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A neurocognitive animal model dissociating between acute illness and remission periods of schizophrenia

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Abstract

Rationale—The development and validation of animal models of the cognitive impairments of schizophrenia have remained challenging subjects.

Objective—We review evidence from a series of experiments concerning an animal model that dissociates between the disruption of attentional capacities during acute illness periods and the cognitive load-dependent impairments that characterize periods of remission. The model focuses on the long-term attentional consequences of an escalating-dosing pretreatment regimen with amphetamine (AMPH).

Results—Acute illness periods are modeled by the administration of AMPH challenges. Such challenges result in extensive impairments in attentional performance and the “freezing” of performance-associated cortical acetylcholine (ACh) release at pretask levels. During periods of remission (in the absence of AMPH challenges), AMPH-pretreated animals’ attentional performance is associated with abnormally high levels of performance-associated cortical ACh release, indicative of the elevated attentional effort required to maintain performance. Furthermore, and corresponding with clinical evidence, attentional performance during remission periods is exquisitely vulnerable to distractors, reflecting impaired top-down control and abnormalities in fronto-mesolimbic-basal forebrain circuitry. Finally, this animal model detects the moderately beneficial cognitive effects of low-dose treatment with haloperidol and clozapine that were observed in clinical studies.

Conclusions—The usefulness and limitations of this model for research on the neuronal mechanisms underlying the cognitive impairments in schizophrenia and for drug-finding efforts are discussed.

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Keywords

Schizophrenia; Cognition; Amphetamine; Clozapine; Haloperidol

Introduction

Despite the often reflexive attribution of the initial conceptualization of schizophrenia as a cognitive disorder to Kraepelin and Bleuler, or Morel (“*démence-précoce*”; Morel 1860), the “cognitive revolution”, beginning with the 1950s, and the subsequent birth of cognitive science during 1960s and 1970s (Miller 2003) have fostered a wider acceptance of theories that consider abnormal cognitive, specifically attentional, processes as central, disease-defining characteristics of schizophrenia (McGhie and Chapman 1961; Venables 1964; Nuechterlein and Dawson 1984). However, it is noteworthy that Kraepelin already embraced a relatively dynamic conceptualization of the central role of attentional impairments in schizophrenia (“*In dementia praecox a striking disorder of the attention is present from almost the inception of the disease*”; p. 19; Kraepelin 1907). Furthermore, Kraepelin dissociated between levels of severity of attentional impairments (blunting, suppression, blockade, retardation of attention) and stressed the long-term consequences of such impairments in terms of the general weakening of the perceptual process and the accessibility and accuracy of memories. Kraepelin also conceptualized the effects of impairments in the ability to sustain attention (“*Unsteadiness of attention*”; p. 6; Kraepelin 1919), specifically in the presence of distractors, and the long-term consequences of such impairments for reality monitoring (“*The more distractable a man is, the less perception is controlled by inner motives arising from experience, and the less coherent and uniform is the conception of the external world.*”; p. 22; Kraepelin 1907). Likewise, Bleuler attributed the distractibility of schizophrenic patients to their general inability to select stimuli for attentional processing (“*Thus, the facilitating as well as the inhibiting properties of attention are equally disturbed*”; p. 68; Bleuler 1950).

Both Bleuler and Kraepelin understood that similar attentional processes govern the detection, selection, and extended processing of exogenous stimuli, as well as the selection and maintenance of internal stimuli (or associations). Consequently, they were able to consider the profound, escalating consequences of attentional impairments for the general cognitive capacity of patients.

Contemporary research has confirmed that attentional impairments represent an essential component of the cognitive symptomatology of schizophrenics and perhaps even a vulnerability factor for schizophrenia (Braff 1993; Nuechterlein et al. 1994; Green 1996; Cohen et al. 1998, 1999; Kapur 2003; Braff and Light 2004; Silver and Feldman 2005; Filbey et al. 2008; Gur et al. 2007). Although the view that the diverse cognitive symptoms of schizophrenia reflect, and escalate from, a single fundamental cognitive dysfunction remains debated (Goldstein and Shemansky 1995; Lieh-Mak and Lee 1997), such a reductionistic perspective underlies our focus on the modeling of attentional, particularly sustained attentional impairments of schizophrenia in animals. Studies that attempted to dissociate the attentional impairments present during active disease periods (disease periods characterized by the presence of florid psychotic symptoms and severe disability) versus the persistent deficits observed in patients experiencing symptomatic remission (i.e., disease periods during which patients experience attenuated symptoms below diagnostic threshold) have remained unexpectedly scarce (Andreasen et al. 2005; Remington and Kapur 2005). However, the available evidence is indicative of severe impairments present during active periods, manifesting in the absence of special demands on cognitive processes (Nuechterlein et al. 1994). In contrast, heightened demands on attentional effort (for definition of attentional effort, see Sarter et al. 2006) as a result, for example, of the presentation of distractors, expose the

limited attentional capacities that persist outside active disease periods (Grillon et al. 1990, 1991; Nuechterlein et al. 1994; Servan-Schreiber et al. 1996; Robert et al. 1997; Goldberg et al. 1998; Seidman et al. 1998; Smith et al. 1998; Gorissen et al. 2005; Fuller et al. 2006; Gold et al. 2007; Jazbec et al. 2007). As will be pointed out below, different forms of dysregulation in telencephalic–limbic–basal forebrain circuitry are hypothesized to underlie the severe attentional impairments in baseline attentional performance of animals modeling active disease periods versus the impairments in attention that persist during periods of remission and that become apparent in response to increased demands on attentional effort. Treatment with low doses of antipsychotic drugs benefits, albeit to a limited degree, the attentional performance during both disease periods. Different neuro-psychopharmacological mechanisms may mediate these beneficial drug effects during periods of psychosis and remission (below).

As the measurement of attentional performance in laboratory rodents represents a central component of the evaluation of this model, we begin this review by describing the task, measures of performance, and the effects of distractors that are thought to recruit top-down mechanisms. The role of the cholinergic system for attentional performance will be briefly reviewed. We then introduce and discuss the parameters and validity of the pharmacological model, followed by separate discussion of the modeling of the two disease states, including predictive validity and underlying neurobiological mechanisms.

Measurement of top-down control of sustained attention in rodents and cholinergic mediation

The operant task employed in our experiments for the measurement of sustained attention and a set of data exemplifying the measures of performance generated by healthy rats, in the presence and absence of a distractor, are illustrated in Fig. 1.

