of a previously learned association following extinction occurs as the result of new learning rather than an erasure of the original CS–US association. Pavlovian associations, particularly those related to aversive stimuli can re-emerge after unsignaled exposure to an unconditioned stimulus, following a change in context or with the passage of time, and reconditioning occurs faster than initial conditioning

(Pavlov, 1927; Rescorla and Heth, 1975; Bouton and Bolles, 1979; Bouton *et al*, 2006; Robbins, 1990; Westbrook *et al*, 2002). This new learning may act to suppress subcortical memory systems, which generate conditioned responses. In the rat, the ventromedial region of the PFC has been implicated in facilitating the consolidation of extinction learning, both for aversive (Quirk *et al*, 2000) and appetitive (Rhodes and Killcross, 2004) stimuli.

Studies investigating pharmacological approaches to enhancing extinction have focused primarily on suppression of conditioned fear responses (Quirk and Mueller, 2008). The vast majority of these studies have shown that treatment with certain agents either before or immediately after initial extinction training enhances the consolidation of extinction learning assessed 24 h later. Of these studies, the glutamate NMDA receptor partial agonist D-cycloserine has received much attention, as it has been shown repeatedly to accelerate and strengthen extinction of fear, when administered either systemically or directly into the basolateral amygdala or infralimbic PFC (Weber *et al*, 2007; Woods and Bouton, 2006; Mao *et al*, 2006; Lee *et al*, 2006; Parnas *et al*, 2005; Walker *et al*, 2002; Burgos-Robles *et al*, 2007). It is generally believed that D-cycloserine facilitates this form of learning by enhancing synaptic plasticity in prefrontal–amygdala circuits (Quirk and Mueller, 2008). Interestingly, the facilitatory effects of D-cycloserine on extinction may be limited to aversive Pavlovian associations, as similar treatments actually impaired extinction learning of an instrumental response for food reward (Port and Seybold, 1998).

Drug-induced enhancements in consolidation of extinction memories have typically been observed in the absence of an effect on initial, short-term extinction. One exception to this comes from studies on the role of the endocannabinoid system. Inhibiting endocannabinoid reuptake or administration of a CB1 agonist enhances both short- and long-term extinction of conditioned contextual fear, whereas blockade of CB1 receptors has the opposite effect (Pamplona *et al*, 2006, 2008). The NMDA NR2B receptor has also been implicated in mediating short-term extinction learning, as selective blockade of these receptors disrupts the acquisition of extinction (Sotres-Bayon *et al*, 2007; Dalton *et al*, 2008). Therefore, the development of drugs that may selectively enhance activity at NMDA NR2B sites may reveal another potential target for facilitating rapid acquisition of extinction learning.

There have been relatively few studies on how manipulation of monoamine systems may facilitate extinction learning. Systemic treatment with the dopamine D_2-like antagonist sulpiride enhanced consolidation of extinction memories without affecting initial extinction learning (Ponnusamy *et al*, 2005). This effect may be mediated in part by antagonism of D_4 receptors, as similar effects have been observed following infusion of the dopamine D_4 antagonist L-741,741 directly into the medial PFC (Pfeiffer and Fendt, 2006). Likewise, treatment with the alpha-2 adrenoceptor antagonist yohimbine, which would be expected to increase noradrenaline release, also enhances consolidation of extinction learning (Cain *et al*, 2004; Morris and Bouton, 2007). Curiously, there has been very little work investigating how manipulations of the 5-HT system may affect extinction learning. Stimulation of 5-HT_{1A} receptors disrupts both the acquisition and extinction of conditioned fear (Quartermain *et al*, 1993), but whether blockade of these receptors may have the opposite effect and facilitate extinction learning is a topic for further investigation. In contrast, increasing 5-HT release with fluoxetine reduces instrumental cocaine-seeking behavior on the first day of extinction testing in the cocaine self-administration context (Burmeister *et al*, 2003). However, it is unclear whether these effects were due to a general decrease in responding via actions on the 5-HT_{2C} receptor (Grottick *et al*, 2000) or specifically attributable to enhanced short-term extinction learning. Conversely, the 5-HT_{1A} receptor agonist tandospirone reverses extinction deficits induced by postnatal stress (Koseki *et al*, 2009). In light of the fact that 5-HT exerts complex regulation over response inhibition and higher-order forms of behavioral flexibility discussed below, further research on how targeting 5-HT receptors may affect extinction could potentially reveal novel targets for enhancing this form of flexibility.

