Putative cognitive enhancers in preclinical models related to schizophrenia: The search for an elusive target

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ABSTRACT

Several developments have converged to drive what may be called “the cognitive revolution” in drug discovery in schizophrenia (SCZ), including the emphasis on cognitive deficits as a core disabling aspect of SCZ, the increasing consensus that cognitive deficits are not treated satisfactorily by the available antipsychotic drugs (APDs), and the failure of animal models to predict drug efficacy for cognitive deficits in clinical trials. Consequently, in recent years, a paradigm shift has been encouraged in animal modeling, triggered by the NIMH sponsored Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative, and intended to promote the development and use of behavioral measures in animals that can generate valid (clinically relevant) measures of cognition and thus promote the identification of cognition enhancers for SCZ. Here, we provide a non-exhaustive survey of the effects of putative cognition enhancers (PCEs) representing 10 pharmacological targets as well as antipsychotic drugs (APDs), on SCZ-mimetic drugs (NMDA antagonists, muscarinic antagonist scopolamine and dopaminergic agonist amphetamine), in several tasks considered to measure cognitive processes/domains that are disrupted in SCZ (the five-choice serial reaction time task, sustain attention task, working and/or recognition memory (delayed (non)matching to sample, delayed alternation task, radial arm maze, novel object recognition), reversal learning, attentional set shifting, latent inhibition and spatial learning and memory). We conclude that most of the available models have no capacity to distinguish between PCEs and APDs and that there is a need to establish models based on tasks whose perturbations lead to performance impairments that are resistant to APDs, and/or to accept APDs as a “weak gold standard”. Several directions derived from the surveyed data are suggested.

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1. Introduction

1.1. A very brief background

Several developments have converged to drive what may be called "the cognitive revolution in drug discovery in schizophrenia (SCZ)." First, the renewed recognition that cognitive deficits are a core disabling aspect of SCZ (Heinrichs, 2005; Marder, 2006b; Marder and Fenton, 2004; Tamminga, 2006). Second, the increasing consensus that cognitive deficits are a core disabling aspect of SCZ, namely, attention/vigilance; working memory; verbal learning and memory; visual learning and memory; speed of processing; reasoning and problem-solving (and social cognition) and recommended a battery of neuropsychological tests measuring these cognitive constructs to be used in clinical assessments of potential cognitive enhancers (Fenton et al., 2003; Green, 1996; Marder and Fenton, 2004; Nuechterlein et al., 2004, 2008). Third, FDA's refusal to register compounds intended to treat cognitive deficits in SCZ, independent of treating psychosis per se. Fourth, the failure of animal models/assays to predict drug efficacy in clinical trials, which raised fundamental doubts regarding the capacity of behavioral measures in animals to generate valid (clinically relevant) measures of cognition.

In response, NIMH-established program, "Measurement and Treatment Research to Improve Cognition in Schizophrenia" (MATRICS), identified seven orthogonal domains of cognition that are deficient in SCZ, namely, attention/vigilance; working memory; verbal learning and memory; visual learning and memory; speed of processing; reasoning and problem-solving (and social cognition) and recommended a battery of neuropsychological tests measuring these cognitive constructs to be used in clinical assessments of potential cognitive enhancers (Fenton et al., 2003; Green, 1996; Marder and Fenton, 2004; Nuechterlein et al., 2004, 2008). MATRICS also
Scores of experiments have shown that animals can represent multiple spatial, temporal, and object properties of complex events and event sequences as well as detailed information about action–outcome and event–outcome relations, gained from several different learning experiences, and use this information flexibly and adaptively to guide behavior (Foote and Crystal, 2007; Gallistel, 1993; Kepecs et al., 2008; MacKintosh, 1994; Matzel and Kolata, 2010; Penn et al., 2008; Pickens and Holland, 2004; Terrace, 1984; Terrace and Son, 2009; Urcelay and Miller, 2010; Wasserman and Zentall, 2006; Wasserman, 1997; Wasserman and Miller, 1997; Zentall, 2001). Such demonstrations have fostered a greater acceptance of animal models of human cognition (Pickens and Holland, 2004; Zentall, 2001), and a continuity of certain cognitive capacities across phylogeny (Matzel and Kolata, 2010; Urcelay and Miller, 2010; but see Penn et al., 2008; Penn and Povinelli, 2007). “However, it is important to recognize that animal models will seldom permit the examination of exactly the same cognitive processes or behaviors as expressed in humans. Models are by their very nature not the same as what they model. Although we presume there should be some evolutionarily conserved neurobiological similarities between humans and other animals, there also will almost certainly be evolutionarily driven differences. Also, despite our best efforts to induce our animal subjects to use particular processes and solution strategies in our designated tasks, it is often very difficult to be certain that they have done so. …A good animal model is characterized first by evidence that the cognitive processes used are comparable in the model and modeled system, and second, by evidence for similar neural circuitry and mechanisms in the model as in the modeled human cognitive function” (Pickens and Holland, 2004, p. 625). While the latter is becoming increasingly attainable with the advent of noninvasive imaging techniques albeit still with too low resolution, the former remains a formidable task requiring a painstaking process of ingenious parametric comparisons that can never result in fully confident conclusions.

1.3. Cognitive domains in SCZ and their modeling in animals

Both MATRICS and CNTRICS emphasized that although overall cognitive function is often described as being deficient in SCZ, cognition is not a unitary construct as evidenced by neuropsychological and cognitive neuroscience studies demonstrating phenomenological and neurobiological separations between the domains of cognition deficient in SCZ (Luck and Gold, 2008; Nuechterlein et al., 2004). CNTRICS chose the following constructs of cognition and their measures (tasks) for the development and use in clinical trials and model animals. 1. Attentional control (emphasizing that control rather than implementation of input selection is deficient in SCZ), defined as “the ability to guide and/or change the focus of attention in response to internal representations”. Two tasks were selected: visual search task, which is unavailable in rodents, and sustained attention task (SAT) available in rodents (Bushnell et al., 1994; McAulughy and Sarter, 1995). 2. Two components of executive control: a. Rule generation and selection, defined as “the processes involved in activating task-related goals or rules based on endogenous or exogenous cues, actively representing them in a highly accessible form, and maintaining this information over an interval during which that information is needed to bias and constrain attention and response selection”. Animal models in this domain include reversal and intra-dimensional/extra-dimensional (ID/ED) shifts, in particular the attentional set shifting task (ASST; Birrell and Brown, 2000)). The second task is biconditional discrimination requiring animals to use contextual information to modify responses to specific stimuli (Haddon et al., 2008) considered to parallel the switching Stroop test. a. Dynamic adjustments in control defined as “the processes involved in detecting the occurrence of conflict or errors in ongoing processing, identifying the type of control adjustments needed, and recruiting additional control processes.” This domain is measured in animals in post-error slowing (Narayanan and Laubach, 2008), and the stop signal tasks (Eagle et al., 2007). 2. Two
components of working memory: a. Goal maintenance, defined as: "The processes involved in activating task-related goals or rules based on endogenous or exogenous cues, actively representing them in a highly accessible form, and maintaining this information over an interval during which that information is needed to bias and constrain attention and response selection", and b. Interference control defined as "The processes involved in protecting the contents of working memory from interference from either other competing internal representations or external stimuli". Because manipulation in contrast to maintenance of information held in working memory is emphasized by CNTRICS, existent animal tasks of WM were deemed inappropriate.

1.4. Using animal models of cognition to discover cognition enhancers for SCZ

Below we provide a non-exhaustive survey of the effects of putative cognition enhancers (PCEs) representing 10 pharmacological targets, on several tasks considered to measure cognitive processes/ domains that are disrupted in SCZ. Since only three tasks selected by CNTRICS have been characterized at least to some extent pharmacologically, namely, discrimination reversal, ASST and SAT, we added tasks that are quite consensually considered to test selective attention/attention/vigilance (the five choice serial reaction time (5CSRT) task, latent inhibition (Li)), and working and/or recognition memory (delayed (non-)matching to sample (D(N)MTS), delayed alternation task (DAT), radial arm maze (RAM), novel object recognition (NOR)). Our list is very similar to that proposed by Hogan and Jones (2005). Initially we intended to leave out APDs but as will become clear below, it is not yet time to do so.

While the different tasks may be seen as models of human cognition, animal models of SCZ include not only SCZ-relevant behavioral measures but also SCZ-relevant inducing factors, namely, manipulations that induce the "disease state" which in turn presumably induces abnormalities in the cognitive process assessed. Inducing manipulations can be pharmacological, genetic, or neurodevelopmental, but here we survey only pharmacological manipulations, because in pharmacological models of SCZ the inducing factors are drugs that produce and exacerbate SCZ symptoms in humans and thus have strong construct validity (Weiner and Arad, 2009) and because systemically administered drugs correspond more readily to effects seen in humans. These include the DA releaser amphetamine (AMPH) which produces and exacerbates positive (psychotic) symptoms and the NMDA receptor antagonists phencyclidine (PCP), ketamine or dizocilpine (MK801) that produce and exacerbate the entire spectrum of SCZ symptoms including cognitive deficits. We included here both SCZ-mimetics, because AMPH at low doses improves cognition and because with certain administration regimes it was shown to produce cognitive impairments (Fletcher et al., 2005, 2007). We also included scopolamine (SCOP) as an inducing agent, because cholinergic antagonists produce psychotic and cognitive symptoms in humans (Barak, 2009; Yeomans, 1995), and because the cholinergic system is most intimately linked to cognition (Bartus et al., 1982; Everitt and Robbins, 1997; Fibiger, 1991; Sarter et al., 2003).

The review is not intended to provide a listing of either currently available animal models or PCEs, nor will it discuss the advantages and limitations of specific models. We apologize a-priori for our omissions of any relevant papers; while they might be extensive, none is intentional. A summary is presented in Table 1.

2. Attention

2.1. Five-choice serial reaction time task (5CSRT)

The 5CSRT (Bari et al., 2008; Robbins et al., 1993; Robbins, 2002) is an operant task testing rats’ ability to sustain spatial attention divided among a number of locations (usually 5) over a large number of trials (about 100). Each trial is initiated by the rat pushing open the food magazine door, followed by a fixed 5-s inter-trial interval (ITI), after which a 0.5-s light stimulus is presented randomly in one of the holes. A nose-poke in the hole where the light appeared is rewarded. The task generates several measures of performance including attention (accuracy and latency of reporting the stimuli and errors of omission); impulsivity ( premature responses), and executive function (perseverative responses). The difficulty of the 5-CSRTT can be varied by changing the brightness, duration, frequency or predictability of the target stimuli, or by interpolating distracting stimuli into the inter-trial interval.

2.1.1. Effects of SCZ-mimetic drugs

Low doses of AMPH (0.05–0.6 mg/kg) reduced latency to respond and increased accuracy in adult (0.1–0.8 mg/kg) and aged rats (0.05–0.4 mg/kg) (Bizarro et al., 2004; Cole and Robbins, 1987; Grottick and Higgins, 2002). Likewise, methylphenidate (0.5 mg/kg and 2.5–10 mg/kg) increased accuracy (Bizarro et al., 2004; Paine et al., 2007). Both systemic (0.3–2.3 mg/kg) and intra-accumbal AMPH increased premature responding at doses having no effects on response accuracy (Cole and Robbins, 1987, 1989; Robbins, 2002). Repeated, intermittent, escalating doses of AMPH (three injections per week for 5 weeks at 1–5 mg/kg per week) and withdrawal (several weeks) increased omissions without affecting accuracy; reducing stimulus duration impaired response accuracy in AMPH-sensitized rats more than in controls (Fletcher et al., 2007). Low doses of SCOP (0.03–0.3 mg/kg) induced a mild impairment in choice accuracy in young rats under no distraction conditions but a greater impairment with high distraction (Jones and Higgins, 1995). Higher doses of SCOP (0.1–2 mg/kg) produced more disruptive effects on response accuracy, and also increased omission rates, in rats and mice (Humby et al., 1999; Mirza and Stolerman, 2000; Robbins, 2002). NMDA antagonists also induce attentional deficits in the 5CSRT in rats and mice. Thus, acute or subchronic PCP administration impair response accuracy (Amitai and Markou, 2010b, 2009; Amitai et al., 2007; Auclair et al., 2009; Jin et al., 1997; Le Pen et al., 2003). Similarly, acute MK-801 administration at low doses impaired accuracy (0.05–0.06 mg/kg) (Grottick and Higgins, 2000), and at higher doses increased omissions in addition to reduced accuracy (Amitai and Markou, 2010b; Paine and Carlezon, 2009). Withdrawal from chronic MK-801 progressively increased omissions and response latencies but decreased premature responding (Paine and Carlezon, 2009). Finally, ketamine (20 mg/kg) reduced correct responding and increased omissions without affecting overall accuracy, or impulsivity (Nemeth et al., 2010). Acute or subchronic PCP administration also increased premature and perseverative responding (Amitai and Markou, 2010b, 2009; Amitai et al., 2007; Auclair et al., 2009).