The task consists of trials involving the presentation of signals or the absence of signal events, followed by the extension of the levers, triggering a 4-s response period. Subjects report the presence of a signal by pressing one lever and the absence of a signal by pressing the opposite lever. Correct responses are hits and correct rejections, respectively, and are rewarded. Incorrect responses are misses and false alarms, respectively, and trigger the next intertrial interval (ITI). Signal duration (Parasuraman and Mouloua 1987; Koelega et al. 1990) and other task parameters vary by species to ensure construct validity of the performance measures (for details on construct validity in animals and humans, see Demeter et al. 2008; McGaughy and Sarter 1995; Mar et al. 1996; Bushnell et al. 2003).

Figure 1(c–h) depicts the major measures of performance generated by this task and the performance of intact rats. The analysis of performance from a test session (162 trials total) typically divides data into three blocks of 54 trials, primarily in order to allow comparisons with data from sessions during which a distractor was presented during the second (Fig. 1) or the second and third blocks of trials. Standard-task performance is characterized by signal duration-dependent hit-rates (c–e), relatively high levels of correct rejections (>80%), and low numbers of errors of omission (<10% of all trials). As detailed in the legend of Fig. 1, hits and correct rejections are collapsed into a single measure of performance [vigilance index (VI); Fig. 1h; for formula, see Kozak et al. 2007]. This measure indicates that intact animals typically exhibit a small but robust decline in performance across the three blocks of trials, consistent with the classification of the standard version of the task as a sustained attention task. Disruption of neuronal processing usually augments this decrement in performance.

The standard version of this task has been interpreted as based largely on bottom-up, signal-driven processes (Sarter et al. 2005a). In other words, during well-practiced standard-task performance, cognitive processes are not required to supervise and influence the detection of

signals, the discrimination of non-signal events, or the processing of response rules for each trial type. Following extensive practice, such rules are executed on the basis of a relatively automatic level of processing (Fisk and Scerbo 1987), as indicated by their insensitivity to reversal learning (e.g., Sarter 1990).

In order to recruit top-down mechanisms, distractors are presented during one or several blocks of trials, depending on species (Nobre et al. 2002; Weissman et al. 2002; Gilbert and Sigman 2007). A substantial amount of evidence from human imaging studies, as well as animal experiments, indicates that such mechanisms are mediated via prefrontal efferent circuitries, which act to optimize receptive field properties and suppress distractor representation in sensory and sensory-associational cortical regions (see references and Table 1 in Sarter et al. 2006). These mechanisms act to stabilize and recover attentional performance depending on the specific task version and distractor parameters. Figure 1(c–h) illustrates the effects of a distractor on performance. The distractor consisted of operant chamber houselights flashing on–off at 0.5 Hz during the second (middle) block of trials. For hits to longest and medium-duration signals, the effects of the distractor manifest primarily in the third block of trials. This effect of the distractor in rats corresponds with effects in humans (Demeter et al. 2008) and is hypothesized to indicate the exhaustion of the subjects' detection capacity in response to the distractor presence. For shortest signals, “floor effects” likely prevented the manifestation of distractor effects (Fig. 1e). With respect to the performance on non-signal trials, the distractor acutely leads to an increase in the number of false detections (1f). However, following the termination of a distractor, the animals' correct rejection rate immediately recovers. The contrast between the lasting effects on hits and the immediate recovery of non-signal trial performance is consistent with the assumption that non-signal trial performance does not depend on attentional resources and resource management (see below). Importantly, presentation of the distractor does not robustly increase errors of omission (1g), reflecting the close relationships between motivational processes and increases in attentional effort (Maunsell 2004; Small et al. 2005; Sarter et al. 2006; Watanabe 2007). The effects of the distractor will be addressed again further below in the context of the modeling of remission states.¹

Cholinergic mediation of attentional performance

Studies assessing the effects of selective lesions of the cortical cholinergic input system and the effects of cholinergic receptor antagonists consistently indicated that the cholinergic system in general and the cortical cholinergic input system in particular is necessary for the performance of a wide range of attentional functions and capacities and attention-dependent learning (Everitt and Robbins 1997; Hasselmo and McGaughy 2004; Sarter et al. 2005a; McGaughy et al. 2000). Cholinergic lesions selectively disrupt the detection of signals in the task described above, sparing non-signal trial performance (McGaughy et al. 1996). This finding indicates that the lesion does not affect the processing of response rules and corresponds with the general hypothesis that the cortical cholinergic input system mediates the detection, selection, and processing of stimuli but is less involved in the associational (or intrinsic) processing underlying trials not involving stimulus detection (Sarter et al. 2005a). Moreover, cholinergic lesions of the right but not left hemisphere reproduce the effects of bilateral lesions on performance (Martinez and Sarter 2004), corresponding with results from human imaging studies that collectively suggest that sustained attention is mediated primarily via right-hemispheric circuitry (e.g., Pardo et al. 1991; Cohen et al. 1992).

¹The task described in this manuscript was recently selected by the CNTRICS initiative (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia) for development for assessing the domain “control of attention” (<http://cntrics.ucdavis.edu/meetings.shtml>).

Studies measuring the release of acetylcholine (ACh) in task-performing animals demonstrated that the increases in cortical ACh release that are reliably observed in attention task-performing animals are not reproduced in animals performing tasks controlling for operant responding, reward rate, motor activity, or non-contingent stimulus presentation (Himmelheber et al. 1997, 2000; Passetti et al. 2000; Dalley et al. 2001, 2005; Arnold et al. 2002). More recent experiments made use of a new electrochemical technique that allows the monitoring of second-to-second changes in ACh release in task-performing animals. Evidence from initial experiments suggest that phasic (on the scale of seconds) cholinergic signals in the medial prefrontal cortex selectively mediate the incorporation of signals into ongoing cognitive and behavioral processes, allowing such a signal to control behavior (Parikh et al. 2007). This finding corroborates the conclusion that was deduced from the lesion studies. In the absence of cholinergic transients, the probability and efficacy of the detection process is decreased, and, thus, a large proportion of signals are missed. Non-signal trial performance does not require signal detection and thus remains unaffected by such lesions.

Levels of prefrontal ACh release in attentional task-performing animals do not seem to be correlated with levels of performance but rather with the maintenance of (residual) performance under challenging conditions (Kozak et al. 2006). Although more evidence is required to substantiate this hypothesis, it is consistent with the general view that cholinergic activity in prefrontal regions specifically contributes to the recruitment of top-down mechanisms to combat further performance decline and support performance stabilization and recovery in the presence of a distractor (Sarter et al. 2006).