Reversal Learning and Set-shifting

Reversal learning has long been used to assess the ability of animals to shift between stimulus and reward contingencies within a particular dimension. In these assays, animals are initially trained to discriminate between two or more stimuli (eg, objects, spatial locations, olfactory cues) to obtain a reward, while ignoring the other, initially irrelevant stimuli. During the reversal shift, one of the previously irrelevant stimuli is now linked to reward. A variation of this type of task has been employed to assess set-shifting abilities, requiring rats to shift between visual cue and egocentric spatial response-based discrimination strategies (Block *et al*, 2007; Floresco *et al*, 2006b, a; Ragozzino, 2002). The use of these types of shifts (originally termed a 'non-reversal shift' (Mackintosh *et al*, 1968; Mackintosh and Holgate, 1969) were initially used in conjunction with reversal tasks to explore mechanisms of discrimination learning. Recent work with this type of 'strategy set-shifting' task has been conducted either on a cross-maze (Block *et al*, 2007) or an operant chamber (Floresco *et al*, 2008) (Figure 3b). Using these procedures, a reversal phase may also be included (eg, always turn right) (Ghods-Sharifi *et al*, 2008). Throughout the task, the stimuli remain constant across different phases in this maze-based procedure, making it similar to the Wisconsin Card Sorting task used in human beings. This task places a heavier emphasis on response conflict, because the same set of stimuli are used during initial discrimination learning and during the set-shift (Slamecka, 1968). However, a key advantage of these tasks is that they permit a detailed analysis of the type of errors made during the shift that can be used to distinguish

between different types of impairments in set-shifting and reversal learning, such as perseverative deficits, or impairments in the ability to acquire or maintain a new strategy (Floresco *et al*, 2009).

Birrell and Brown (2000) developed a procedure based on the intradimensional shift/ extradimensional shift (IDS/EDS) task used with primates and human beings (Dias *et al*, 1996; Pantelis *et al*, 1999) (Figure 3c). In this attentional set-shifting task, rats discriminate between two bowls that can be distinguished based on a variety of features (eg, digging medium, odor, the texture of the outer surface of the bowl). This task has multiple phases that assess different components of learning, starting with simple and then compound discriminations to obtain food reward hidden in the digging medium of one of the bowls. During this and all subsequent stages, only one of the stimulus dimensions can be used to locate the food reliably. For example, if odor is the relevant dimension, then during each trial the correct bowl will be scented with a particular odor, but the bedding media and the texture of that bowl varies between trials. In the subsequent reversal phase, the location of food is switched, so that the bowl that did not contain food previously is now baited. During the critical extradimensional set-shift, rats are presented with two novel stimuli, but must now disregard the previously relevant stimulus dimensions (eg, odor) and attend to a formerly irrelevant dimension (eg, shift from odor to texture) to locate the food reward. This procedure ensures that impairments in performance during this stage of the task are likely attributable to disruptions in the ability to shift attentional set to different aspects of compound stimuli, rather than an impaired ability to stop approaching a specific stimulus previously associated with reward.

The use of these procedures has revealed dissociable roles for different regions of the frontal lobes in the mediation of these complex forms of behavioral flexibility. Lesions of the orbitofrontal cortex impair reversal learning in both primates and rats (Dias *et al*, 1996; McAlonan and Brown, 2003; Ghods-Sharifi *et al*, 2008), whereas the lateral PFC in primates or the medial PFC in rats plays a key role in shifting between rules, strategies, or attentional sets (Dias *et al*, 1996; Ragozzino *et al*, 1999; Birrell and Brown, 2000; Floresco *et al*, 2008). Moreover, there appears to be further differences in the importance of prefrontal monoaminergic systems to these forms of flexibility, with PFC 5-HT facilitating reversal learning, but not set-shifting (Clarke *et al*, 2004, 2007), whereas mesocortical DA appears to play a key role in the formation of attentional sets and in facilitating shifts from one strategy to another (Roberts *et al*, 1994; Crofts *et al*, 2001; Ragozzino, 2002; Floresco *et al*, 2006b). The frontal–striatal circuits that mediate these forms of shifts also have been dissociated, with the dosomedial, but not ventral striatum contributing to reversal learning, whereas the medial PFC appears to interact with both the nucleus accumbens and dorsal striatum to facilitate set-shifting (Ragozzino *et al*, 2002; Floresco *et al*, 2006a; Block *et al*, 2007; Castañé *et al*, 2010).