2.1.2. Effects of PCEs

2.1.2.1. Naïve animals. The acetylcholinesterase (AChE) inhibitor phystostigmine (0.1 mg/kg) had no effect on impaired performance in naïve animals (Mirza and Stolerman, 2000). In contrast, and in agreement with findings in normal humans (Levin et al., 1998; Min et al., 2001), nicotine (0.05–0.4 mg/kg) improved performance (increased response accuracy and decreased omissions and/or correct response latency) in normal animals (Day et al., 2007; Grottick and Higgins, 2000; Hahn et al., 2002; Mirza and Stolerman, 1998; Young et al., 2004), particularly with conditions that tax performance such as decreased stimulus duration and shortened, but not extended ITI (Mirza and Stolerman, 1998), and presence of noise distractors (Hahn et al., 2002), as well as in aged rats (Grottick et al., 2003). Importantly, nicotine tended to impair accuracy under asymptotic performance (Day et al., 2007; Mirza and Stolerman, 1998). Unlike nicotine, alpha7 nAChR agonist AR-17779 (3–24 mg/kg) or an antagonist of this receptor did not affect performance in the 5CSRT in young or aged
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<th>Model</th>
<th>Attention</th>
<th>Working memory</th>
<th>Recognition/working memory</th>
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<td>NMDA ant (chronic)</td>
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<td>Scopoline</td>
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5CSRT = five choice serial reaction time; SAT = sustained attention task; D(N)MTS = delayed (non)-matching to sample; DAT = delayed alternation task; NOR = novel object recognition; ASST = attentional set shifting task; Amph = amphetamine; Scop = scopolamine; NMDA ant = NMDA antagonist; AChE = acetylcholinesterase inhibitor; mGluR = metabotropic glutamate receptor; ↑ = increase/enhance/improve; ↓ = decrease/reduce/disrupt; ≡ = no effect; ∆ = reverses.
In contrast, an alpha4beta2 nAChR agonist increased correct responding and decreased response latencies (Grottick and Higgins, 2000), suggesting that the latter receptor subunit mediates the pro-attentive effects of nicotine on 5CSRT. Intra-medial prefrontal cortex (mPFC) as well as intra-accumbal infusion of the D1 agonist SKF38393 improved accuracy under taxing conditions (short stimulus duration) at a low dose, but increased premature responding at higher doses (Pezze et al., 2007). The alpha2 adrenergic agonist dexmedetomidine had no effect on response accuracy but increased the number of omissions and response latency, and decreased the number of premature responses (Sirvio et al., 1994). Similarly, the norepinephrine reuptake inhibitors desipramine (DMI) and atomoxetine increased omissions and correct response latencies while decreasing premature responses and reward latencies (Paine et al., 2007; Robinson et al., 2008). The metabotropic glutamate receptor (mGluR)-2/3 allosteric agonists LY379268 and LY354740 impaired accuracy in rats and monkeys, respectively (Amitai and Markou, 2010b; Spinelli et al., 2005). Finally, the 5-HT6 antagonist SB-271046 had no effect on 5CSRT performance (Talpos et al., 2006).

### 2.1.2.2. Pharmacological impairments.

The AChE inhibitors tacrine, donepezil, and physostigmine all reversed SCOP-induced deficits in performance, predominantly by normalizing omission levels (Kirkby et al., 1996; Lindner et al., 2006). AChE inhibitors also reversed impairments in 5CSRT induced by lesion of the nucleus basalis (Balducci et al., 2003; Muir et al., 1995). The nicotinic agonist SIB-1553A reversed NMDA-induced deficits in 5CSRT (Terry et al., 2002b), and relatedly, improved performance induced by nicotine was reversed by NMDA receptor blockade (Quarta et al., 2007). Acute administration of the mGluR2/3 allosteric agonists LY379268 exacerbated subchronic PCP-induced disruption of attentional performance in 5CSRT at a dose that had no effect when given on its own, whereas chronic administration of the mGluR2/3 antagonist LY341495 attenuated the

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<td><strong>Attention</strong></td>
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impairing effects of PCP (Amitai and Markou, 2010b). In addition, LY379268 failed to reverse response accuracy deficits induced by acute PCP in mice although it ameliorated PCP adverse effects on anticipatory and perseverative responding (Greco et al., 2005). Finally, infusion of the D1 agonist SKF38393 (0.6 μg/site) into the mPFC reversed the attentional deficit induced by sensitization to AMPH (Fletcher et al., 2007).

2.1.3. Effects of APDs

The typical APD haloperidol (0.125 mg/kg) and the atypical APDs clozapine (2.5–3 mg/kg), risperidone (0.3 mg/kg), quetiapine (7.5 mg/kg), and olanzapine (1 mg/kg) disrupted 5-CSRT performance under baseline conditions only at the doses indicated, but not at lower doses (Amitai et al., 2007; Paine and Carlezon, 2009). In another study, lower doses of olanzapine (0.03–0.3 mg/kg) and risperidone (0.01–0.1 mg/kg) as well as the atypical APD asenapine (0.3 mg/kg), impaired 5CSRT response accuracy (Marston et al., 2009). Chronic clozapine (4 mg/kg) reversed repeated PCP-induced impairment in response accuracy and premature responding (Amitai et al., 2007). The effects of acute high dose of MK-801 (0.25 mg/kg) on response accuracy and omissions were exacerbated by haloperidol (0.032–0.063 mg/kg) but reversed by low (0.16–0.32 mg/kg) but not higher doses of clozapine (Paine and Carlezon, 2009). These APDs were ineffective, however, in reversing the effects of a chronic regimen of MK-801 (Paine and Carlezon, 2009).

2.1.4. Summary

The three SCZ-mimetics we survey here induce distinct effects on the different performance measures provided by the SCSRT task. Specifically, although in a repeated administration regime AMPH was reported to induce omissions, suggesting it may impair attention, AMPH given acutely at low doses improves response accuracy (attention), but also premature responses (impulsivity). On the contrary, measures of attention are impaired by both SCOP and NMDA antagonists, whereas only the latter also induce impulsive and perseverative responses. Thus, SCOP is the only SCZ-mimetic that specifically impairs attentional performance in this task. APDs on their own impair attentional performance, but atypical APDs reverse, whereas typical APDs exacerbate, the effects of NMDA blockade. Among all the PCEs we included in this review, a clear reversal of NMDA antagonist-induced 5CSRT impairment (mainly attentional) was reported only for a nicotinic agonist, whereas mGlur agonists were reported to exacerbate or spare the NMDA-induced attentional deficit, but to reverse its perseverative and impulsivity effects. When given to naive animals, nicotinic agonism (apparently through the alpha4beta2 receptor) was also the only treatment improving attention, whereas mGlur and alpha adrenergic agonism, and serotonergic antagonism impaired or had no effect on accuracy.

2.2. Sustained attention task (SAT)

The SAT (Bushnell et al., 1994; McGaughy and Sarter, 1995; Turchi and Sarter, 2001) is an operant task that requires the detection of a target signal, which is presented just before the presentation of two levers. The animal is then required to press one lever (signal lever) if it detected the signal, and the other lever (non-signal lever) if it did not detect the signal. The task generates measures of hits (correct presses on the signal lever following presentation of the signal), misses (incorrect presses on the non-signal lever following presentation of the signal), correct rejections (correct presses on the non-signal lever after the signal was not presented), and false alarms (incorrect presses on the signal lever after the signal was not presented), as well as omissions. In the distracter version of the task (dSAT), introduction of distracters (e.g., a changing background) reduces the discriminability of the signal.

2.2.1. Effects of SCZ-mimetic drugs

Repeated intermittent administration of AMPH (1, 2, and 3 mg/kg) impairs performance in the task by increasing false alarm rates (Deller and Sarter, 1998). Likewise, escalating dosing regimen (1–10 mg/kg) of AMPH followed by low dose challenges (0.5, 1 mg/kg) impairs SAT (Martinez et al., 2005). The NMDA receptor antagonists ketamine (8 mg/kg) and MK-801 (0.05 mg/kg) impaired performance in SAT by increasing false alarm rates or lowering hit rates and correct rejections (Nelson et al., 2002; Rezvani and Levin, 2003a,b). Finally, SCOP (0.03–0.1 mg/kg) also disrupts SAT performance by decreasing detection of signals and increasing false alarm rate (Bushnell et al., 1997).

2.2.2. Effects of PCEs

2.2.2.1. Naïve animals. Nicotine (acute 0.025–0.75 mg/kg or chronic 5 mg/kg/day) given on its own did not improve, and even impaired, SAT performance in normal rats (Bushnell et al., 1997; Howe et al., 2010; Rezvani and Levin, 2004, 2003b). Similarly, AChE inhibitors failed to improve SAT performance in normal or cholinergically lesioned rats (McGaughy et al., 1999, 1996; McGaughy and Sarter, 1998). In contrast, the alpha4beta2 nAChR agonist S-38232 improved SAT performance (Howe et al., 2010).

2.2.2.2. Pharmacological impairments. Nicotine (acute 0.025–0.75 mg/kg or chronic 5 mg/kg/day) reversed SAT impairments induced by MK-801, or APDs (Rezvani et al., 2007; Rezvani and Levin, 2003a,b).

2.2.3. Effects of APDs

SAT impairments induced by escalating regimen of AMPH followed by low dose challenges of this drug were reversed by subchronic low doses of haloperidol (0.025 mg/kg) and clozapine (2.5 mg/kg) (Martinez and Sarter, 2008). Given on their own, subchronic clozapine (2.5 mg/kg), but not haloperidol (0.025 mg/kg), impaired performance (Martinez and Sarter, 2008). Likewise, acute treatment with haloperidol (0.01–0.02 mg/kg), clozapine (0.625–2.5 mg/kg) and risperidone (0.1 mg/kg) impaired rat performance on this task (reduced percentage hit and correct rejections) (Rezvani et al., 2006; Rezvani and Levin, 2004). Interestingly, in the latter studies, nicotine reversed the effects of APDs while impairing accuracy on its own (Rezvani et al., 2006; Rezvani and Levin, 2004). Thus, the latter can be also interpreted as APD-induced reversal of the impairing effects of nicotine in this task.

2.2.4. Summary

All three SCZ-mimetic drugs impair SAT. Notably, performance in this task is impaired by drugs that improve attentional performance in humans, such as amphetamine and nicotine. However, the latter reverses SAT impairments induced by APDs and SCZ-mimetics. Unfortunately, PCEs were hardly tested on this task.

3. Working memory (WM) and recognition memory

Our descriptions of WM tasks below are based on a review of rodent WM tasks by Dudchenko (2004). In addition to the tasks we survey below, the odor/olfactory span task was suggested to model WM as defined by CNTRICS. However very few SCZ-relevant pharmacological studies have been published on this task to date. Scopolamine (0.1 mg/kg; Rushforth et al., 2010) and MK-801 (0.17–0.3 mg/kg; Macqueen et al., 2011) were shown to impair performance in this task, whereas nicotine (0.05–0.1 mg/kg), as well as alpha4beta2 and alpha7 nAChR agonists improved performance on their own (Rushforth et al., 2010).
3.1. Radial arm maze (RAM)

RAM (Olton and Samuelson, 1976; Olton, 1987) consists of central chamber with eight arms radiating from it. Food reward is available at the end of each arm and the animal is required to enter each arm and retrieve the reward therein. Thus to complete the task with maximal efficiency, the animal must not re-enter a previously visited arm (a win-shift strategy). The number of baited arms entered prior to re-entering a previously visited arm is the measure of WM span capacity in this task (Young et al., 2009). Variants of RAM may include interposed delay, extended session challenges, reduced number of baited arms, and change in the number of accessible arms.