As the activity of cholinergic inputs to the prefrontal cortex influences the activity of cholinergic inputs to other cortical regions (Nelson et al. 2005), the basal forebrain cholinergic input system has been hypothesized to contribute functionally to the mediation of top-down effects in two different ways. First, cholinergic inputs to the prefrontal cortex are particularly active during challenges on attention, thereby assisting in the activation and orchestration of the prefrontal efferent circuitry that mediates top-down effects (see also the distractor-induced neurophysiological effects in the prefrontal cortex described in Gill et al. 2000). Second, cholinergic inputs to other cortical regions contribute to the mediation of top-down effects including receptive field optimization and amplification of thalamic input processing (McKenna et al. 1989; Oldford and Castro-Alamancos 2003; Puckett et al. 2007). Cholinergic projections to other cortical regions are regulated in part by direct prefrontal projections to the basal forebrain, as well as multi-synaptic circuits involving prefrontal projections to the nucleus accumbens (NAC) and other limbic regions, which in turn project to the basal forebrain (e.g., Zaborszky et al. 1997; for an illustration of this model, see Fig. 3 in Sarter et al. 2006).

Taken together, accumulating evidence indicates the necessity of the cortical cholinergic input system for attentional performance and specifies that cholinergic activity selectively mediates the detection of signals. Furthermore, prefrontal cholinergic activity is particularly high during performance challenges, indicating the special role of prefrontal cholinergic inputs in the recruitment of top-down mechanisms. The available evidence about the dynamic changes in cholinergic activity in task-performing animals that underwent the amphetamine (AMPH)-pretreatment regimen will be discussed below in the sections on the modeling of the two major stages of schizophrenia.

Cholinergic mechanisms of attention and cholinergic neurotransmission in schizophrenia

As discussed above, extensive evidence supports the general hypothesis that the cortical cholinergic input system is necessary for, and the cortical cholinergic activity mediates, a wide range of attentional processes and capacity. Therefore, abnormalities in the temporal and spatial

orchestration of cholinergic activity in the cortex can be predicted to cause robust impairments in the ability to detect and select stimuli for extended processing and to perform cognitive tasks involving demands on attentional processes. Given the crucial role of the cortical cholinergic system in fundamental aspects of cognition, it seems likely that abnormalities in cholinergic neurotransmission are a necessary component of the abnormally regulated circuitry that mediates the cognitive symptoms of schizophrenia (Heimer 2000).

For several reasons, our knowledge about the role of cholinergic dysregulation in schizophrenia has remained limited. It is presently not possible to monitor *in vivo* dynamic abnormalities in cholinergic neurotransmission in humans. Furthermore, the post-mortem determination of levels of choline acetyltransferase or acetylcholinesterase is unlikely to indicate regulatory abnormalities (Powchik et al. 1998), largely because these enzymes are present at relatively high concentrations that do not limit the synthesis and hydrolysis, respectively, of ACh. Moreover, the evidence from the model (see below) suggests that the demonstration of such abnormalities would require recruitment of the cholinergic system and thus cognitive performance in patients (Sarter et al. 2007). However, postmortem and *in vivo* imaging studies consistently indicated abnormally low levels of muscarinic M1 and M4 receptor densities, as well as elevated levels of M2 receptors in the cortex (Crook et al. 2000, 2001; Lai et al. 2001; Dean et al. 2002, 2003; Mancama et al. 2003; Raedler et al. 2003; Deng and Huang 2005; Newell et al. 2007; Scarr et al. 2008). Based in part on our evidence concerning the mesolimbic regulation of basal forebrain cholinergic neurons (e.g., Zmarowski et al. 2005, 2007; Neigh et al. 2004), these changes in muscarinic receptor density were suggested to reflect abnormal interactions between mesolimbic dopaminergic and basal forebrain cholinergic systems (Hyde and Crook 2001; Raedler et al. 2007). Furthermore, a potential role of dysregulated nicotinic acetylcholine receptors has been suggested (De Luca et al. 2006).

Circumstantial evidence often cited in support of a role of the cholinergic system in the development of the symptoms of schizophrenia includes the potency of clozapine to increase basal ACh release (Ichikawa et al. 2002), the considerable affinity of clozapine and other second-generation antipsychotic drugs to muscarinic receptors (Raedler et al. 2000), and the muscarinic receptor agonist-like properties of a major metabolite of clozapine, *N*-desmethylozapine (Weiner et al. 2004; Li et al. 2005; Lameh et al. 2007). Finally, it should be noted that the use of acetylcholine esterase inhibitors as adjunctive treatment produced little or no beneficial cognitive effects (MacEwan et al. 2001; Friedman et al. 2002; Friedman 2004; Aasen et al. 2005; Erickson et al. 2005; Keefe et al. 2008). Similar to the limited efficacy of these drugs in senile dementia, this lack of therapeutic efficacy has been hypothesized to reflect the limited capacity of these drugs to reinstate or amplify the second-based, phasic cholinergic activity that mediates signal detection in attention tasks (above; Sarter and Bruno 1999). Further below, we will discuss attentional performance-associated cholinergic activity in the animal model that is in the central subject of this review.

Repeated amphetamine exposure as an animal model

The psychotogenic effects of repeated exposure to psychostimulants, primarily but not exclusively the AMPHs, have been extensively documented (Wallis et al. 1949; O'Flanagan and Taylor 1950; Weiner 1964; Bell 1965; Snyder et al. 1972, Snyder 1973; Bell 1973; Janowsky and Risch 1979; Kokkinidis and Anisman 1981; LeDuc and Mittleman 1995; Bartlett et al. 1997). Generally, the effects of repeated exposure to AMPH reproduce the main features of paranoid schizophrenia (hallucinations in all modalities, paranoid delusions, thought disorder, obsessive and compulsive cognitive activity and behaviors). Following discontinuation of drug use, subjects remain more sensitive to the psychotogenic effects of AMPH (Segal and Janowski 1978; Robinson and Becker 1986).

In addition to this important face validity of the model, ample evidence indicates that repeated psychostimulant exposure reproduces important neurobiological and cognitive hallmarks of schizophrenia (Segal and Mandell 1974; Segal and Janowski 1978; Lieberman et al. 1997; Strakowski et al. 1997; Castner and Goldman-Rakic 1999, 2003; Yui et al. 1999; Kapur 2003). Perhaps the most important feature of the model is the increased sensitivity of the mesolimbic dopamine system to the effects of psychostimulants. Such a hyper-responsive mesolimbic system appears to be present in schizophrenic patients, including never-medicated schizophrenic patients (Strakowski et al. 1997), and has been associated specifically with acute psychotic disease periods (Breier et al. 1997; Abi-Dargham et al. 1998; Laruelle and Abi-Dargham 1999; Laruelle et al. 1999, Laruelle 2000). Repeated psychostimulant exposure was demonstrated to produce lasting impairments in cognitive information processing and disruption of prefrontal circuit function (e.g., Homayoun and Moghaddam 2006; see below for effects on attention).