One issue to consider when evaluating pharmacologically induced enhancements of reversal and set-shifts is whether or not perceived 'improvements' in shifting are related to facilitation of cognitive flexibility, or instead, to a disruption of initial discrimination learning that in turn leads to more rapid shifting. For example, earlier studies reported that repeated treatment with amphetamine facilitated reversal learning, but not shifts between strategies (Weiner and Feldon, 1986). Yet, subsequent studies revealed that the improvements in reversal learning were only apparent when administered during initial discrimination training, suggesting that these treatments attenuated the stability of the initial association leading to more rapid acquisition of the reversal (Weiner *et al*, 1986). In a similar vein, depletion of prefrontal dopamine in marmosets improved extradimensional set-shifting (Roberts *et al*, 1994), but this later was found to be due to a disruption of the initial formation of an attentional set (Crofts *et al*, 2001).

Of the classes of drugs that can enhance reversal learning and set-shifting, those acting on the monoamine systems have received the most attention. With respect to the dopamine system, systemic blockade of D_2 but not D_1 receptors impairs reversal learning (Lee *et al*, 2007), with the likely locus of this effect being disruption of dopamine signaling in the dorsal striatum, rather than prefrontal regions or nucleus accumbens (O'Neill and Brown, 2007; Haluk and Floresco, 2009). However, administration of the D_2 receptor agonist quinpirole, either systemically or directly into the nucleus accumbens, also impairs reversal learning (Haluk and Floresco, 2009; Boulougouris *et al*, 2009). Interestingly, although local supranormal stimulation of D_1 receptors can impede working memory functions mediated by the PFC (Zahrt *et al*, 1997; Floresco and Phillips, 2001), similar treatments in either the medial PFC or nucleus accumbens neither improve nor impair strategy set-shifting (Floresco *et al*, 2006b; Haluk and Floresco, 2009). These findings indicate that selective dopaminergic receptor agonists, particularly those acting on D_1 or D_2 receptors may not represent the most effective targets for enhancing these complex forms of flexibility in normal animals. One potential exception to this may be antagonists at D_4 receptors, as intra-PFC infusions of L-745,870 has been shown to facilitate shifts between strategies (Floresco *et al*, 2006b). Conversely, there is evidence to suggest that increasing endogenous mesocortical dopamine activity with the COMT inhibitor tolcapone can facilitate extradimensional set-shifting in normal animals (Tunbridge *et al*, 2004).

Despite the above-mentioned findings, there have been reports that D_1 receptor agonists can normalize impairments in these forms of behavioral flexibility induced by certain animal models of cognitive dysfunction. For example, impairments in extradimensional set-shifting induced by repeated amphetamine treatments can be attenuated by direct application of a D_1 agonist into the PFC, although these treatments did not alter performance in control rats (Fletcher *et al*, 2005). Likewise, impairments

in reversal learning induced by subchronic PCP are ameliorated by treatment with the D_1 agonist SKF 38393 (McLean *et al*, 2009a). Along similar lines, modafanil, which can facilitate dopamine release (Zolkowska *et al*, 2009), abolishes PCP-induced impairments in extradimensional set-shifting (Goetghebeur and Dias, 2009). Thus, although dopaminergic drugs may have somewhat equivocal effects on set-shifting and reversal learning in normal animals, increasing prefrontal dopamine transmission may have some benefit at alleviating impairments in flexibility in experimentally perturbed subjects. In contrast, classical antipsychotics such as haloperidol do not appear to alleviate deficits in set-shifting induced by subchronic PCP exposure, consistent with their clinical profile (McLean *et al*, 2008; Goetghebeur and Dias, 2009), although there have been some reports that the atypical antipsychotic clozapine can attenuate PCP-induced impairments in set-shifting when administered subchronically (McLean *et al*, 2008; Rodefer *et al*, 2008).