3.1.1. Effects of SCZ-mimetic drugs

Acute administration of NMDA antagonists (PCP, ketamine or MK-801) impair performance in RAM (for a review, see Myhrer, 2003). Conversely, withdrawal from PCP (10 mg/kg) after subchronic administration was reported not to affect RAM (Li et al., 2003; Marquis et al., 2003). Muscarinic blockade, typically using SCOP (0.1–2.4 mg/kg), has frequently been shown to impair performance in this task (e.g. Braida et al., 1998; Cassel and Kelche, 1989; Eckerman et al., 1980; Lindner et al., 2006; Ortega-Alvaro et al., 2006). Finally, AMPH was shown to impair RAM performance at 0.5 mg/kg (Ennaceur, 1998) or to have no effects at 0.1–3 mg/kg (Eckerman et al., 1980).

3.1.2. Effects of PCEs

3.1.2.1. Naïve animals. Although improved performance in RAM is difficult to demonstrate due to ceiling effects, some studies demonstrated such improvement by nicotinic agonists (a small effect of nicotine (Addy and Levin, 2002), and a more pronounced effects of alpha7 or alpha4beta2 nAChR agonists (Addy et al., 2003; Marigotto et al., 2008)). In addition, the AChE inhibitor physostigmine improved RAM performance (Ennaceur, 1998). Likewise, the ampakine CX516 et al., 2008)) increased accuracy in D(N)MTS in a delay-dependent manner in rats (typically 3–10 mg/kg) or MK-801 (0.1–0.2 mg/kg) also improved accuracy in DMTS in young and aged rats (Ruske and White, 1999). Nicotine, as well as several alpha7 agonists improved performance in D(N)MTS in rats and monkeys (e.g., Baron and Wenger, 2001; Baron et al., 1998; Harper et al., 2005; Kesner et al., 1981; Sahgal, 1987; but see Schulze and Paule, 1990). Harper et al. (2005) found that this impairment was delay-independent, suggesting that AMPH impairs learning or attention rather than memory. However, in other reports, the effect was delay-dependent (e.g., Sahgal, 1987). NMDA antagonists like PCP (3–10 mg/kg) or MK-801 (0.1–0.2 mg/kg) also impair accuracy in DMTS in rats and monkeys (e.g., Baron and Wenger, 2001; Baron et al., 1998; Cole et al., 1993; Fadda et al., 2006; Pontecorvo et al., 1991; Stephens and Cole, 1996), again in a delay-independent manner (Clissold et al., 1992; Cole et al., 1993; Pontecorvo et al., 1991; Stephens and Cole, 1996). MK801 at 0.05 mg/kg had no effect (Cole et al., 1993). Finally, numerous studies have demonstrated that SCOP disrupts accuracy in D(N)MTS in a delay-dependent manner in rats (typically doses lower than 0.6 mg/kg were used) and monkeys (e.g., Baron et al., 1998; Buccafusco et al., 2008; Clissold et al., 1992; Fadda et al., 2006; Higgins et al., 2002; Kesner et al., 1981; Plakke et al., 2008; Pontecorvo et al., 1991).

3.1.2.2. Pharmacological impairments. Cholinergic agonists reverse drug-induced impairments in RAM. Thus, for example, SCOP (0.125–0.25 mg/kg in rats, 2 mg/kg in mice)–induced deficits in this task were reversed by various AChE inhibitors, including donepezil (0.5 mg/kg) and tacrine (2 mg/kg) (Braud et al., 1998; Ogura et al., 2000; Xiong and Tang, 1995; Xiong et al., 1995; Zhang et al., 2009). Donepezil (0.1–1 mg/kg) failed to reverse SCOP (0.2 mg/kg)–induced impairments in one study (Lindner et al., 2006). Impairments in RAM induced by NMDA antagonists such as MK-801, were reversed by the AChE inhibitor huperzine-A, as well as by a combined treatment with the alpha2 adrenergic antagonist idazoxan and D2/3 DA antagonist raclopride (Carbony et al., 2004; Huang et al., 2004; Marcus et al., 2005; Xiong et al., 1995). Administration of alpha2 adrenergic agonist also prevented impairments of RAM performance induced by PCP and ketamine (McCann et al., 1987). In contrast, DCS (0.03–10 mg/kg) failed to reverse MK-801–(0.1 mg/kg) induced deficits (Pitkanen et al., 1995). Finally, nicotine (0.4 mg/kg) reversed impairments in RAM induced by clozapine (1.25–2.5 mg/kg) (Addy and Levin, 2002; Levin and Christopher, 2006; Levin et al., 2005; McGurk et al., 1989; Ortega-Alvaro et al., 2006). Other studies showed that acute clozapine (5 mg/kg) did not affect RAM performance, and reversed MK-801–induced deficits in this task (Marcus et al., 2005). Finally, haloperidol (0.04–0.08 mg/kg) reversed SCOP (0.1 mg/kg)–induced, but potentiated mecamelamine (nicotinic antagonist)–induced, impairments in RAM (McGurk et al., 1989).

3.1.4. Summary

Cholinergic agonists (particularly AChE inhibitors) have been the most extensively tested PCEs in this task and seem to be beneficial in normal animals, as well as effective in reversing SCOP– as well as NMDA antagonist–induced deficits. Performance in naïve animals is also improved by ampakines. Interestingly NMDA antagonist–induced RAM impairments were resistant to the NMDA enhancer DCS, but reversed by an alpha2 adrenergic agonist. Most of the PCEs surveyed here have not been tested in this task. Given that RAM is considered to measure working memory span capacity as is common in the human tests of working memory, a broader characterization of its SCZ–relevant pharmacological profile would be desirable.

3.2. Delayed matching/non-matching to sample/position (D(N)MTS/P)

D(N)MTS tasks require a rat to remember a stimulus/position over a delay, in which the stimulus/position is no longer available. Following the delay, the rat is presented with the original, to-be–remembered stimulus/position and an alternative, and is reinforced for making a response towards the original (DMTS/P) or the alternative (DNMTS/P) stimulus/position (Dudchenko, 2004). Since much of the relevant data on this task have been obtained in monkeys, we include these results as well.

3.2.1. Effects of SCZ-mimetic drugs

Amphetamine (0.6–3 mg/kg) impairs DMTS in rats and monkeys by decreasing accuracy (e.g., Baron and Wenger, 2001; Baron et al., 1998; Harper et al., 2005; Kesner et al., 1981; Sahgal, 1987; but see Schulze and Paule, 1990). Harper et al. (2005) found that this impairment was delay-independent, suggesting that AMPH impairs learning or attention rather than memory. However, in other reports, the effect was delay-dependent (e.g., Sahgal, 1987). NMDA antagonists like PCP (3–10 mg/kg) or MK-801 (0.1–0.2 mg/kg) also impair accuracy in DMTS in rats and monkeys (e.g., Baron and Wenger, 2001; Baron et al., 1998; Cole et al., 1993; Fadda et al., 2006; Pontecorvo et al., 1991; Stephens and Cole, 1996), again in a delay-independent manner (Clissold et al., 1992; Cole et al., 1993; Pontecorvo et al., 1991; Stephens and Cole, 1996). MK801 at 0.05 mg/kg had no effect (Cole et al., 1993). Finally, numerous studies have demonstrated that SCOP disrupts accuracy in D(N)MTS in a delay-dependent manner in rats (typically doses lower than 0.6 mg/kg were used) and monkeys (e.g., Baron et al., 1998; Buccafusco et al., 2008; Clissold et al., 1992; Fadda et al., 2006; Higgins et al., 2002; Kesner et al., 1981; Plakke et al., 2008; Pontecorvo et al., 1991).

3.2.2. Effects of PCEs

3.2.2.1. Naïve animals. The M1 mAChR agonist AF150(S) improved accuracy in DMTS in young and aged rats (Ruske and White, 1998). Nicotine, as well as several alpha7 agonists improved performance in D(N)MTS in rats and monkeys (Bittner et al., 2010; Briggs et al., 1997; Buccafusco et al., 2007; Hironaka et al., 1992; Spinelli et al., 2006). The AChE inhibitors physostigmine and tacrine had no effect in rats (Buxton et al., 1994; Sirvio et al., 1992). In contrast, the AChE inhibitor donepezil increased accuracy in normal monkeys (Buccafusco and Terry, 2004; Buccafusco et al., 2008). Chronic treatment with AChE inhibitors, as well as the M1 mAChR agonist talsacidine also induced improvement in accuracy in aged monkeys (Buccafusco...
The GABAα α5 inverse agonists RO4938581 and MRK-536 (in rodents water maze) (Atack, 2010; Atack et al., 2006; Chambers et al., 2003, 2004; Collinson et al., 2006; Dawson et al., 2006), but not RO4938581 (in operant chambers) (Ballard et al., 2009) improved DMTP performance in rats (Ballard et al., 2004; Porrino et al., 2005). In addition, the mGlUR agonist LY354740 impaired operant-based DMTP and DNMT in rats, whereas an antagonist of the receptor improved performance (Higgins et al., 2004). The GABAA α5 inverse agonists L-655,708, alpha5IA, alpha5IA-II and MRK-536 (in rodents water maze) (Atack, 2010; Atack et al., 2006; Chambers et al., 2003, 2004; Collinson et al., 2006; Dawson et al., 2006), but not RO4938581 (in operant chambers) (Ballard et al., 2009) improved DMTP performance. These findings were demonstrated with different regimens and routes of drug administration, including acute i.p. (Collinson et al., 2006), subchronic p.o. (Dawson et al., 2006), or slow release pellets (Atack, 2008). Finally, the alpha2 adrenergic agonist and antagonist, dexmedetomidine and atipamezole, respectively, had no effect in young or aged rats on operant-based DNMT (Sirvio et al., 1992, 1991), but the alpha2 adrenergic agonist clonidine improved DMTP in monkeys (Buccafusco et al., 2009).

3.2.2. Pharmacological impairments. AChE inhibitors (e.g. donepezil, physostigmine, TAK-147) reversed SCOP-induced impairments in D(N)MTS in rats and monkeys (Buccafusco et al., 2008; Buxton et al., 1994; Dawson and Iversen, 1993; Higgins et al., 2002; Jackson et al., 1995; Miyamoto et al., 1996). Scopolamine-induced deficits in an operant-based DMTP were also reversed by the M1/M3 mACHr agonist L-687,306 whereas other M1 or M1 agonists (L-689,660 and AF1028) had no such effect (Dawson and Iversen, 1993). The NMDA enhancer DCS reversed scopolamine-induced deficits in mice (Dawson and Iversen, 1993), but failed to reverse the effects of SCOP in rats operant-based DMTP (Harper, 2000). Finally, the GABAA α5 inverse agonists RO4938581 and RO4882224 reversed SCOP-induced deficits in operant-based DMTP in rats (Ballard et al., 2009; Knust et al., 2009).

3.2.3. Effects of APDs

In DMTP in water maze, clozapine (0.1, 0.3 mg/kg) and haloperidol (0.003, 0.1 mg/kg) had no effects, whereas ioperidone (0.03, 0.1 mg/kg) improved accuracy (Gumperle et al., 2003). Treatment with risperidone (1 mg/kg/day) for 8 weeks, but not 2 or 4 weeks, improved water maze DMTP performance in rats (Lim et al., 2007). Chlorpromazine was effective in monkeys (Glick et al., 1969; Hironaka et al., 1992).

3.2.4. Summary

Interpretation of impairments in D(N)MTS that are induced by SCZ-mimetics should be made with caution, since amphetamine and NMDA antagonists induce delay-independent deficits, suggesting that these drugs impair learning or attention rather than working memory. The only SCZ-mimetic drug that consistently induces delay-dependent impairment is SCOP. Cholinergic agonists and GABA inverse agonists improve performance when given on their own, and reverse the effects of SCOP. D(N)MTS performance was also improved in naive rats by NMDA enhancers, amakines and alpha adrenergic agonists, but these drugs failed to reverse the effects of scopolamine, or were not tested on this model. In contrast, APDs conventionally impair D(N)MTS performance on their own, and unfortunately were not tested in the SCOP model. Thus, while several PCEs are superior to APDs when tested on naïve animals in this task, it is impossible to compare the effects on perturbed animals.

3.3. Delayed alternation task (DAT)

DAT is based on rodents tendency to choose alternative maze arms or locations when they are re-exposed to an apparatus (Dudchenko, 2004). DAT is considered a working memory task because the animals must remember their initial response in order to select an alternative response.