Below, we will review important aspects of experimental paradigms used to reproduce the cognitive and non-cognitive consequences of repeated AMPH exposure in laboratory animals. The bewildering heterogeneity of pretreatment regimens used in these experiments and the resulting variability of measures of the cognitive and associated neuronal consequences of such regimens together have rendered a rather confusing literature that requires clarification.

How much and how often? AMPH-pretreatment regimens

The heterogeneity of psychostimulant pretreatment regimens (number, frequency, and doses of AMPH administration) used in experiments focusing on cognitive effects has yielded a complex body of evidence (see Table 1 for a partial list; the issue of neurotoxicity will be addressed separately below). As discussed by Segal and Janowski (1978), anecdotal evidence indicates highly variable self-administration pattern by AMPH users who experienced AMPH-induced psychosis. However, this evidence does not support the widespread view that AMPH-induced psychosis requires the administration of high doses over long periods of time. Indeed, AMPH users more typically begin by administering relatively small doses and incrementally increase doses as tolerance to the autonomic and perhaps also the psychotomimetic effects of AMPH develops (Ellinwood 1972).

Extensive experimental work in animals indicated that compared to continuous AMPH exposure, repeated intermittent AMPH administration produces more effective behavioral and mesolimbic sensitization (Robinson and Becker 1986). Moreover, effective AMPH regimen should model the escalating increases in dose that are administered over several days (termed “runs” in the context of AMPH addiction), as well as the short breaks that separate runs (“crashes”). Ideally, an AMPH administration regimen should be devoid of neurotoxic consequences (below) while producing lasting abnormalities in the animals’ behavioral, cognitive, and neuronal (particularly dopaminergic) responses to stressors and drug challenges.

Numerous administration regimens have been characterized in different species (Segal and Mandell 1974; Paulson and Robinson 1995; Segal and Kuczenski 1997; Castner and Goldman-Rakic 2003; O’Neil et al. 2006). Robinson and colleagues characterized a regimen that involves the administration of escalating doses over 40 days and regular “crash” periods (Robinson and Camp 1987; Robinson et al. 1988; Paulson et al. 1991; Paulson and Robinson 1995). This regimen was employed in our recent experiments on the role of the cholinergic system in the attentional consequences of repeated AMPH exposure (Kozak et al. 2007; Martinez et al. 2005; below), as well as to study the pro-cognitive effects of antipsychotic treatments (Martinez and Sarter 2008; below). This AMPH-pretreatment regimen is illustrated in Fig. 2.

Over a 40-day period, rats are administered successively increasing doses of D-amphetamine sulfate (1–10 mg/kg; i.p.; concentrations include salt weight) twice per day, with approximately

8 h separating the two injections. During weekends, animals are treated with saline to model crashes. Following completion of the pretreatment period, animals undergo a withdrawal period that lasts a minimum of 10 days. This period is characterized by behavioral depression and transient decreases in the concentration of norepinephrine in the hypothalamus and transient attenuation of AMPH-induced stimulation of dorsal and ventral striatal dopamine release (Paulson et al. 1991). Cognitive performance ascertained during the withdrawal period is likely to be modulated by a wide range of sensorimotor, motivational, and behavioral correlates of withdrawal and thus is not the primary focus of models of the cognitive symptoms of schizophrenia (Russig et al. 2003; Dalley et al. 2005). Indeed, the lasting effects of the pretreatment do not emerge, or are difficult to demonstrate, until the cessation of withdrawal effects (Paulson et al. 1991). Thus, it becomes important to identify this period of depression (or withdrawal) and to sufficiently postpone assessing the lasting cognitive effects of prior AMPH exposure and/or the effects of putative therapeutics until after this period has subsided. As a result of this pretreatment regimen, aspects of the animals' behavior, including their attentional performance (below), remain hypersensitive to the detrimental effects of doses of psychostimulants that are ineffective in control animals (Paulson et al. 1991; below).

As experiments involving psychostimulant pretreatment regimens have formed a rather complex literature, it will be crucial that future experiments provide an explicit justification for the selection of doses, the frequency of administration, and the duration of the treatment regimen. Moreover, and as will be discussed further below, the behavioral and cognitive state of the animals during the pretreatment period (passive versus task performing) may determine the long-term consequences of repeated AMPH exposure and therefore requires justification.

Neurotoxicity

Potential neurotoxic effects of repeated AMPH exposure would limit the validity of this animal model for research on schizophrenia. Although repeated AMPH exposure has often been stated to cause neurotoxicity, the neurotoxic efficacy of AMPH is a strict function of dose (high) and administration regimen (continuous), with the methylated form of AMPH generally exhibiting greater neurotoxic efficacy (Robinson and Becker 1986). Concerning the regimen illustrated in Fig. 2, considerable evidence indicates that this pretreatment regimen does not produce neurotoxicity. For example, this regimen does not result in the depletion of dopamine and serotonin in the dorsal and ventral striatum (Robinson and Camp 1987; Robinson et al. 1988). The absence of neurotoxic effects resulting from intermittent, escalating-dosing administration regimen contrasts with the neurotoxic effects resulting from continuous AMPH infusion, administration of high doses of AMPH that are not preceded by lower doses and incremental increases in dose, or the effects of continuously high blood-AMPH levels maintained by implants or mini-pumps (Ellison et al. 1978; Morgan and Gibb 1980; Ridley et al. 1982; Richards et al. 1993; Wallace et al. 2001; Belcher et al. 2006; O'Neil et al. 2006).

Locomotor sensitization, stereotyped behavior, and anorexic effects as confounding variables?

A frequently expressed interpretational concern regarding the behavioral /cognitive effects of repeated AMPH administration stems from the misconception that increases in locomotor activity, stereotypic behavior, and anorexia are compulsive consequences of repeated psychostimulant exposure that therefore necessarily confound the behavioral measures of cognition. However, sensitized locomotor activity and stereotyped behaviors not only depend on the dose of AMPH but also manifest primarily in situations in which the animals' behavior remains unconstrained, such as an open field test. In contrast, if administered in the context of a stable environment, persistent behavioral contingencies and cognitive activity, repeated AMPH exposure, and AMPH challenges do not necessarily produce such behavioral effects (Crombag et al. 1996, 2000, 2001). For example, if stereotyped behaviors and locomotor

hyperactivity were compulsive consequences of AMPH pretreatment and challenge, performance in the operant sustained attention task (described above) would be characterized by high omission rates and side and lever biases.