There have been a multitude of recent reports showing that a variety of drugs acting on 5-HT receptors can improve reversal learning in both normal and pharmacologically perturbed animals. What is particularly striking about these findings is that, even though depletion of 5-HT in the orbital PFC impairs reversal learning, selective blockade of certain 5-HT receptor subtypes facilitates reversal shifts. Thus, in normal animals, improved reversal performance has been observed following treatment with antagonists at 5-HT_3 (ondansetron; Barnes *et al*, 1990) or 5-HT_{2C} (SB242084; Boulougouris *et al*, 2008) receptors. The effect of 5-HT_{2C} antagonism appears to be specific to blockade of these receptors in the orbital PFC (Boulougouris and Robbins, 2010), and may be mediated in part by a facilitation in 5-HT release via actions on 5-HT neurons in the dorsal raphé (Sharp *et al*, 2007), which in turn may activate other 5-HT receptors to facilitate reversal shifts. In contrast, systemic 5-HT_{2A} receptor blockade with M100907 impairs reversal performance (Boulougouris *et al*, 2008), although infusions of this drug into the orbital PFC were without effect (Boulougouris and Robbins, 2010). This suggests that endogenous 5-HT may act on 2A receptors in regions such as the dorsal striatum to facilitate reversal shifts. Curiously, although 5-HT_{2A} antagonism impairs reversal learning in normal animals, similar treatments with M100907 actually alleviates subchronic PCP-induced reversal impairments (Idris *et al*, 2010), as does blockade of 5-HT_{2C}, 5-HT_6, and 5-HT_7 receptors (McLean *et al*, 2009b; Idris *et al*, 2010).

The findings described above indicate that reducing signaling at certain 5-HT receptor subtypes has beneficial effects on reversal learning in both normal and experimentally-impaired animals. Yet, a recent report by Lapiz-Bluhm *et al* (2009) showed that acute increases in 5-HT release, via blockade of reuptake with citalopram, alleviated impairments in reversal learning induced by repeated stress. These authors also showed that repeated stress reduced 5-HT release in the orbital PFC, which likely was a primary contributing factor to these impairments. Thus, either blockade of certain 5-HT receptors or enhancing 5-HT release can improve performance of reversal shifts disrupted by certain experimentally induced alterations in neurochemical functioning. In addition, chronic blockade of 5-HT reuptake with fluoxetine reduced perseveration during reversal learning in normal mice (Brigman *et al*, 2010). These finding highlights the fact that when targeting the 5-HT system to normalize deficits in this form of behavioral flexibility, one must take into account the types of neural alterations that may be the underlying cause of these impairments. Furthermore, they suggest that increasing endogenous 5-HT release can have a net beneficial effect on performance in normal animals, although the receptors and brain regions through which these effects are mediated remain to be clarified.

As depletion of 5-HT does not appear to affect EDS performance (Clarke *et al*, 2005), there has been less work on how drugs acting on this monoamine system can affect set-shifting. However, there are some reports that targeting 5-HT_6 receptors facilitates extradimensional set-shifting, although there appears to be discrepancies in the literature. Hatcher *et al* (2005) showed that repeated treatment with the 5-HT_6 antagonist SB399885 improved both reversal learning and set-shifting in normal animals tested on the IDS/EDS task. Yet, another antagonist for this receptor (SB271046) only induced statistically significant improvements in reversal performance. In a similar vein, acute 5-HT_6 antagonism alleviated EDS and reversal impairments induced by subchronic PCP (Rodefer *et al*, 2008; Idris *et al*, 2010). These findings are contrasted by observations of Burnham *et al* (2010), who showed that the 5-HT_6 *agonist* WAY181187 also selectively improved EDS performance in normal rats. In that study, WAY181187 enhanced set-shifting even when administered after an attentional set had been acquired, thereby ruling out impairments in attentional set formation. These findings suggest that further studies on the potential cognitive-enhancing effects of drugs acting on 5-HT_6 receptors are warranted, particularly to clarify whether blockade or stimulation of these receptors (or both) can exert pro-cognitive effects.