3.3.1. Effects of SCZ-mimetic drugs

Amphetamine improved accuracy in DAT at 0.25 mg/kg (Aultman and Moghaddam, 2001) or 1 mg/kg (Shoblock et al., 2003), but reduced accuracy at higher doses (also see (Kesner et al., 1981)). Similarly, methylphenidate improved DAT with an inverted U dose–response curve, whereby moderate doses (1–2 mg/kg, p.o.) improved DAT performance, whereas higher doses caused perseverative errors (Arnett and Dudley, 2005). Acute or subchronic PCP, MK-801 (0.05–0.5 mg/kg) and ketamine (12–30 mg/kg) treatment reduced accuracy in DAT (Aultman and Moghaddam, 2001; Bardgett et al., 2009; Baron et al., 1998; Imre et al., 2006; i; Seilier and Giuffrida, 2009; Verma and Moghaddam, 1996; Wedzony et al., 2000). In contrast, twice daily treatment with PCP (5.0 mg/kg) or AMPH (2.5 mg/kg) for 5 days did not produce impairments in DAT, but subsequent challenge with PCP produced DAT impairments in vehicle, PCP, and AMPH pre-treated groups (Stefani and Moghaddam, 2002). Relatedly, subchronic PCP treatment (10 mg/kg for 14 days) followed by 48 withdrawal resulted in DAT impairment but only in continued (as opposed to discrete) trial version of the task (Marquis et al., 2007). Finally, SCOP (0.05–1 mg/kg) reduces accuracy in DAT (Baron et al., 1998; Dudchenko and Sarter, 1992; Locchi et al., 2007; Shannon et al., 1990a,b). However, methscopolamine, which does not cross the blood brain barrier, also disrupted DAT performance, suggesting that some SCOP effects could be mediated peripherally (Baron et al., 1998; Dudchenko and Sarter, 1992).

3.3.2. Effects of PCEs

3.3.2.1. Naïve animals. The M1 mACHr agonist subacemoline improved DAT performance in young animals (Hatcher et al., 1998), whereas physostigmine improved DAT in middle-aged and aged, but not in young, rats (Ordy et al., 1988; Shannon et al., 1990b). Similarly, the beta4 nACHR agonist SIB-1553A improved DAT in aged mice (Bontempi et al., 2003). The GlyT1 inhibitor SSR504734 improved DAT performance in mice (Singer et al., 2009) whereas the mGlu2/3 agonist LY534740 impaired DAT in rats (Aultman and Moghaddam, 2001). The alpha2 adrenergic agonists clonidine, medetomidine and guanfacine had no effect on DAT in adult animals (Birnbaum et al., 2000; Ordy et al., 1988). However, systemic and intra-prefrontal cortex infusion of the alpha2 adrenergic agonist medetomidine improved DAT in aged and young rats, respectively (Carlson et al., 1992; Tanila et al., 1996). Finally, the D1 agonist A77636 improved DAT performance in rats (Zhang and Cai, 2003), but the D1 agonist SKF 81297 impaired DAT in mice (Izquierdo et al., 2006). Relatedly, while infusion of this drug into the prelimbic cortex improved DAT deficits in aged rats at low doses (Mizoguchi et al., 2009), it impaired DAT at a higher dose (Zahrt et al., 1997).

3.3.2.2. Pharmacological impairments. The AChE inhibitors physostigmine, donepezil and THA, as well as the beta4 nACHR agonist SIB-1553A, reversed SCOP-induced impairments (Bontempi et al., 2003; Hareri et al., 1997; Ordy et al., 1988; Shannon et al., 1990b; Yamazaki et al., 1989). The mGlu2/3 agonist LY534740 (10 mg/kg) reversed PCP (5 mg/kg)-impaired performance in a T-maze discrete-trial DAT (Moghaddam and Adams, 1998), however, the drug (at 2.5, 5 mg/kg) failed to reverse MK-801 (0.2 mg/kg)-induced deficits (Ossowska et al., 2000). Relatedly, the same drug (3–10 mg/kg) also failed to alleviate PCP (2 mg/kg)-induced effects on spontaneous alternation
(Sclumberger et al., 2009). Finally, the alpha2 adrenergic agonist clonidine reversed DAT impairment induced by MK-801 (Bardgett et al., 2008).

3.3.3. Effects of APDs
Clozapine (5 mg/kg) and olanzapine (0.5 mg/kg) disrupted performance in DAT in Y maze (Castro et al., 2007), whereas chronic risperidone (0.2 mg/kg) slightly improved performance in a T-maze (Bardgett et al., 2006). Haloperidol (0.1 mg/kg) was without an effect on its own, but reversed ketamine-induced DAT deficits (Aultman and Moghaddam, 2001; Verma and Moghaddam, 1996).

3.3.4. Summary
Amphetamine at low doses improves DAT performance. Conversely, NMDA and mAChR blockade disrupt DAT accuracy. While the results with APDs are mixed, cholinergic agonists tend to improve performance on their own and to reverse the effects of SCOP. Results with glutamatergic, adrenergic and dopaminergic agents are also consistent whereby some of these agents improve performance in aged animals (alpha adrenergic agonists) or young animals (NMDA enhancers but not alpha adrenergic agonists) animals, and others disrupt performance in young animals (mGluR agonist) but reverse the deleterious effects of NMDA blockade (mGluR and alpha adrenergic agonists). Thus, cholinergic agonists, which were most widely characterized in this task, possess the most promising pharmacological profile in this task.

3.4. Novel object recognition (NOR) test
NOR (Ennaceur and Delacour, 1988) is widely used in rats and mice as a test of recognition memory (Bevins and Beshear, 2006; Dere et al., 2007). In this task, animals are first familiarized with two identical objects and after a delay (ranging from minutes to days), the animals are returned to the same apparatus and presented with one of the familiar objects and an additional, novel object. Since rodents normally tend to explore novel objects in their environment, animals spend more time exploring the novel than the familiar object (Dere et al., 2007). The NOR effect is strong with short intervals between familiarization and test stages, whereas longer delays such as 24 h usually lead to weak or no NOR effect. It should be pointed out that NOR can be seen as a WM task (Dudchenko, 2004): furthermore, the test resembles radial arm alternation, where the animal spontaneously shows preference for the novel arm.

3.4.1. Effects of SCZ-mimetic drugs
NOR was enhanced in Fischer rats that were sensitized to and withdrawn from AMPH, but was impaired in Lewis rats with the same treatment regimen (Peleg-Raibstein et al., 2009). In male Sprague-Dawley rats, repeated injections of high doses of AMPH (4 injections of 5 mg/kg) had no effect on NOR, but subchronic treatment with methAMPH (4–7 injections of 1–4 mg/kg) abolished NOR (Belcher et al., 2005; Kamei et al., 2006; also see Belcher et al., 2008). Withdrawal from chronic AMPH resulted in NOR disruption (Bisagno et al., 2003). NMDA antagonists such as ketamine, MK-801 and PCP (the latter administered using acute or subchronic regimen) impair NOR at a variety of doses (e.g. Boulidakis and Pitsikas, 2010; Karasawa et al., 2008; McLean et al., 2010a; Pichat et al., 2007; Roncarati et al., 2009). Finally, NOR is impaired by mAChR blockade, typically using SCOP (0.5–2 mg/kg), at short delays (1–60 min) but the drug is less effective in disrupting NOR with longer intervals between the familiarization and test stages (Ennaceur and Meliani, 1992; Roncarati et al., 2009; Woolley et al., 2003; but see Vannucchi et al., 1997).

3.4.2. Effects of PCEs
3.4.2.1. Naïve animals. Alpha7 nAChR agonists improved NOR in rats and mice when tested with long interval (Boess et al., 2007; Hauser et al., 2009; Haydar et al., 2009; Pichat et al., 2007; Roncarati et al., 2009; Wishka et al., 2006). Conversely, the AChE inhibitor physostigmine was without an effect at lower doses and impaired NOR at a high (0.2 mg/kg) dose (Ennaceur and Meliani, 1992). The mGluR5 positive allosteric modulator CDPPB enhanced NOR, with lower dose (10 mg/kg) being more efficient than higher dose (30 mg/kg), although the latter was more effective in reversing MK-801-induced deficits (Uslaner et al., 2009). However, other mGluR5 positive modulators did not affect NOR (Chan et al., 2008). Other mGlu5 positive allosteric modulators improved NOR dose dependently (Liu et al., 2008), or had no effects (Chan et al., 2008), possibly due to a ceiling effect. The AMPA agonists CX691 and 5 18986-1 improved NOR with a long delay following both acute and subchronic administration (Lebrun et al., 2000; Woolley et al., 2009). The DA D1 agonist SKF81297 impaired performance with a short (15 min) delay, but improved NOR with an intermediate 4 h delay, by decreasing exploration of the familiar object, rather than increasing exploration of the novel object (Hotte et al., 2005). 5-HT6 antagonists improved NOR with a long delay (King et al., 2004) and reversed age-related NOR deficits (Mitchell and Neumaier, 2005). Finally, the M1 mAChR agonist EUK1001 improved NOR in aged mice with a short (1 h) or long (24 h) delay (Cui et al., 2008).

3.4.2.2. Pharmacological impairments. NMDA antagonist-induced impairment in NOR (with short intervals) were reversed by subchronic administration of the AChE inhibitor donepezil (1 mg/kg/day) (Kunitachi et al., 2009b), as well as by acute or chronic administration of alpha7 nAChR agonists in mice and rats (Hashimoto et al., 2008b; Haydar et al., 2009; McLean et al., 2010a; Pichat et al., 2007; Roncarati et al., 2009). Likewise, N-desmethyl-clozapine, which possesses M1 mAChR agonism, reversed the effects of PCP (Snigdha et al., 2010). NMDA function enhancers like D-serine and glyT1 inhibitors (Karasawa et al., 2008) or mGluR5 positive allosteric modulators (Chan et al., 2008; Uslaner et al., 2009) were also shown to reverse the effects of MK-801 or ketamine on NOR. A D1 agonist and the amapakines CX546 and CX516 reversed NOR impairments induced by prior subchronic PCP treatment (Damgaard et al., 2010; McLean et al., 2009). Chronic PCP-induced NOR impairment with a long retention interval (24 h), was reversed in mice by NMDA function enhancers such as D-serine and glyT1 inhibitors (Hashimoto et al., 2008a), alpha7 nAChR agonists (Hashimoto et al., 2008b) or subchronic treatment with the AChE inhibitor donepezil, but not physostigmine (Kunitachi et al., 2009a). Finally, scopolamine-induced impairments in NOR were reversed by AChE inhibitors (Rispoli et al., 2004), the alpha7 nAChR agonists SEN12333 and compound 24 (Haydar et al., 2009; O’Donnell et al., 2010), and 5-HT6 receptor antagonists (Hirst et al., 2006; Lieben et al., 2005; Woolley et al., 2003).

3.4.3. Effects of APDs
On their own, APDs either impair NOR performance or have no effect. For example, chronic oral treatment with olanzapine (0.5 mg/kg/day, i.p.), risperidone (2.5 mg/kg/day, p.o.) or haloperidol (2 mg/kg/day, p.o.) (Orselli et al., 2007; Terry et al., 2007), or acute haloperidol (0.05–0.25 mg/kg, i.p.) (Abdul-Monim et al., 2003) impaired NOR. In contrast, chronic haloperidol (0.2 mg/kg/day, i.p.) (Orselli et al., 2007) or subchronic haloperidol (1 mg/kg/day, p.o.) or clozapine (3 mg/kg/day, p.o.) (Kamei et al., 2006) had no effect. Subchronic or acute i.p. treatment with atypical APDs such as clozapine (1–5 mg/kg), olanzapine (2 mg/kg) and risperidone (0.1–0.2 mg/kg) improved NOR impairments induced by chronic PCP or acute MK-801 treatment in mice or rats. In contrast, the typical APDs haloperidol (0.03–0.1 mg/kg) or chlorpromazine (2 mg/kg), failed to reverse the NMDA antagonist-induced impairment (Abdul-Monim et al., 2003, 2006; Grayson et al., 2007; Hashimoto et al., 2005; Karasawa et al., 2008; Snigdha et al., 2010). Finally, subchronic clozapine (3 mg/kg/day p.o.), but not haloperidol (1 mg/kg/day, p.o.), reduced methAMPH-induced NOR deficits (Kamei et al., 2006).
3.4.4. Summary

NOR is the most widely characterized task surveyed in this review, and the majority of the PCEs were tested in this task in normal as well as perturbed animals. APDs impair NOR or have no effects in naïve rodents, whereas atypical, but not typical APDs are active in the NMDA antagonist NOR model. Cholinergic agonists are generally beneficial in the SCOP and NMDA antagonist NOR model, and nicotinic and muscarinic agonists also improve NOR. However, AChE inhibitors impair or do not affect task performance. Glutamatergic agonists and 5-HT6 antagonists improve NOR in naïve animals, and reverse the effects of NMDA and mAChR antagonists, respectively. Thus, virtually all the PCEs tested in this task exhibit a similar profile of efficacy in normal and perturbed animals.