Although such effects were observed during the AMPH-pretreatment period, particularly following the administration of higher doses, they did not manifest following the withdrawal period or following low-dose challenges that revealed specific performance impairments. Rather, the performance impairments observed during AMPH challenges were specific in nature, as indicated by signal duration-dependent performance and the absence of high levels of errors of omission or abnormal response latencies. Collectively, task performance was not confounded by the presence of overt motor stereotypies or response biases.

Likewise, there is strong evidence indicating that the anorexic effects of AMPH undergo contingent tolerance. In simplified terms, this means that the dissipation of such effects is not merely the result of the repeated presence of the drug but of adaptive appetitive and consummatory behavior that develops in response to the repeated presence of the drug while reward is retrieved and consumed (Hughes et al. 1998; Wolgin 2002; Wolgin and Jakubow 2004). Thus, locomotor hyperactivity, stereotyped behavior, and the anorexic effects of repeated AMPH exposure are not observed in animals that learned to perform tasks in the presence of AMPH. Although these findings do not detract from the importance of analyzing the potential role of such behaviors in the long-term effects of AMPH, they permit the conclusion that such behaviors do not compulsively confound the cognitive consequences of AMPH exposure.

Modeling the severe attentional impairments during active illness periods, neurobiological mechanisms, and predictive validity

Severe attentional impairments

The demonstration of lasting behavioral, cognitive, and neuronal consequences of AMPH pretreatment typically, but not necessarily (below), requires the administration of a challenge dose of AMPH and the demonstration of unusually high potency and/or efficacy of such challenges. The need for such challenges has occasionally been considered to represent a weakness or even a limitation of this pharmacological disease model. However, there are several arguments that suggest that such challenges in fact model an essential symptom-provoking characteristic of the disorder. Recurrence of AMPH psychosis in humans is often triggered by flashbacks, stress, and psychostimulant administration (e.g., Yui et al. 1997, 1999, 2000). Thus, low-dose AMPH challenges in animals are considered to model the ability of such events to elicit acute disease periods (prodromal, initial, and relapse periods) and reveal the underlying neuronal dysfunction (Antelman et al. 1980).

Furthermore, psychostimulant challenges reveal the hyper-responsive mesolimbic dopamine system that is present during active illness periods (Lieberman et al. 1990; Laruelle and Abi-Dargham 1999; Laruelle 2000; Kapur 2003; Tenn et al. 2003). Therefore, the cognitive impairments observed in response to challenges may model primarily the impairments that are associated with acute disease periods (Featherstone et al. 2007; see further below for a discussion of the relationship between such impairments and the presence of positive symptoms). We administered the pretreatment regimen described in Fig. 2 to animals during daily practice of the previously acquired sustained attention task (Fig. 1). Following completion of this pretreatment regimen, animals regained baseline performance over 8–10 days (Martinez et al. 2005; Kozak et al. 2007; Martinez and Sarter 2008). Although the severity and nature of the performance effects of AMPH challenges varied slightly among experiments due primarily to the presence or absence of tethering and intracranial microdialysis probes, the results from

four separate studies (see Table 1) uniformly indicated that AMPH challenges resulted in a profound disruption of performance. As indicated by random selection of levers in both trial types (signal, non-signal trials) that is nearly 50% hits for all signal durations and 50% correct rejections, the selection of response levers was no longer governed by the presence or absence of a cue. As animals continued to perform with minimal increases in omissions and without exhibiting overt lever or side biases, their performance reflected a complete loss of stimulus control and/or the inability to process the response rules that are a function of the presence of absence of signals and/or the execution of the response (Kozak et al. 2007). Because of the interpretation of challenges as triggers for acute disease periods and because of the severity of the disruption of attentional performance evoked by challenges, the effects of AMPH challenges in this model on performance are hypothesized to model the cognitive symptoms of acute illness periods.

Neurobiological mechanisms underlying the disruption of attentional performance during active illness periods

We monitored prefrontal ACh release in animals that were pretreated and challenged with AMPH during performance of the sustained attention task. Moreover, we also monitored ACh release in AMPH-pretreated animals that were challenged with AMPH but never acquired or performed the sustained attention task (Kozak et al. 2007). The results from this experiment were straightforward. In animals pretreated with vehicle and “challenged” with a low dose of AMPH (1 mg/kg), performance was not affected and performance-associated increases in prefrontal ACh release did not differ from animals that never received AMPH. In contrast, ACh release in AMPH-pretreated and AMPH-challenged animals remained unchanged relative to pretask baseline levels. Specifically, ACh release in AMPH-pretreated and AMPH-challenged animals did not display any degree of performance-associated increase in ACh release.

Importantly, when the attentional performance of AMPH-pretreated animals was assessed in the absence of a challenge dose, performance was comparable to control animals. However, performance-associated increases in ACh release reached, and in fact exceeded, the increases observed in vehicle-pretreated control animals (below). This result clearly rejects the possibility that the AMPH-pretreatment regimen per se attenuated the reactivity of the cortical cholinergic input system. This conclusion was also supported by the finding that in non-performing animals that underwent the AMPH-pretreatment procedure, AMPH challenges resulted in increases in ACh release that were similar to those seen in drug-naïve animals. Collectively, these results indicate that the “frozen” cholinergic system in AMPH-pretreated and task-performing animals was not merely a result of AMPH preexposure alone but a result of interactions between task performance and the AMPH pretreatment. This point deserves emphasis: AMPH pretreatment and challenge per se did not disrupt cholinergic neurotransmission. Rather, interactions between task performance and AMPH challenge are necessary to reveal cholinergic dysregulation. This conclusion corresponds with the general view that disease-related, dynamic dysregulation of neuronal system is a function of the recruitment of this system, and thus of cognitive activity (see also Sarter et al. 2007).

Causal relationships between ACh release and performance

Because of the severe disruption of attentional performance in AMPH-pretreated and AMPH-challenged animals, the demonstration of a frozen cholinergic system may be considered a mere correlate of disrupted performance. However, the available evidence supports an alternative view.

Following the administration of the AMPH challenges and before the task was initiated, ACh release levels in vehicle-pretreated animals robustly increased. Presumably, exposure to the

chambers and the expectation of task onset alone were sufficient to initiate such preperformance increases in ACh release. In contrast, in AMPH-pretreated animals, this preperformance increase in ACh release did not take place (Kozak et al. 2007). Because ACh levels failed to increase before task onset, it can be concluded that such failure during task performance was not merely a correlate of the failure to perform above chance levels. Rather, the disruption of performance in AMPH-pretreated and AMPH-challenged animals was a result of the failure of the cholinergic system to activate and subsequently mediate attention performance. To reiterate, such “freezing” of ACh release at baseline levels was not observed in non-performing animals, excluding the possibility the AMPH preexposure per se resulted in the failure of the cortical cholinergic input system to activate. Thus, interactions between task performance and pretreatment resulted in a major dysregulation of the cortical cholinergic input system that is revealed in the presence of low doses of AMPH. This cholinergic dysregulation likely caused the disruption of attentional performance (Kozak et al. 2007).