There have been a handful of reports that drugs, which increase noradrenergic activity, appear to also facilitate reversal learning and set-shifting in a manner similar to their ability to facilitate response inhibition and extinction. Earlier reports noted that treatment with high, but not low doses of the alpha-2 adrenergic receptor agonist guanfacine improves reversal performance in aged monkeys (Steere and Arnsten, 1997). In a similar vein, acute or repeated treatment with the noradrenaline reuptake blocker atomoxetine or desipramine reduced perseveration during reversal performance without affecting retention of a previously acquired discrimination (Seu and Jentsch, 2009; Seu *et al*, 2009). The fact that drug-induced increases in noradrenergic transmission can enhance reversal learning is particularly notable, in light of the fact that selective depletion of prefrontal noradrenaline does not affect reversal learning,

although these treatments do impair extradimensional set-shifting (Tait *et al*, 2007). This more complex form of flexibility has also been shown to be sensitive to pharmacological enhancement by noradrenergic drugs. Acute desipramine treatment causes mild improvements in all components of the IDS/EDS task in rats, whereas chronic treatment selectively facilitated the EDS phase (Lapiz *et al*, 2007). Using the same task, Lapiz and Morilak (2006) showed that blockade of noradrenergic autoreceptors with atipamezole improved performance during both the reversal and EDS phases of the task. Likewise, atomoxetine alleviated set-shifting impairments induced by noradrenaline depletion (Newman *et al*, 2008), although in this study, reversal performance was unaffected in both control and lesioned rats. These enhancements in set-shifting induced by systemic increases in noradrenergic release appear to be mediated in part by the activation of alpha-1 receptors in the PFC (Lapiz and Morilak, 2006).

It is interesting to note that although manipulations of acetylcholine muscarinic or nicotinic receptors have been shown to enhance memory and attention, there has been little work done investigating how these drugs may enhance reversal and set-shifts. One reason for this is that the contribution of the cholinergic system to these functions remains to be more completely clarified, as there have been some discrepant findings in the literature (Robbins and Roberts, 2007). That said, there has been one report that the beta-4 subtype-selective nicotinic agonist SIB-1553A improved reversal learning (but not set-shifting) in monkeys treated with MPTP as a model of Parkinson's disease (Decamp and Schneider, 2006). These findings provide some evidence that, like their effects on working memory and attention, nicotinic receptors may also be a suitable target for treating impairments in certain forms of flexibility.

Other potential drug targets for improving behavioral flexibility include, augmenting glutamate transmission with ampakines, as treatment may have some utility in alleviating impairments in this aspect of executive functioning (Broberg *et al*, 2009). In a similar vein, a recent study by Stefani and Moghaddam (2010) showed that the mGluR5 receptor agonist CDPPB alleviated impairments in strategy set-shifting induced by acute NMDA receptor blockade, even though this treatment had no effect in normal rats. There is some evidence that targeting the endocannabinoid system may also be a potential strategy for improving this executive function. Blockade of CB1 receptors have also been reported to facilitate strategy set-shifting in normal rats, whereas stimulation of these receptors impaired performance (Hill *et al*, 2006), although it is unclear whether this facilitation is due specifically to improved flexibility or attenuated retrieval of a previously acquired strategy. Of particular interest are multi-target agents such as asenapine, which has affinities for multiple monoamine receptors, and, somewhat curiously, has been shown to ameliorate impairments in extradimensional set-shifting induced by lesions of the medial PFC (Tait *et al*, 2009).