4. Executive function

4.1. Discrimination reversal

Discrimination reversal involves adaptation of behavior according to changes in stimulus-reinforcement contingencies. In reversal, animals are first trained to discriminate between two stimuli or positions, by being reinforced for responding to one stimulus (S+) or position but not the other (S−). Once the animal reached criterion performance, the contingencies are reversed so that the animal is reinforced for responding to previously non-reinforced stimulus/position.

4.1.1. Effects of SCZ-mimetic drugs

Studies on the effects of AMPH on discrimination reversal yielded mixed results. Thus, AMPH (1 mg/kg) or methylAMPH were shown to facilitate (in Y maze; (Calhoun and Jones, 1974; Kulig and Calhoun, 1972; Weiner et al., 1986a,b; Weiner and Feldon, 1986), spare (in Skinner box lever press discrimination task (0.16, 0.7 mg/kg; Fundaro et al., 1983) or impair (Skinner box, female rats (0.5 mg/kg; Idris et al., 2009; Idris et al., 2005) and male rats (0.75 mg/kg; McLean et al., 2010b) reversal performance. In addition, following withdrawal from repeated administration of AMPH, reversal in mice in Morris water maze was improved (Russig et al., 2003). Systemically administered SCOP was shown to disrupt discrimination reversal (Chen et al., 2004; Wongwitdecha and Marsden, 1996), and so did intra-striatal administration of the drug, but only at high doses (Ragozzino et al., 2002). Finally, NMDA antagonists also retard discrimination reversal. Thus, both acute and subchronic PCP administration impair discrimination reversal in various procedures (Abdul-Monim et al., 2003, 2006; Didriksen et al., 2007; Idris et al., 2010, 2005; McLean et al., 2010b), and so does acute MK-801 (Csernansky et al., 2005).

4.1.2. Effects of PCEs

4.1.2.1. Naïve animals. M1 agonists were without an effect in mice (Fisher et al., 2003; Shirey et al., 2009), presumably due to a floor effect. In contrast, AChE inhibitors such as donepezil and physostigmine, but not galantamine, improved discrimination reversal in rats (Chen et al., 2009). The NMDA function enhancer n-serine (600 mg/kg) improved discrimination reversal in mice in Morris water maze (Duffy et al., 2008) whereas DCS had no effect in aged rats (Riekikinen et al., 1997). The norepinephrine transporter inhibitor atomoxetine improved discrimination reversal in rats (Seu et al., 2009). Subchronic administration the ampakine CX691 improved discrimination reversal measured in ASST (Woolley et al., 2009). Finally, the D1 agonist SKF81297 was shown to impair discrimination reversal in mice at the early stages (Izquierdo et al., 2006).

4.2. Pharmacological impairments. The AChE inhibitors donepezil and physostigmine, but not galantamine, reversed MK-801-induced deficits (Csernansky et al., 2005). Similarly, the alpha7 nAChR agonist PNU-282987 reversed impairments induced by subchronic PCP administration (McLean et al., 2010a). Chronic n-serine treatment reversed PCP-induced deficits in Morris water maze-based reversal learning (Andersen and Pouzet, 2004). Likewise, acute treatment with the D1 agonist SKF81297 reversed subchronic PCP-induced operant discrimination reversal deficits (McLean et al., 2009).

4.1.3. Effects of APDs

In Skinner-box reversal, the typical APD haloperidol (0.1–0.25 mg/kg) impaired discrimination reversal as well as initial discrimination (at 0.25 mg/kg), while the atypical APDs ziprasidone (0.25–2.5 mg/kg) had no effect on both in naïve rats (Abdul-Monim et al., 2003). In contrast, impaired reversal following acute or subchronic PCP administration, haloperidol (0.05 mg/kg) had no effect (Abdul-Monim et al., 2003; Didriksen et al., 2007; Idris et al., 2005), whereas a range of atypical APDs including sertindole (2.5 mg/kg), ziprasidone (2.5 mg/kg), clozapine (5 mg/kg), and olanzapine (1.5 mg/kg) reversed PCP-induced impairments (Abdul-Monim et al., 2003, 2006; Didriksen et al., 2007; Idris et al., 2010, 2005; McLean et al., 2010b). Notably, atypical APDs showed better efficacy at low, compared to high doses. In contrast, AMPH-induced deficits in reversal were reversed by haloperidol (0.05 mg/kg) and risperidone (0.2 mg/kg), but not clozapine (5 mg/kg) (Idris et al., 2005; McLean et al., 2010b).

4.1.4. Summary

Although the effects of AMPH on discrimination reversal are controversial, it is clear that both SCOP and NMDA antagonists impair reversal learning. While typical, but not atypical APDs impair discrimination reversal on their own, atypical, but not typical APDs reverse the effects of NMDA antagonists. Several PCEs were reported to improve discrimination reversal when given on their own. NMDA antagonist-induced impairments in discrimination reversal are reversed by cholinergic agonists, NMDA enhancers and a D1 agonist (although the latter impairs performance on its own), but overall the reports are numbered.

4.2. Attentional set shifting task (ASST)

The rodent ASST involves a series of increasingly complex discriminations, that use dimensions of odor (e.g. lemon vs. nutmeg), digging medium (e.g. sand vs. beads), and bowl texture (e.g. smooth vs. rough) presented in one test session. Rats are consecutively trained on a simple discrimination (SD), compound discrimination (CD; two stimulus dimensions, with only one relevant dimension consistent with SD), CD reversal (CDR; previously irrelevant stimuli within the same dimension are now relevant), intra-dimensional (ID) shift (a novel stimulus within the same dimension now relevant), ID reversal (IDR; the novel stimulus within the same dimension is now relevant), extra-dimensional (ED) shift (EDS; stimulus in a novel, previously irrelevant dimension is now relevant), and ED reversal (EDR; the previously irrelevant stimulus within the novel dimension is relevant). Rodents are said to have formed an attentional set if the number of trials taken for the ED shifting is higher than that taken for the ID shifting (Birrell and Brown, 2000).

4.2.1. Effects of SCZ-mimetic drugs

ASST has been shown to be impaired by NMDA antagonists administered with a variety of administration regimens. Thus, EDS was selectively impaired by acute (Darrah et al., 2008; Egerton et al., 2005) and subchronic (Broberg et al., 2009; Laurent and Podhora, 2004; McLean et al., 2008) PCP treatments, or when this drug was administered with a variety of administration regimens. Thus, EDS and ED shifting is higher than that taken for the ID shifting (Birrell and Brown, 2000).
become relevant. Depending on the status of LI in control animals: disrupted LI under conditions producing LI in controls, and persistent LI under conditions preventing the expression of LI in controls.

mGlu5 (Darrah et al., 2008; Stefani and Moghaddam, 2010), by the DA or ketamine were also reversed by a positive allosteric modulator of mGlu5 (Darrah et al., 2008; Stefani and Moghaddam, 2010). Finally, intra-prefrontal cortex infusion of the D1 agonist CX691 improved ASST following subchronic administration (Woolley et al., 2009). The 5-HT6 antagonist SB-271046 (Rodefer et al., 2008). Acute administration of the atypical APD sertindole (1.25 mg/kg) were ineffective in reversing subchronic PCP-induced de ASST (Fletcher et al., 2005; Haluk and Floresco, 2009). The ampakine CX691 improved ASST following subchronic administration (Woolley et al., 2009). The 5-HT6 antagonist SB-271046 improved both ID and EDS performance (Hatcher et al., 2005). Finally, a positive allosteric modulator of mGlu5 did not affect EDS in naïve animals (Darrah et al., 2008; Stefani and Moghaddam, 2010).

4.2.2. Pharmacological impairments. Impaired ID/ED shift induced by PCP treatment, either subchronic or early postnatal, was reversed by the ampakine CX516, with a U-shape dose response curve (Broberg et al., 2009), as well as by the alpha7 nAChR partial agonist RG3487 (Wallace et al., 2010). The effects of NMDA blockade by acute MK-801 or ketamine were also reversed by a positive allosteric modulator of mGlu5 (Darrah et al., 2008; Stefani and Moghaddam, 2010), by the DA and norepinephrine reuptake inhibitor mazindol (Nikiforuk et al., 2010) and by the 5-HT6 receptor antagonist SB 271046 (Rodefer et al., 2008). Finally, intra-prefrontal cortex infusion of the D1 agonist reversed impairments in EDS induced by sensitization to AMPH (Fletcher et al., 2005).

4.2.3. Effects of APDs

The effects of atypical APDs on ASST are somewhat confusing. Subchronic PCP-induced impaired EDS was reversed by subchronic clozapine (2.5 mg/kg) or risperidone (0.2 mg/kg) (McLean et al., 2008), but not by subchronic or acute haloperidol (0.05 mg/kg) (Goethebeur and Dias, 2009; McLean et al., 2008). In contrast, in another study, acute risperidone (0.1–0.3 mg/kg), clozapine (0.1–5 mg/kg), and olanzapine (1.5–3 mg/kg), as well as haloperidol (0.01–0.1 mg/kg) were ineffective in reversing subchronic PCP-induced deficits (Rodefer et al., 2008). Acute administration of the atypical APD sertindole (1.25–2.5 mg/kg) was effective in reversing ASST impairment induced by subchronic PCP (Broberg et al., 2009; Rodefer et al., 2008), or acute ketamine (Nikiforuk et al., 2010).

4.2.4. Summary

While it is well established that NMDA antagonists selectively impair ED in ASST, only a handful of studies tested the effects of AMPH and SCOP on this task. Interestingly, although Fletcher’s group showed that sensitization to AMPH impaired ASST, in a subsequent study the same group used both ASST and a maze-based strategy shifting task, as well as other memory-related tasks (Featherstone et al., 2008), in which repeated AMPH only impaired the EDS of the ASST. Thus, although sensitization to AMPH impairs ASST, it does not affect other schizophrenia-related tasks requiring set shifting. Although findings from studies testing the effects of APDs on subchronic PCP ASST disruption are inconclusive, atypical APDs do seem to exhibit better efficacy than typical APDs. Unfortunately, these studies did not test the effects of APDs on naïve animals, so a comparison between APDs and PCEs on naïve animals cannot be made. Although few of the PCEs surveyed here were tested on this task, there is some evidence that glutamatergic agonists are active in the NMDA antagonist model although only the former was active in naïve animals. Activity in both normal and perturbed animals was shown for serotonergic and adrenergic agents.

5. Latent inhibition (LI)

In LI, animals in the “stimulus pre-exposed” (PE) group are repeatedly exposed to a stimulus (e.g., tone) which is not followed by a significant consequence, whereas those in the “non-pre-exposed” (NPE) group are exposed to the apparatus alone. Both groups then undergo conditioning in which the pre-exposed stimulus is paired with a reinforcer. LI is manifested in poorer performance of the PE compared to the NPE group. In terms of cognitive processes underlying LI manifestation, the reduced attentional response (or reduced associability/salience) to the stimulus resulting from its non-reinforced pre-exposure, interferes with the subsequent formation and/or expression of the conditioned response to the pre-exposed stimulus (Hall, 1991; Lubow et al., 1981; Lubow and Weiner, 2010; Weiner, 2003). Such interference is temporary, so as conditioning proceeds, the organism switches to respond according to the new stimulus-reinforcement contingency, and ceases to express LI.

5.1. Effects of SCZ-mimetic drugs: disrupted and persistent LI

The pharmacology of LI from its very inception has focused on both the disruption and the induction of the phenomenon. The latter effect, termed interchangeably LI potentiation, enhancement or persistence, is indexed by comparison to the absence of LI in drug non-treated controls. Thus, psychoactive drugs can produce disrupted LI under conditions which yield LI in normal rats, or abnormally persistent LI under conditions which do not yield LI in normal rats (Fig. 1).

![Fig. 1. Disruption and induction of LI](image-url)
Disrupted and persistent LI reflect two poles of dysfunctional attentional selectivity, namely, a failure to inhibit/withhold attention to irrelevant stimuli and a failure to re-deploy attention when previously irrelevant stimuli become relevant, or attentional over-switching and attentional perseveration, respectively. Both disruption and persistence of LI can stem from drug action in the pre-exposure stage or in the conditioning stage (Weiner, 2003; Weiner and Arad, 2009). In addition to un unraveling the psychological mechanism by which a given drug affects LI, stage-specific action allows a refined discrimination between the effects of different drugs on LI.