Hypothetical neuronal mechanisms

Neuronal activity in the NAC is necessary for the demonstration of performance-associated increases in cortical ACh release (Neigh et al. 2004). This NAC-basal forebrain interplay does not take place in situations not involving motivated cognitive activity (Neigh et al. 2001). While there is no direct evidence to support the hypothesis that a hyper-responsive mesolimbic dopamine system inhibits the basal forebrain to the point that cortical cholinergic projections can no longer be recruited, circumstantial evidence is consistent with this hypothesis. For example, reduced dopaminergic neurotransmission in the NAC was shown to benefit cognitive performance following cholinergic lesions (Grigoryan et al. 1996). Furthermore, evidence indicates that manipulations of neurotransmission in the NAC on cortical ACh release affect cortical ACh release exclusively in prefrontal regions (Zmarowski et al. 2005, 2007). Collectively, this evidence is consistent with the general hypothesis that neuronal dysregulation, manifesting at multiple sites within prefrontal–mesolimbic–basal forebrain–prefrontal circuits, is essential for the expression of the cognitive symptoms of schizophrenia (Moore et al. 1999; Sarter and Bruno 1999; Floresco et al. 2005; Goto and Grace 2005; Sarter et al. 2005b; see Fig. 4). The exact neuronal mechanisms that underlie the interactions between the effects of repeated AMPH on NAC-basal forebrain interactions, and the recruitment of these circuits by attentional performance, remain poorly understood.

Predictive validity: effects of treatment with low doses of haloperidol and clozapine on AMPH-challenge-evoked disruption of attention

The administration of relatively low doses of typical and atypical antipsychotic drugs has been repeatedly shown to produce moderately beneficial cognitive effects in schizophrenic patients (Green et al. 2002; Keefe et al. 2004, 2006; Mishara and Goldberg 2004). This evidence contrasts with the frequently expressed view that first generation antipsychotic drugs lack pro-cognitive therapeutic efficacy, whereas second-generation antipsychotic drugs possess a more promising pro-cognitive profile. Thus, given the absence of more potent, true cognition enhancers in schizophrenia, the demonstration of moderately beneficial effects of antipsychotic drugs provides an opportunity for a test of the predictive validity of animal models (Hagan and Jones 2005).

In animals pretreated with AMPH as described in Fig. 2, semi-chronic treatment with low-dose haloperidol (0.025 mg/kg) or clozapine (2.5 mg/kg) attenuated the attentional disruption produced by AMPH challenges (1 mg/kg; Martinez and Sarter 2008). Low doses were defined, in accordance with Kapur (2003), as resulting in <50% D2 receptor occupancy. Although the effects of clozapine statistically were more robust, the efficacy of the two compounds did not differ, consistent with clinical evidence (references above). Thus, and although more pharmacological evidence is necessary, these results indicate that this aspect of the model,

concerning the disruption of attentional performance during active disease periods, is capable of detecting the moderately efficacious, beneficial effects of low-dose antipsychotic treatment.

Antipsychotic or true pro-cognitive effects?

Repeated exposure to AMPH causes positive symptoms in psychostimulant abusers, and AMPH triggers acute disease periods in schizophrenics (references above). Thus, it is important to address whether the component of this model that is thought to reproduce acute disease periods, as a result of AMPH challenges, merely indicates the collapse of attentional performance in association with, and perhaps even due to, the expression of “positive symptoms” in the animal model. Likewise, we need to discuss further the possibility that the beneficial attentional effects of low-dose antipsychotic-drug treatment were merely secondary to their antipsychotic efficacy. This discussion does not concern the attentional impairments observed during periods of remission and in the absence of AMPH challenges (below).

In the animal model, AMPH challenges resulted in a disruption of performance that in essence reflected random lever selection in signal and non-signal trials. However, the number of errors of omissions did not robustly increase. Thus, it was not the case that animals simply disengaged from task and engaged in competing behaviors that interfered with operations of the levers. Rather, they maintained orientation toward the intelligence panel and retrieved the rewards earned during approximately 50% of all trials. Thus, AMPH challenges in AMPH-pretreated animals did not seem to generate repetitive or perseverative behaviors as such behaviors would likely cause cessation of responding or at least strong side or lever biases. As repetitive perseverative behaviors were suggested to represent animal analogues of positive symptoms (Segal et al. 1981), our evidence does not provide support for the possibility that symptoms analogous to positive symptoms in humans were present in AMPH-pretreated and AMPH-challenged animals. Consequently, it seems highly unlikely that the disruption of performance was secondary to the presence of positive symptoms. Likewise, the evidence does not support the possibility that the beneficial effects of the treatments on attentional performance were merely due and secondary to the attenuation of behavioral analogues of positive symptoms in animals.

Although interactions between repeated AMPH exposure and attentional performance may primarily model the cognitive symptoms of the disease, the potential relationships between antipsychotic effects and pro-cognitive effects of treatments in patients remain a conceptually challenging subject. The general assumption that positive symptoms and cognitive deficits are poorly correlated is not universally shared (Kay 1990; Mortimer et al. 1990; Strauss 1993; Berman et al. 1997; Brebion et al. 1999). Moreover, numerous studies indicated that the treatment-induced improvement of positive symptoms is associated with alleviation of cognitive, specifically attentional symptoms (Gruzelier and Hammond 1978; Oltmanns et al. 1978; Wahba et al. 1981; Braff and Saccuzzo 1982; Marder et al. 1984; Cassens et al. 1990; King 1990; Addington et al. 1991; Dollfus and Petit 1995). The present animal model does not appear to be capable of addressing these potential interactions between positive and cognitive symptoms. However, this limitation could also be considered an advantage as the model therefore allows a more exclusive assessment of the therapeutic efficacy of potential pro-cognitive treatments.