SUMMARY AND FUTURE DIRECTIONS

Rather than focus on one aspect of cognition or one class of drug, a key objective of this review was to emphasize some of the mechanistic differences and similarities through which drugs may enhance different types of memory and executive functioning. With regard to attentional functions, the most significant performance benefits arise from the administration of nicotinic agonists, particularly targeting the high-affinity beta-2-containing and low-affinity alpha-7-containing receptors. These effects have been observed in both normal and experimentally impaired animals, suggesting that targeting nicotinic receptors may be a particularly effective strategy in normalizing attentional impairments associated with a number of disorders. This being the case, new molecular targets for study in the control of attention, including the high-affinity choline transporter (Sarter and Parikh, 2005), deserve further study. Improved attention has also been reported using drugs that enhance catecholamine transmission that have been approved for the treatment of inattentive disorders (eg, stimulants, atomoxetine, guanfacine), although the contribution of dopamine *vs* noradrenaline receptors to these effects remain to be clarified.

Working memory has also been reported to be enhanced by nicotinic receptor agonists, although how much of this effect is attributable to improvements in attention remains to be clarified. Catecholamine agonists (particularly dopamine D_1 and alpha-2 adrenoceptor agonists) also enhance working memory, but in a much more complex manner, that depends on the biological integrity of the subject (eg, young *vs* aged, normal *vs* catecholamine depleted) and the task. Future work on modulators of glutamatergic function also holds great promise for the enhancement of working memory. Notably, the majority of the studies investigating pharmacological improvements in working memory have been conducted in normal animals, and there remains a relative dearth of studies of ameliorating working memory deficits induced in certain animal models of neuropsychiatric disorders (eg, Enomoto and Floresco, 2009). Continued research assessing the effects of potential pro-cognitive compounds using these models may provide novel insights into approaches for treating working memory deficits associated with certain disease states.

Different forms of behavioral flexibility display a striking complexity in terms of the neurochemical mechanisms that mediate these functions, providing a host of systems that may be targeted to enhance them. A key finding across these studies is that even though there is some overlap among drug targets that can enhance certain domains of behavioral flexibility, there also exist prominent dissociations in how certain compounds may affect one aspect of flexibility *vs* another. These observations further highlight the fact that behavioral flexibility is a collection of different processes with distinct neurochemical mechanisms. As such, one complication that arises when attempting to enhance a particular form of flexibility is that drugs which may

improve one aspect of functioning may do so at the expense of others. For example, 5-HT_{2C} receptor antagonists can not only enhance reversal learning (Boulougouris *et al*, 2009), but also impair other aspects of response inhibition (Winstanley *et al*, 2004b). Targeting CB1 receptors may facilitate Pavlovian extinction, but this may also interfere with between-strategy shifts (Pamplona *et al*, 2006, 2008; Hill *et al*, 2006). Nevertheless, an important direction for future research is to fill some of the substantial gaps in our understanding of how certain drugs, which have been shown to enhance one form of flexibility, may alter other related, but distinct processes. These include assessing the effects of different 5-HT receptor agonists/antagonists on extinction, glutamate receptor allosteric modulators on response inhibition and set-shifting, and cannabinoids on waiting/stopping. Furthermore, given that nicotinic drugs have been shown to enhance working memory and attentional functions mediated by the frontal lobes, an important avenue for future research would be to assess how these drugs may enhance different forms of flexibility in both normal and perturbed animals. A comprehensive analysis of how these and other drugs affect different domains of flexibility may reveal other targets that may enhance this type of executive functioning without hampering others.

Although each of the mnemonic and executive functions discussed in this review have somewhat distinct profiles in terms of pharmacological enhancement, it bears mentioning that some classes of drugs appear to exert beneficial effects on multiple domains of cognition in normal and/or perturbed animals. Thus, drugs acting on nicotinic receptors improve attention (Hahn *et al*, 2003), recognition memory (Pichat *et al*, 2007), working memory (Bontempi *et al*, 2003), and reversal learning in Parkinsonian monkeys (Decamp and Schneider, 2006) (Figure 4). Similarly, the noradrenaline reuptake inhibitor atomoxetine has been reported to positively modulate aspects of attentional performance (Jentsch *et al*, 2009), behavioral flexibility (Seu *et al*, 2009), response inhibition, and more complex forms of cognition related to impulsive decision making (Robinson *et al*, 2008) (see Figure 5). The multiple aspects of cognition that are enhanced by this compound suggests that it may act on multiple frontal subregions, including the prelimbic and anterior cingulate cortices responsible for controlled aspects of attention and the orbitofrontal cortex, which mediates the other functions (Eagle *et al*, 2008a, b; Winstanley *et al*, 2004c; Schoenbaum *et al*, 2006). These effects probably implicate catecholamine mechanisms localized within the PFC. Importantly, noradrenaline reuptake inhibition increases activity-dependent synaptic levels of both noradrenaline and dopamine, because noradrenergic terminals appear to be largely responsible for clearing synaptic dopamine in cortical, but not subcortical regions (Bymaster *et al*, 2002). These effects likely correspond to the positive therapeutic benefit of atomoxetine in the treatment of attention deficit/hyperactivity