5.2. Effects of SCZ-mimetic drugs

Amphetamine at low doses (typically 1 mg/kg) disrupts LI (Joseph et al., 2000; Killcross et al., 1994; Killcross and Robbins, 1993; Solomon et al., 1981; Weiner et al., 1984, 1981, 1988). This action is exerted in conditioning, indicating that increased DA transmission weakens the inhibiting effect of reduced stimulus salience on behavior (Weiner, 2003). LI is disrupted also after, as well as during withdrawal from, repeated AMPH administration (Murphy et al., 2001; Russig et al., 2002; Solomon et al., 1981; Tenn et al., 2005a,b). Unlike AMPH, low doses of non-competitive NMDA antagonists, including PCP, ketamine, and MK-801, spare LI (Aguado et al., 1994; Robinson et al., 1993; Tenn et al., 2005b; Turgeon et al., 2000; Turgeon et al., 1998; Weiner and Feldon, 1992). Furthermore, low doses of MK801 that do not disrupt associative learning (0.05 mg/kg in rats, 0.15–1 mg/kg in mice) induce persistent LI (Barak et al., 2009, 2008; Gaisler-Salomon et al., 2008; Gaisler-Salomon and Weiner, 2003; Lipina et al., 2005).Higher doses that impair conditioning disrupt LI (Gaisler-Salomon and Weiner, 2003; Lewis and Gould, 2004). NMDA antagonists produce LI persistence via conditioning (Gaisler-Salomon and Weiner, 2003; Palsson et al., 2005), indicating that they impair rats’ capacity to switch responding based upon changed relationships between stimuli and outcomes, consistent with the demonstrations of inflexible behavior following NMDA blockade in other selective attention tasks such as discrimination reversal and ED shift surveyed above. SCOP can produce both LI disruption and persistence as a function of dose (Barak, 2009; Barak and Weiner, 2010, 2007, 2009). Low doses of SCOP (0.15, 0.5 mg/kg) disrupt LI (Barak and Weiner, 2007), supporting the pro-psychotic quality of this agent (Barak, 2009; Yeomans, 1995). The mechanisms underlying this psychotic-like state differ however from those of AMPH because SCOP disrupts LI via effects at the pre-exposure stage (Barak and Weiner, 2007). Higher doses of SCOP (1, 1.5 mg/kg) spare LI under conditions yielding LI in controls, and induce persistent LI (Barak and Weiner, 2007, 2009). The latter action is exerted in conditioning (Barak and Weiner, 2009). Thus, SCOP at low doses prevents the development of inattention and at high doses produces attentional perseveration (For review, see Barak, 2009).

5.3. Effects of PCEs

5.3.1. Naïve animals

LI is potentiated by the NMDA function enhancers (glycine (0.8 g/kg) [Barak and Weiner, 2010], d-serine (600 mg/kg), glycine1 inhibitors ALX5407 (1 mg/kg) [Lipina et al., 2005], SSR103800 (1 and 3 mg/kg) and SSR504734 (1 and 10 mg/kg) [Black et al., 2008]), as well as by cholinomimetic drugs (nicotine (0.125–0.5 mg/kg; Gould et al., 2001), the alpha7 nAChR agonist SSR170811 (0.3, 1, 3 mg/kg) [Barak et al., 2009] and the M1/M4 preferring mAChR agonist xanomeline (5 and 15 mg/kg) [Barak and Weiner, in press] but not by phystostigmine (0.05, 0.15 mg/kg) [Barak and Weiner, 2006, 2007]).

5.3.2. Pharmacological impairments

AMPH- and low SCOP-induced disrupted LI, although reflecting distinct psychological processes, are reversed by NMDA function enhancers (Black et al., 2008), SCOP- but not AMPH-induced LI disruption is reversed by phystostigmine (Barak and Weiner, 2007). MK801-induced persistent LI is reversed by a wide range of compounds that potentiate NMDA transmission including glycine (0.8 g/kg), DCS (15 mg/kg and 30 mg/kg) d-serine (600 mg/kg), and the GlyT1 inhibitors GDA (0.05 g/kg and 0.1 g/kg), ALX5407 (1 mg/kg), as well as SSR103800 (1 and 3 mg/kg) and SSR504734 (3 and 10 mg/kg) (Black et al., 2008; Gaisler-Salomon et al., 2008). Likewise, ketamine-induced persistent LI is reversed by SSR103800 and glycine (unpublished observations). Importantly, MK801 is the only model that discriminates between atypical APDs and glycine enhancers (Black et al., 2008).}

5.4. Effects of APDs

APDs are long known to produce persistent LI under conditions of weak or absent LI in controls (Weiner and Arad, 2009). This effect, better known as LI facilitation or enhancement, is produced by a wide range of typical and atypical APDs differing in their in vivo pharmacology, and is the most widely used index of antipsychotic action in LI (Felden and Weiner, 1987, 1991; Killcross et al., 1994; Moran et al., 1996; Peters and Joseph, 1993b; Shadach et al., 1999b; Trimble et al., 1998; Weiner and Feldon, 1987; Weiner et al., 1996). The LI potentiation action of APDs is exerted at the conditioning stage, and is mediated by DA D2 receptor blockade (Peters and Joseph, 1993a; Shadach et al., 1999a, 2000; Weiner et al., 1997). Although APD-induced LI potentiation is very robust, it does not discriminate between typical and atypical APDs. Such discrimination is manifested under conditions that produce LI in controls. Whereas typical APDs do not affect LI, atypical APDs can, depending on dose and stage of administration, either spare or disrupt LI (Shadach et al., 2000). Shadach et al. (2000) showed, using different doses of risperidone (0.25, 0.5, 1.2 and 2.5 mg/kg) that the LI disruptive action is exerted in pre-exposure and mediated by 5HT2A antagonism, which competes with conditioning-based LI potentiation action, mediated by D2 antagonism. While the capacity of atypical APDs to disrupt LI is at first sight incongruent with a therapeutic action, such a capacity is “therapeutic” for abnormally persistent LI, because in the latter case, LI needs to be disrupted in order to obtain normal performance.

Both typical (e.g., 0.1 mg/kg haloperidol) and atypical (e.g., 10 mg/kg clozapine, 0.312 mg/kg olanzapine) APDs reverse AMHP– (Gosselin et al., 1996; Solomon et al., 1981; Warburton et al., 1994; Weiner et al., 1996) as well as low SCOP-induced (Barak and Weiner, 2007) disrupted LI. In both cases, APDs act via the conditioning stage, the stage via which they potentiate LI in naïve animals (Barak and Weiner, 2007; Weiner and Arad, 2009). Atypical APDs (e.g., clozapine, 3 mg/kg, 5 mg/kg rats) and risperidone (0.25 and 0.067 mg/kg) but not haloperidol (0.1 mg/kg) reverse MK801-induced persistent LI (Gaisler-Salomon and Weiner, 2003; Lipina et al., 2005). As expected, atypical APDs exert this alleviating action via the pre-exposure stage, the stage at which they disrupt LI in naïve animals (Gaisler-Salomon and Weiner, 2003). Neither haloperidol (0.1–0.2 mg/kg) nor clozapine (5–10 mg/kg) reversed high SCOP-induced persistent LI (Barak and Weiner, 2009). While the inefficacy of haloperidol is expected based on its ineffectiveness in models of negative/cognitive
symptoms including MK801-induced persistent LI, the inefficacy of clozapine sets this abnormality apart from MK801-induced as well as all other known instances of drug-induced LI persistence. Finally, haloperidol-induced persistent LI is alleviated by the atypical APDs clozapine (5 mg/kg) and risperidone (0.5 but not 0.25 mg/kg) (unpublished observation). The effects of APDs and PCEs are summarized in Table 2.

6. Discussion

6.1. A very brief summary

The data surveyed above show that NMDA antagonism is by far the leading pharmacological inducing factor used to model cognitive deficits in SCZ. As such, the NMDA antagonist-based models are the major and often the only source of information on PCE and APD actions on the different cognitive tasks surveyed here. Overall, typical APDs usually fail to reverse the effects of NMDA antagonists (with some exceptions, e.g., in DAT), whereas both atypical APDs and most PCEs reverse virtually every tested NMDA antagonist-induced impairment. The exception is mGluR agonists, which are not uniformly effective in reversing PCP-induced deficits in DAT and exacerbate PCP effects on 5CSRT. There are no data on the effects of atypical APDs on NMDA-induced deficits in D(N)MTS or DAT. There is also a conspicuous paucity of tests of NMDA enhancers.

Effects of APDs have not been tested on SCOP-induced impairments except for LI and RAM. Studies testing PCEs in the SCOP models have been focused on the WM domain, where SCOP has conventionally been used as an amnestic. Of particular interest are the delay-dependent SCOP-induced deficits in D(N)MTS. These deficits are reversed by M1 mAChR agonists, AChE inhibitors, NMDA enhancers and GABAa inverse agonists; other PCEs were not tested. In addition, SCOP-induced impairments in NOR are reversed by nAChR agonists, AChE inhibitors, and 5-HT6 antagonists.

The least characterized is the AMPH model. Both typical and atypical APDs reverse the effects of AMPH on SAT and LI but not always on discrimination reversal, and atypical but not typical APDs reverse methAMPH effects on NOR. No PCEs were tested in this model, but AMPH sensitization-induced impairments in 5CSRT and ASST were reversed by intra-mPFC infusion of a D1 agonist.

6.2. Decomposing schizophrenia and construct validity

MATRICS and CNTRICS not only focused the spotlight on the cognitive deficit in SCZ but also empowered the approach of decomposing the construct of “cognitive deficit” in SCZ into well-defined separate domains of cognition. The “decomposing” approach is deeply entrenched in the tradition of cognitive neuroscience whose major goal is to unravel brain substrates mediating behavior and cognition. Extensive work using selective brain lesions and intracerebral injections has demonstrated numerous dissociations among the neural substrates of the tasks surveyed here (Belsky et al., 1998; Birkett and Brown, 2000; Bissonette et al., 2008; Carli et al., 1983; Chudasama and Robbins, 2004, 2006; Cole and Robbins, 1989; Floresco et al., 2009; Harrison et al., 1997; Kehagia et al., 2010; McGaughy et al., 2002; Robbins, 2002; Robbins and Arnsten, 2009; Tait and Brown, 2008; Weiner, 2003). Indeed, the known neuroanatomical and neurochemical dissociations between the different tasks have played a major role in lending them construct validity for modeling cognitive deficits in SCZ (Barch et al., 2009a,b; Barch and Carter, 2008; Carter et al., 2008, 2009; Nuechterlein et al., 2009; Ragland et al., 2009).

In the realm of drug discovery and pharmacotherapy of SCZ, the motivation for “decomposing” SCZ cognitive deficit derives from the notion that “psychiatric treatments influence neurobiological substrates that are specific to separate domains of cognition simply because these different domains have distinctive anatomical and neurochemical substrates” (Nuechterlein et al., 2005). By extension, decomposing cognition in animal models is motivated by the expectation that the different domains (identified in both patients and animals), would allow the development/identification of domain-specific treatments. Such specificity is not seen in the data.

Notably, each of the tasks surveyed has in-built aspects/features that make drug effects quite specific to the presumed construct measured. In 5CSRT and SAT this is achieved by measuring several different responses during task performance. NOR and working memory tasks distinguish between drug effects on learning and memory by means of delay, in reversal comparison with initial discrimination provides a distinction between learning and responding in face of changed contingencies, just as conditioning in the non-pre-exposed group serves this function for LI, and in ASST drug effects are specific to the ES component of the task, not affecting learning as well as simpler forms of attentional shifting (i.e., reversal). Irrespective of the above, there is very little differentiation in drug effects across the tasks, both of the SCZ-mimetics and the pre-cognitive compounds.

Performance of all the cognitive tasks surveyed is disrupted by NMDA antagonists, SCOP and AMPH, although the latter yields some inconsistencies probably as a function of administration regime and dose. A mirror lack of differentiation is seen with PCEs and APDs, although it is important to stress that this conclusion is based almost exclusively on the NMDA models. First, there is no evidence that distinct cognitive domains as presumably represented by the different tasks, respond differentially to either PCEs or APDs. Second, there is a conspicuous paucity of tests of NMDA enhancers.