Neuronal mechanisms underlying beneficial attentional effects of haloperidol and clozapine during active illness periods

Evidence concerning the performance-associated activity of the prefrontal cholinergic input system in AMPH-challenged and antipsychotic-drug-treated animals is not available. However, for beneficial attentional effects of treatment to take place, the available evidence suggests that the frozen status of the cortical cholinergic input system (above) needs to be

reversed, restoring the capacity of this system to activate in response to task onset and attentional performance. In support of this hypothesis, results indicate that the beneficial attentional effects of clozapine cannot be demonstrated following restricted removal of medial prefrontal cholinergic inputs (Young et al. 2007). The finding that clozapine increases *basal* cortical ACh release (Parada et al. 1997; Ichikawa et al. 2002) corresponds with the general view that the beneficial effects of this drug is directly related to its effects on cholinergic neurotransmission. However, the exact neuronal mechanisms mediating the beneficial effects of clozapine and, even more so of low-dose treatment with haloperidol, remain unclear.

Modeling the cognitive load-dependent impairments during remission, neurobiological mechanisms, and predictive validity

Increased demands on attentional effort reveal impairments

Cognitive impairments in schizophrenia persist during periods of remission, long after the initial induction of the disease, and outside active illness periods (references above). Prior efforts using pharmacological models to reproduce this aspect of the disease have been frustrated by the absence of robust, residual cognitive impairments. This failure resulted, at least in part, from focusing on the variation of pharmacological pretreatment parameters while ignoring the more likely possibility that increases in cognitive load and top-down control reveal such persistent impairments. Clinically stable, medicated outpatients do not reliably exhibit impairments in attention tasks if such tasks are characterized by salient, fixed, spatially invariant targets and can be performed primarily via bottom-up processes [Mar et al. 1996; Mori et al. 1996; Gold et al. 2007; see Sarter et al. (2001) for a definition and discussion of bottom-up versus top-down mechanisms contributing to attentional performance]. In contrast, tasks involving top-down control evoked by, for example, the presentation of distractors, demands on switching between stimulus attributes, or high event rates, revealed persistent impairments (Oltmanns and Neale 1975; Oltmanns 1978; Grillon et al. 1990; Nuechterlein et al. 1994; Seidman et al. 1998; Smith et al. 1998; Birkett et al. 2006; Fuller et al. 2006; Gold et al. 2007; Gur et al. 2007; Jazbec et al. 2007; Luck and Gold 2008).

The attentional performance of AMPH-pretreated animals likewise remains sensitive to demands on top-down control. Following a 10-day drug-free period during which performance recovers from the effects of the pretreatment regimen, AMPH-pretreated rats (using the regimen shown in Fig. 2) exhibit normal performance in the sustained attention task (Martinez et al. 2005; Kozak et al. 2007; Martinez and Sarter 2008). When presented with a distractor, and compared with vehicle-pretreated controls, AMPH-pretreated animals exhibited greater impairments in performance and delayed performance recovery following distractor termination (Fig. 3; Young et al. 2007). Thus, similar to the performance of schizophrenic patients during periods of remission, baseline attention performance in AMPH-pretreated rats is stable in the absence of AMPH challenges. However, demands on top-down control reveal robust limitations in the capacity to maintain and recover attentional performance. The demonstration of such impairments in an animal model arguably is highly relevant for modeling disease-associated cognitive symptoms.

Abnormally high levels of prefrontal cholinergic activity mediate unimpaired attentional functioning during standard-task performance throughout periods of symptomatic remission. AMPH-pretreated animals exhibit normal attentional performance in the absence of AMPH challenges. However, performance-associated prefrontal ACh release in AMPH-pretreated animals is significantly higher than in normal animals (Kozak et al. 2007). Indeed, levels of ACh release in these animals resembled those observed in response to performance challenges that presumably evoke top-down mechanisms (Kozak et al. 2006). Therefore, we hypothesize that the unimpaired performance of the standard attention task by AMPH-pretreated animals

is mediated via elevated levels of attentional effort and top-down control. Again, we know that these abnormally high levels of ACh release are not a consequence of prior AMPH exposure per se as they are not observed in non-performing animals pretreated with AMPH (Kozak et al. 2007).

In AMPH-pretreated animals, the specific aspects of the performance of the standard attention task that necessitates top-down control are not clear. In control animals, cognitive mechanisms such as trial-type-specific processing of the task rules and the shifting of processing modes between trial types (intrinsic processing of task rules in non-signal trials versus sensory stimulus-evoked rule processing) may be executed rather automatically, akin to habits. In AMPH-pretreated animals, the determination of the signal status may involve more elaborate and less automatic processes and/or the capacity for the processing of the competing response rules may be limited. Forthcoming research designed to measure phasic cholinergic activity in AMPH-pretreated and task-performing animals will inform these speculations.

Cortical cholinergic neurotransmission during distractor-induced disruption of attentional performance

In AMPH-pretreated animals, augmented levels of performance-associated ACh release during standard-task performance are taken to indicate that such performance comes at high costs for attentional effort; the exquisite vulnerability of these animals' performance to distractors is consistent with this hypothesis. In vehicle-pretreated subjects, the distractor transiently impairs performance, reflecting the efficacy of top-down mechanisms. In contrast, in AMPH-pretreated animals, such additional demands more severely impair these animals' performance (as shown in Fig. 3).

The absence of evidence describing cortical cholinergic activity during distractor-induced disruption of attentional performance represents a significant empirical gap. However, the present framework allows the prediction of results with some confidence. As the distractors resulted in a severe impairment in performance in AMPH-pretreated animals that approached the level of impairment observed following AMPH challenges in these animals, and as a frozen cholinergic system is hypothesized to have caused the performance disruption that resulted from AMPH challenges (above), distractors likewise are expected to attenuate or "freeze" ACh release in AMPH-pretreated animals at baseline levels (Kozak et al. 2007; see Fig. 4). Furthermore, distractor effects on performance-associated ACh release in AMPH-pretreated animals are hypothesized to manifest on the basis of recruiting abnormally regulated prefrontal–mesolimbic–basal forebrain circuitry. Clearly, however, these mechanisms remain poorly understood.

Predictive validity: effects of low-dose haloperidol and clozapine during periods of remission

Evidence concerning the efficacy of treatments in reversing the distractor-induced disruption of performance is not available. With respect to standard attention task performance, semi-chronic treatment with low doses of haloperidol and clozapine did not affect the performance of AMPH-pretreated animals. However, AMPH-pretreated animals' performance was protected from the detrimental performance effects of clozapine that manifested in controls (Martinez and Sarter 2008). Detrimental effects of clozapine on cognitive performance of control animals have been rarely documented, in part because control groups treated with antipsychotic drugs were often not included in experiments in this field. However, several studies did report clozapine-induced impairments in attentional performance (Cheal 1984; Amitai et al. 2007). Likewise, there is little evidence describing the cognitive effects of clozapine in healthy volunteers. Olanzapine, however, was reported to disrupt attention in healthy subjects (Beuzen et al. 1999). We may speculate that the antimuscarinic properties of clozapine contributed to the detrimental performance effects of this drug in control animals

(Bymaster et al. 1996; Minzenberg et al. 2004), also because these effects resemble those observed following muscarinic receptor blockade (Bushnell et al. 1997). In attentional task performing, AMPH-pretreated animals, the augmented levels of cortical cholinergic activity required to maintain standard-task performance may be speculated to counteract these antimuscarinic effects of clozapine, thereby preventing clozapine-induced impairments in performance.