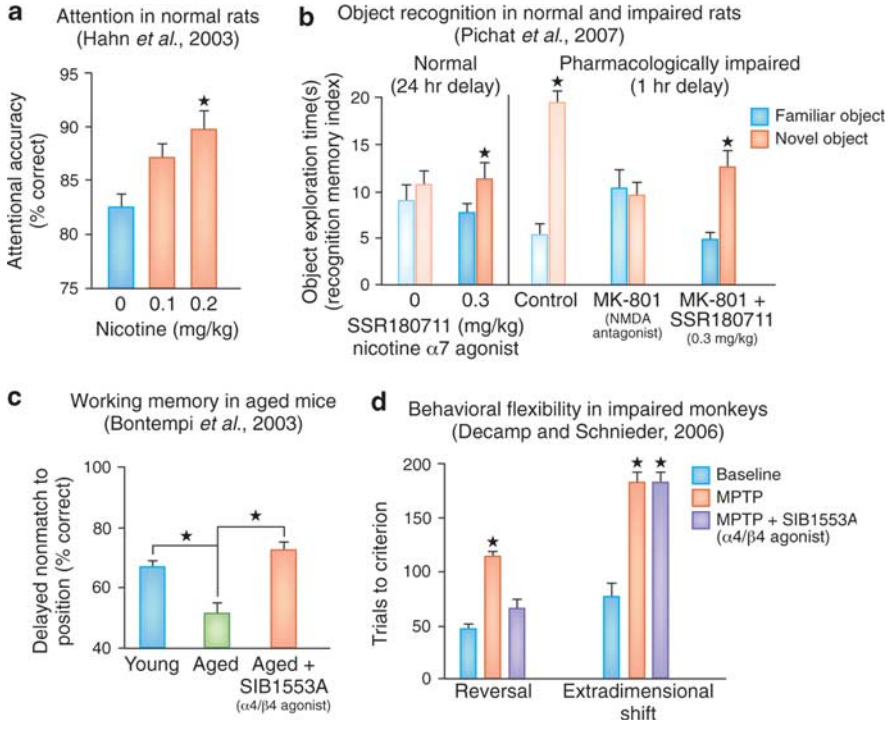

Figure 4. Examples of the broad pro-cognitive effects of nicotinic agonists in normal and experimentally impaired animals. Nicotine, or receptor subtype-selective agonists (a), improves attentional performance on the 5-choice serial reaction time tasks (CSRTT) in normal rats (Hahn *et al*, 2003); (b) augments object recognition memory in normal rats after an extended delay, and ameliorates impairments induced by NMDA receptor antagonism after a short delay (Pichat *et al*, 2007); (c) reverses impairments in delayed responding observed in aged mice (Bontempi *et al*, 2003); and (d) ameliorates impairments in reversal learning (but not set-shifting) in monkeys treated with MPTP (Decamp and Schneider, 2006).