Table 2

Summary of putative cognitive enhancers and representative antipsychotic drugs tested against models of disrupted and persistent LI. + effective; − ineffective; ? unknown; [COND] acts via conditioning stage; [PREEX] acts via pre-exposure stage; * LI in naïve animals; ** the active compound is Glyt1 inhibitor SSR103800.
NMDA antagonist-induced impairments, both within each of the tasks and across the different tasks. The limited available data indicate that also in the SCOP-models, PCEs do not distinguish among the different tasks. As well, where comparison is possible, their action on SCOP-induced deficits is similar to those on NMDA antagonist-induced deficits. The only exception is LI where these drug classes differ in their effects on MK801- and SCOP-induced persistent LI.

What then are the implications of the above findings for construct validity of the different tasks used in pharmacological models? One possibility is that the different tasks measure the same or overlapping cognitive constructs. Indeed, Nuechterlein et al. (2009) acknowledge this problem as it is reflected in CNTRICS choices: “Given the conceptual overlap between attention, working memory and executive control systems in the basic cognitive and cognitive neuroscience literature, a decision was made to emphasize input selection processes under the heading of attention. Some concepts and tasks that might otherwise have been viewed as reflecting attention can be found in the articles in this issue concerning working memory and executive control processes” (see also Barch et al., 2009a, 2009b; Luck and Gold, 2008). However, as noted above, in spite of such overlap, these tasks are amenable to dissociation by lesions, as well as by their response to APDs vs. PCEs in normal animals, suggesting that a different mechanism is responsible for the lack of differentiation with pharmacological manipulations. The most likely explanation is that neurotransmitter perturbations induced by systemic drug administration target many of the independent but interacting neural systems that mediate the cognitive functions assessed by the different tasks, and thus affect performance in most of the tasks, whether or not they involve distinct constructs. This is an inherent disadvantage of disrupting cognitive function by peripherally-administered drugs, as such a disruption typically results in a highly heterogeneous pattern of deficits. The same applies to systemic administration of PCEs and APDs, since both classes of drugs have wide-spread and diverse actions on the brain (Black et al., 2008; Hasselmo and Sarter, 2010; Lieberman et al., 2008).

It should be noted that a wide, non-specific effect of NMDA receptor antagonists is observed also in human volunteers, where such compounds produce positive, negative and cognitive symptoms of SCZ, and within cognitive symptoms, deficits in WM, sustained attentional and executive function (Corlett et al., 2011; e.g., Honey et al., 2005a,b, 2006; Krystal et al., 2003, 1994; Malhotra et al., 1996; Morgan et al., 2004; Newcomer et al., 1999). Interestingly, in a recent review, Corlett et al. (2011) have elaborated how one central cognitive concept taken from formal learning theories, prediction error, can explain all of the above effects of NMDA receptor blockade. A similar approach, based on another basic cognitive concept taken from learning theory, salience, has been suggested to explain all the SCZ-relevant effects of dopaminergic overstimulation (Kapur, 2003). Possibly, interference with any one of the major neurotransmitters activates what we may call “meta-cognitive constructs” such as prediction error, salience, or cognitive inflexibility, that underlie organisms’ competence/incompetence across a wide span of cognitive tasks. Thus, we may be able to decompose “cognition” (different tasks for each construct) but not “cognitive deficit” (different response of these tasks to SCZ-mimetics and PCEs), if the cognitive deficit is induced by systemic drugs, although it remains to be determined if task-selective treatments are found with other SCZ-mimetics. While this may be disappointing, systemic drug administration has also an advantage as it corresponds more readily to effects seen in humans, both as SCZ-symptom inducing and exacerbating manipulation, and therapeutically, when assessing cognitive enhancing treatments in patients. Furthermore, since SCZ does not involve circumscribed damage to specific brain regions but wide-spread structural and neurotransmitter abnormalities, systemic neurotransmitter perturbations may better approximate SCZ neuropathology than restricted brain lesions. Irrespective of the latter, it would be highly desirable to investigate whether APDs and PCEs would produce different results with lesions that dissociate among the various cognitive constructs. If yes, lesion-based preparations could be used as assays for identifying compounds with construct-specific efficacy. Importantly, given that SCZ does not involve circumscribed lesions to specific regions, these preparations would constitute models with strong construct validity for the dependent measure arm but not for the inducing manipulation arm.

6.3. Are APDs CEs?

The lack of cognitive benefit of APDs in SCZ patients has been a main reason for turning to alternative agents and mechanisms for the treatment of cognitive impairments (Buchanan et al., 2007a). This lack of cognitive benefit has also accounted for the problem of predictive validity faced by the existing animal models of cognition, or the lamented “crisis of validation” (Markou et al., 2009). Accordingly, in their broad review of the existing animal models Young et al. (2009) wrote “Because antipsychotics have largely failed in ameliorating cognitive symptoms of SCZ, roden tasks of cognition that are sensitive to existing antipsychotics will be limited by this potentially “false positive” result.”

In spite of such strong notions, APDs remain the mainstay of efforts to discover and develop treatments for cognitive symptoms of SCZ and in fact are restored to the status of “benchmark” albeit a weak one. A recent review (Neill et al., 2010) concludes that NMDA antagonist-induced cognitive disturbances of relevance to SCZ in rodents and their subsequent reversal by first- and second-generation APDs “support the use of NMDA receptor antagonists to model cognitive deficit ... of SCZ ... This will facilitate the evaluation of much-needed novel therapies for improved therapy of cognitive deficits”. In a similar vein, Amitai and Markou (2010a) write: “Administration of ... NMDA ...antagonists disrupts multiple 5CSR performance measures in a way that mirrors various cognitive deficits exhibited by SCZ patients. Some of these disruptions are partially attenuated by antipsychotic medications that exhibit partial effectiveness on cognitive dysfunction in SCZ, suggesting that the model has predictive validity”. The fluctuations in the pre-clinical field parallel those of the clinical studies which have fluctuated between attributing superior pro-cognitive effects to atypical compared to typical APDs, lack of effects for both, and small effect irrespective of the APD class (see references in the Introduction). Given that overall, the clinical field is inclined towards accepting the notion that APDs produce small improvements in cognition (see e.g., the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)), the animal modeling field may indeed be content with APDs providing a “weak gold standard”. Certainly the data from the NMDA models surveyed here demonstrate that at least atypical APDs have cognition enhancing capacity that may parallel their limited cognition enhancing capacity in the clinic.

Importantly, such limitation may be inherent to APD pharmacology. Since DA blockade is deleterious for cognition, as it impairs behavioral/cognitive flexibility and learning (Weiner and Joel, 2002), any APD-induced cognitive enhancement must be due to other effects of these drugs. If non-DA mechanism/s and D2 antagonisms compete like we showed for 5HT2A and DA antagonism in LI, then it is possible that atypical APDs act like CEs but within a narrow window, becoming cognitive disruptors as their DA antagonism becomes their predominant action. The latter could also explain why APDs fail as CEs in naïve animals- possibly, healthy brains are much more sensitive to their DA blocking effects than perturbed brains. The competition between DA and non-DA mechanisms also implies that there is a conflict between anti-psychotic and pro-cognitive effects of APDs. Testing these options would provide important information on the span of cognitive enhancing capacity of APDs and its limitations under specific conditions. Of course, since the “weak gold standard” of APDs for...
cognitive enhancement is based on their action in NMDA antagonist-challenged animals, additional research is needed to characterize the cognition enhancing action of APDs beyond NMDA antagonist-induced impairments. Finally, it should be noted that if APDs are used as a “weak benchmark”, then we presumably require PCEs to be more effective than APDs. For this, we need to refine our behavioral tasks so that they can detect different levels of cognitive enhancement in perturbed animals, which may be difficult.

6.4. Beyond APDs and towards APD-PCE differentiation

APDs may have limited beneficial effect on cognitive function in SCZ patients, which is apparently manifested in their ability to reverse NMDA antagonist-induced cognitive impairments in animals. However, SCZ patients show APD-resistant cognitive impairments and it is this aspect of the disorder for which we seek new treatments. Consequently, we need to search for models that can differentiate between the actions of these two classes of drugs. Below we point out to some directions based on the above survey.

6.4.1. Normal vs perturbed animals

A salient difference between the effects of APDs and those of PCEs emerging from the survey (see Table 1) lies in their effects on naïve animals. Thus, both typical and atypical APDs either impair or have no effect on naïve animals in the different tasks, whereas most PCEs enhance performance in many tasks, and rarely impair performance. This difference begs the question of whether we can use this salient feature for dissociating between the effects of APDs and PCEs so that PCEs should be required to exhibit effectiveness in non-perturbed as well as perturbed animals (Floresco et al., 2005; Hagan and Jones, 2005). Intuitively at least, PCEs should enhance, and definitely not impair, performance under taxing conditions in normal animals. Furthermore, many cognitive enhancers have been characterized as such based on their effects in naïve animals (Levin et al., 2006). However, the relationship between cognitive enhancement in normal and perturbed animals is not clear. Does a normal brain struggling with solving a difficult task recruit the same brain circuits/neurotransmitters as the perturbed (“SCZ”) brain solving the same task? Are we targeting the same neural mechanisms when we administer the PCE to poorly performing controls and pharmacologically perturbed experimental counterparts? In the absence of clear answers to such questions, the conclusion is that drugs which enhance cognition in normal animals may be PCEs, but this action may not necessarily be relevant to cognitive impairments mimicking those observed in SCZ. For the latter, we need drugs that can alleviate cognitive impairments in perturbed animals. It is possible that the same drug exerts different actions in non-perturbed and perturbed animals. This is the case with APDs in LI, where they potentiate LI in naïve rats via their dopaminergic antagonism but reverse MK801-induced persistent LI via their serotonergic antagonism. The same may explain the disruptive and enhancing actions on WM of mGlurR2/3 agonist in naïve and PCP-treated rats, respectively (Darrah et al., 2008). In the absence of clear answers to such questions, the conclusion is that drugs which enhance cognition in normal animals may be PCEs, but this action may not necessarily be relevant to cognitive impairments mimicking those observed in SCZ. For the latter, we need to ensure that our drugs can alleviate cognitive impairments in perturbed animals.

6.4.2. APD-PCE dissociation in perturbed animals

In order to model APD-resistant cognitive deficits in SCZ, there is a need to establish models based on tasks whose perturbations lead to performance impairments that are resistant to APDs. Here several leads can be suggested.

An important direction to follow with the NMDA model is to investigate in-depth tasks where NMDA antagonist-induced disrupt-
and/or APDs will be effective in targeting the cognitive deficits induced by each of these neurochemical disturbances.

LI provides a blueprint of such a model. As detailed above and summarized in Table 3, we demonstrated three LI abnormalities, MK801-, SCOP- and HAL-induced persistent LI, that exhibit distinct responses to PCEs and APDs depending on the underlying neurotransmitter perturbation: MK801-induced persistent LI is reversed by atypical APDs and PCEs but not by typical APDs. SCOP-induced persistent LI is reversed by PCEs but is resistant to both typical and atypical APDs. Finally, HAL-induced persistent LI is reversed by atypical APDs but is resistant to PCEs. It should be noted that all three SCZ-mimetics produce persistent LI by action at the conditioning stage without impairing associative learning, implying a common cognitive dysfunction, namely, cognitive/behavioral inflexibility. Nevertheless, the three persistent LI models exhibit distinct pharmacological profiles. Furthermore, as shown in Table 3, the pharmacological profiles of all three persistent LIs differ from that of disrupted LI, induced by either amphetamine or SCOP, which is reversed by both typical and atypical APDs. In the latter case, Clearly, further research using additional PCEs and atypical APDs is necessary to substantiate the capacity of LI to dissociate between these drug classes. However, the extant LI data indicate that it might be possible to establish models of cognitive impairments that respond differentially to APDs and PCEs depending on the inducing factor and the task.

6.6. Combined APD-PCE administration

Even an ideal PCE will be given clinically as adjunct treatment, and there is a very viable possibility that APDs alter in some ways the effects of add-on PCEs (Harvey, 2009). Consequently, there is an urgent need to characterize the effects of joint APD-PCE administration on all the models. While this is a trivial and most obvious path to take, it has been given neither serious consideration nor is being routinely evaluated in animal models. The reason is quite clear: this alternative requires the evaluation of everything we have from scratch. Another source of reticence is the number of experimental groups required when examining polypharmacy at this level (SCZ-relevant manipulation, numerous combinations of several APD and PCE doses to account for putative confounds such as one drug shifting the dose response of another, etc.), and consequent multiple-way ANOVAs whose results are likely to be difficult to interpret. However, until we clarify this, there remains a possibility that results from animal models fail to predict clinical response simply because in the clinic, APDs and PCEs are given together. Some evidence for such an interaction comes from Edward Levin’s and our data, showing in-

teractions between APDs and nicotine/alpha7 nAChR agonists. Our results with NMDA enhancers show that these compounds do not interact with haloperidol in LI, but clinical data show that combinations with atypical APDs like clozapine are deleterious. Given that much remains to be characterized, we must start incorporating into this characterization joint PCE-APD administration. We would like to point out that full efficacy of APDs in the models does prevent the identification of beneficial adjunctive therapies because we can use combinations of ineffective doses; we have recently used this approach to demonstrate such an effect for estradiol (Arad and Weiner, 2009).