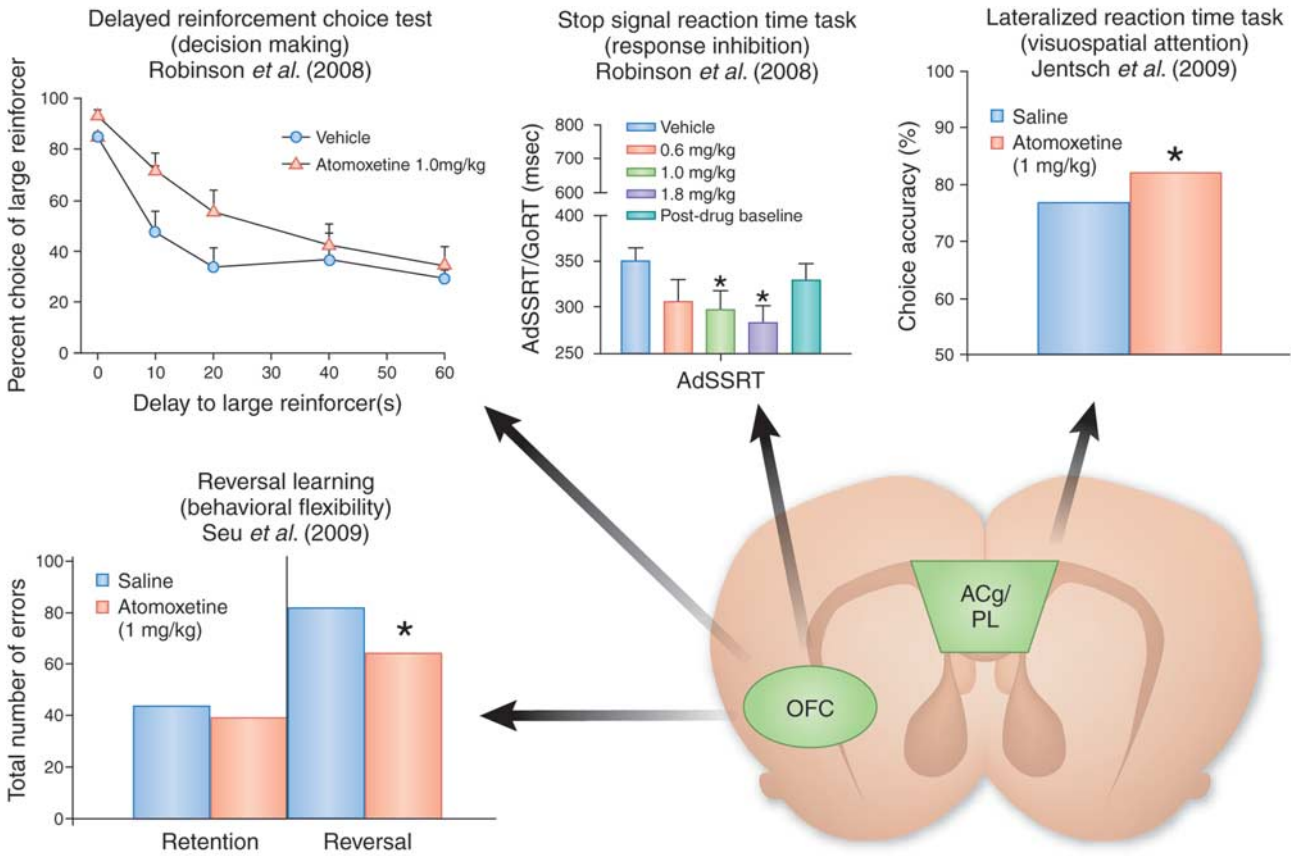

Figure 5. The noradrenaline reuptake inhibitor has also been shown to exert fairly broad performance-enhancing effects in measures of attentional function (Jentsch *et al*, 2009), behavioral flexibility (Seu *et al*, 2009), response inhibition (Robinson *et al*, 2008), and decision making with respect to delayed rewards (Robinson *et al*, 2008). These effects implicate multiple discrete prefrontal cortical subregions, and hence, distinct frontostriatal loops indicating that this mechanism spans multiple functional cognitive networks.

disorder, but probably also indicate its potential for exerting cognitive enhancement in disorders associated with the dysregulation of cortical dopamine/noradrenaline (eg, schizophrenia). The two main points to bear in mind when viewing studies of the pro-cognitive effects of these compounds are (1) drugs that may selectively target nicotinic or prefrontal catecholamine transmission may be particularly beneficial in enhancing multiple aspects of cognitive function, and (2) more generally, that identification of novel and more effective cognitive-enhancing drugs will come from a thorough assessment of their effects on multiple aspects of memory and cognition in both normal and experimentally impaired laboratory animals.

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DISCLOSURE

The authors declare no conflict of interest.

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