6.7. Going forward or lost in translation?

It is clear from the present survey that a great deal of research aimed at a thorough, systematic pharmacological and behavioral characterization of the different models is needed before we can start reaching meaningful conclusions regarding SCZ-relevant cognitive enhancement based on these models. Even for the NMDA antagonist model, where there is a huge number of papers testing their effects on cognitive tasks (see references 60–137 in Amitai and Markou, 2010a), the numbers go down drastically when searching for papers testing the effects of PCEs on these deficits. Thus, at present there is not much to translate, and we should beware of the tendency to translate before enough evidence for translation exists, as pointed out by Markou et al. (2009): “unless there is complete failure to show proof of concept at any level of experimental testing, a feed-forward loop tends to occur for lead compounds. This situation is highly detrimental to the drug discovery process and is one of the several reasons that in vivo animal models are considered nonpredictive of the clinical assessment of putative medications.”

Among the different tasks, the characterization of WM deficits is of high priority, given the centrality of WM deficits in SCZ. As noted above, CNTRICS considered the available WM tasks unsatisfactory because they do not involve active manipulation of information during the delay. Although it is not clear whether the delay-dependent representation of stimuli that are used to guide behavior within a task is an active or passive process (Dudchenko, 2004), it would be desirable to start using more taxing WM tasks and in particular span capacity tasks (see Matzel and Kolata, 2010). In this context, we await more SCZ-relevant research on additional tasks chosen by CNTRICS, e.g., the stop signal task (SST) that addresses inhibitory response control (Eagle et al., 2008).

More research should be dedicated to understanding the dynamic interactions between changes in procedural parameters and the resulting changes in the action of the drugs. Understanding how drug actions are modulated by procedural manipulations can provide important information on the span of cognitive enhancing capacity and its limitations under specific conditions. Possibly this would make our tasks behave less consistently and would yield more negative answers but would also strengthen considerably the positive ones. As emphasized by Sarter (2004, 2006), task construct validation, consisting of systemic variation of theoretically important variables on task performance, must be an ongoing process. Such validation is indeed continuously and systematically conducted in basic neuroscience and animal learning fields (Bouton and Moody, 2004; Dudchenko, 2004; Eichenbaum, 1997; Howe et al., 2010; Kesner,

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Table 3

Five LI abnormalities (low AMPH- and low SCOP-induced disrupted LI; MK801-, high SCOP- and haloperidol-induced persistent LI) that exhibit distinct pharmacological profiles depending on the underlying neurotransmitter perturbation, and that can model four domains of pathology in schizophrenia. AMPH- and SCOP-induced disrupted LI, the two abnormalities that are reversed by both typical and atypical APDs, represent the domain of positive symptoms. NMDA antagonist-induced persistent LI represents a domain of (hypoglutamatergia-driven) negative/cognitive symptoms that respond to atypical APDs and cognitive enhancers but not to typical APDs. SCOP-induced persistent LI represents a domain of (antimuscarinic-driven) cognitive symptoms that are responsive to cognitive enhancers but are resistant to APDs. Finally, haloperidol-induced persistent LI represents a domain of (hypodopaminergia-driven) negative symptoms that are treatable by atypical antipsychotics but are resistant to cognitive enhancers (Weiner and Arad, 2009).

<table>
<thead>
<tr>
<th>Pharmacological response</th>
<th>Model</th>
<th>Disrupted LI</th>
<th>Persistent LI</th>
<th>Haloperidol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversed by</td>
<td>Amphetamine</td>
<td>typical and atypical APDs and some cognitive enhancers</td>
<td>cognitive enhancers</td>
<td>atypical APDs</td>
</tr>
<tr>
<td></td>
<td>Scopolamine</td>
<td>typical and atypical APDs; cognitive enhancers</td>
<td>atypical APDs; cognitive enhancers</td>
<td>atypical APDs</td>
</tr>
<tr>
<td>Resistant to</td>
<td></td>
<td>some cognitive enhancers</td>
<td>typical and atypical APDs</td>
<td>cognitive enhancers</td>
</tr>
<tr>
<td>Symptom domain</td>
<td></td>
<td>Positive</td>
<td>Cognitive</td>
<td>Negative/cognitive</td>
</tr>
</tbody>
</table>

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1984; Matzel and Kolata, 2010; McDonald et al., 2004; Mishkin et al., 1984; Morris, 1984), ensuring that the extant tasks have a reasonable level of construct validity. Drug discovery field needs to incorporate both the theoretical and the empirical approaches of this research into its practices. Furthermore, if we want to achieve anything remotely similar to “decomposition” using systemic pharmacology and behavior, the only way is to systematically manipulate the two arms of the model—doses, regimes of administration, stages of administration on the one hand, and task parameters on the other hand.

There also remains the theoretical question of how critical is decomposition of the construct of “cognitive deficit” into separate domains of cognition for refined PCEs identification, because as detailed above, pharmacological models may be characterized by inability to decompose. This is certainly the case with the nMMA antagonist-induced deficits, and remains to be clarified in further research with additional SCZ-mimetics. If de-composition is critical for refined PCEs identification as claimed, this characteristic of pharmacological models may present a serious obstacle. Already we see that the tasks surveyed here differentiate between APD and PCEs as well as between some PCEs in normal animals, but not in NMDA antagonist- or in scopolamine-treated animals in the available tasks. While the former supports distinct constructs of the tasks, such distinctiveness is lost in the disease model/s. As we noted above, it is possible that such a differentiation will be obtained based on certain neurotransmitter dysfunction-cognitive function combinations.

While steps of this kind will increase our confidence in the preclinical data and may reveal cognitive deficits that discriminate between APD and PCEs or between different PCEs, we suspect that predictive validity of pharmacological animal models will not change dramatically. This is because there are inherent differences between preclinical and clinical testing, which reach far beyond the issues of construct validity of animal tasks typically held responsible for the poor predictive power of animal models for efficacy in humans (see Introduction).

The practice and principles of preclinical testing (like animal experimentation in general) is to create an isolated, maximally unconfounded case, manipulating only a few factors at a time, with the aim of obtaining “full deficit” and “full reversal” (as represented by statistical significance). Preclinical testing is conducted on homogenous samples, and the experimental designs manipulate and adjust the experimental parameters, the drug doses and n per group to obtain these data. This is the strength of animal testing: it can focus on a single phenomenon/question/manipulation, have proper controls, reduce variability, and obtain a clear answer. But this is of course far removed from the situation of clinical testing where heterogeneity of the samples is the most outstanding characteristic, as are low power, subject attrition, variability and instability of cognitive capacity and performance between and within individuals, and of course an outstandingly complex and variable disease process involving neurodevelopmental disturbances of brain structure and neurotransmission at multiple levels, to mention just a few radical differences (for a thorough review see Barnett et al., 2010).

Given such differences, we are bound to continue facing the situation of positive findings with compounds in preclinical testing, which will not be shown sufficiently effective for cognitive treatment in SCZ.

Thus, the critical question facing the field of preclinical drug testing is: does the observation of full efficacy of APDs or some PCEs invalidate a model? If the goal is to fully predict clinical efficacy, the observation of full efficacy in the model could be regarded as a false positive result. Indeed, it has been suggested that “one should exclude models that lead to false positives” (Markou et al., 2009). As detailed above, the field does not seem ready or capable to apply this recommendation, and with a good reason. While the focus of such recommendations is usually on the cognitive tasks arm, this survey clearly indicates that excluding models that lead to false positives requires the exclusion of the NMDA antagonist model, and by extension, a refutation of the glutamatergic hypothesis of SCZ. Surely we are not ready to do this (Corlett et al., 2011). While no sufficient data are available at present, a similar problem may apply to other neurotransmitter perturbations. As we stated above, rather than being excluded, pharmacological models that yield “false positives” should be viewed as representing a subset of SCZ patients. Indeed, given that pharmacological models capture one aspect of the disease process (one neurotransmitter dysfunction) that manifests itself in some cognitive deficits, their advantage as compared to clinical trials is precisely their ability to isolate specific effects and to test them on specific tasks, allowing to explain the source of the obtained differences. In other words, if a PCE X reverses NMDA antagonist-induced deficit in DAT, the sole information the model provides is that certain cognitive (hopefully homologous or analogous) processes that are disrupted by NMDA hypofunction can be alleviated in some individuals by PCE X. Unfortunately, also such restricted information, which is likely to be accurate, can get easily lost in clinical trials. As noted by Insel (2009) “Is it surprising that individual responses to treatment may vary from what is seen with group means from clinical trials? Have we fully considered that absence of a statistically significant mean effect in 500 patients could obscure a profound effect in 50?”.

We therefore need to change our conceptualization of and expectations from pharmacological animal models. We should take statistically significant and widely replicable reversal in pharmacological animal models as an indication for potential partial reversal in some subsets of patients. While this may be disappointing, we should remember that pharmacological models are only one step in a long process of drug discovery and development and is/should be supplemented with biochemical, genetic, psychophysiological, and brain imaging measures, as well as other animal models, particularly those using neurodevelopmental perturbations, environmental and genetic. Within this process of drug discovery development, animal models have a unique and irreplaceable function: they are the only way to show, prior to clinical testing, that a compound exerts effects (beneficial or deleterious) on cognitive processing of live, and quite intelligent, organisms. One very important function that such models may fulfill is “to increase the confidence in the functional significance of a target and determine the pathway for further drug development to facilitate a rapid ‘win or kill’ decision-making process” (Markou et al., 2009).

Alternatively, we could change the methodology and statistical analysis of preclinical testing so that it becomes more geared towards identifying “partial” rather than “full” efficacy, e.g., we could focus on individual variability in response to drugs rather than on group means, or design our experiments to include combinations of several inducing factors and several measures, presumably better mimicking the heterogeneity of SCZ, and show that some measures are affected by a treatment while others are not (as is often the case with clinical testing; Harvey, 2009)). Although defining “partial reversal” in animal preclinical testing is problematic because we typically use statistical analyses that do not distinguish between small and large effects but rather between full (statistically significant) and no effect, some statistical analyses, such as effect size, can provide relevant information. While this will complicate immensely our designs and analyses and compromise our ability to interpret results, it might provide better approximations to the partial response in the clinic.

We believe that continuous enhancement of the expertise in animal cognition and pharmacologically-mediated brain-cognition relationships, thorough characterization of the models independent of short-term goals of drug discovery, and promoting realistic expectations from animal models while not forgetting their unique advantages, will facilitate the identification of PCEs and help to overcome the current “crisis of translation”.

Pharmacological animal modeling for drug discovery in SCZ is an ongoing venture, and one that has been undergoing a transformation in recent years. While the main goal of psychopharmacology has traditionally lied in uncovering brain-behavior relationships using
pharmacological means, in recent decades this commitment has weathered somewhat in the areas related to drug discovery. As a result, while there is an extremely rich literature on cognition in the animal learning field, complemented by increasing understanding of its neural substrates, pharmacology of cognition has lagged behind. The problem does not lie in the lack of valid animal tasks. In fact, we have no doubt that most if not all the tasks required for complex cognitive testing relevant to SCZ exist in the animal learning/ cognition and cognitive neuroscience literature (e.g., Floresco et al., 2006; Matzel and Kolata, 2010; Ragozzino, 2007). Bringing back sophisticated behavior to drug discovery amounts in our eyes to a paradigm shift. However, the road back to sophisticated psychopharmacology in drug discovery is only at its beginning. Testing cognition and its pharmacology as advocated today differs dramatically from the prevailing zeitgeist in the last two decades, when high throughput was all we needed. It is unrealistic to expect that the field will instantly regain confidence not to mention expertise. Training cadres of psychopharmacologists who are the next generation of the psyche, driven by theoretical questions on pharmacology of brain-cognition relationships, will ultimately pave the road to successful drug discovery.

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