Conclusions

Table 2 summarizes the available evidence in support of the usefulness of the present animal model in terms of dissociating between the cognitive status during active disease periods and periods of remission.

Acute disease periods are modeled by AMPH challenges in AMPH-pretreated animals and are characterized by the loss of stimulus control as a result of, at least in part, a frozen cortical cholinergic input system (see Fig. 4). Treatment with low-dose antipsychotic drugs partly ameliorates this impairment. During periods of remission, normal attentional performance is mediated via abnormally high levels of ACh release that are hypothesized to indicate the abnormally high demands on attentional effort required to maintain normal performance. Consequently, the attentional capacities of AMPH-pretreated animals are extremely vulnerable to manipulations, such as distractors, that further tax prefrontal circuitry and the (top-down) processes required to support unimpaired levels of performance in these animals. The standard-task performance of AMPH-pretreated animals is not affected by antipsychotic-drug treatment; evidence concerning antipsychotic-drug effects on distractor-induced performance deficits and associated ACh release in AMPH-pretreated but not AMPH-challenged animals currently is not available.

Given the crucial role of cognitive load in revealing cognitive deficits in patients, particularly during periods of remission, it is perhaps to be expected that simpler behavioral tasks which, by definition, involve little cognitive control and little recruitment of prefrontal efferent circuits for top-down modulation of input functions do not effectively reveal the cognitive deficits of schizophrenia. Although there may be less effortful experimental means to produce abnormalities in the mesolimbic–telencephalic circuits that mediate the expression of cognitive symptoms, it may be of critical importance that repeated AMPH exposure consistently interacts with task-associated neuronal activity. Our evidence clearly indicates that, with regards to the regulation of cortical cholinergic inputs, the pathophysiological manipulation (i.e., AMPH pretreatment) remains ineffective if these circuits are inactive (in non-performing animals) during exposure to AMPH. As the manifestation of the cognitive symptoms of schizophrenia is likely to involve, perhaps necessarily, long-term interactions between dysregulated forebrain systems and cognitive activity, this aspect of the model may be considered additional support for its validity, rather than an aspect that complicates or even limits the usefulness of this model.

This review is guided by the general view that animal models of the cognitive symptoms of schizophrenia ideally dissociate between the cognitive correlates of acute versus chronic illness states. The available evidence suggests substantial dissociations between neurobiological mechanisms mediating the symptoms of the two major disease states. Animal models that dissociate between the symptoms of major disease states allow the test of differential psychopharmacological treatment approaches for the cognitive and non-cognitive symptoms of acute versus remitted states. The present model may assist in discovering and characterizing non-antipsychotic compounds that could be administered as adjunctive treatments to benefit the patients' cognitive abilities specifically during periods of remission.

The evidence and hypotheses summarized in Table 2 also reinforce the general view that non-dynamic, global hypotheses concerning the status of individual neurotransmitter systems in schizophrenia are of limited usefulness (Sarter et al. 2007). As stressed throughout this review, it is crucial that neurobiological hypotheses differentiate not only between disease states but more importantly the impact of demands on cognitive processes. In other words, it is plausible that conventional, global hypotheses concerning the role of a neurotransmitter system in schizophrenia (e.g., “too much dopamine”) will have to be replaced by hypotheses that not only specify the state of the neurotransmitter system during a particular disease state but also with respect to the specific cognitive target function and, finally, the demands on cognitive control.

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Fig. 1.

Illustration of the main events (**a**), response categories and outcome (**b**) of the sustained attention task, and illustration of performance data from sessions involving the presence and absence of a distractor (**c–h**). The task consists of a random sequence of signal and non-signal events that occur unpredictably following a variable ITI. Following a signal (center panel light illumination for 500, 50, or 25 ms) or a non-signal event, levers are extended into the chambers 2 s later and remained active for 4 s. In the version illustrated in **a**, following a signal, a left lever press is counted as a hit and rewarded (water port situated between the levers; not shown). Following a non-signal event, a right lever press indicated a “correct rejection” and is also rewarded. Incorrect responses are misses and false alarms, respectively, and trigger an ITI. An

error of omission is defined as the failure to operate a lever within 4 s. Note that *arrows* indicating the four responses are *color-coded* to match the *arrows* in the outcome matrix in **b**. Top-down control of attention is tested by the presentation of a distractor, requiring the recruitment of top-down effects designed to stabilize residual attentional performance (see text). The performance data shown in **c–h** depict performance over blocks of trials as, in this example, the distractor (chamber houselights flashing on/off at 0.5 Hz) was presented during the second block of trials only (standard task: *black lines, squares*; distractor condition: *orange lines, triangles*). As illustrated in **c** and **d**, the distractor reduced the relative number of hits to 500 and 50 ms signals in block 3, suggesting that as a result of distractor presentation, animals were not able to sustain levels of signal detection during the remainder of the task. For hits to shortest signals (**e**), floor effects prohibited the demonstration of the detrimental effects of the distractor. In contrast to the effects of the distractor on hits, the ability to respond correctly in non-signal trials was acutely disrupted by the distractor but completely recovered during block 3 (**f**). Errors of omission were not robustly affected by the distractor and generally remained below 10% of all trials, substantiating the persistent motivation of the animals to stay-on-task and to regain performance in response to distractor challenges (Sarter et al. 2006). The performance in signal and non-signal trials is collapsed into one measure of performance, the VI (**h**). VI values range from -1 to $+1$. Values of 0 indicate randomized lever selection (scores close to zero were seen in AMPH-pretreated animals challenged with AMPH; for formula and data, see Kozak et al. 2007), $+1$ indicates perfect response accuracy, and -1 indicates perfect inaccuracy. VI can be calculated for each signal duration (500, 50, 25 ms; $VI_{500,50,25}$) or averaged over all signal durations as shown in **h**. The VI scores shown in **h** illustrate that the overall performance of intact animals in the standard task declines over blocks of trials, further supporting the construct validity of this task (McGaughy and Sarter 1995). Moreover, this particular distractor robustly impaired overall performance and continued to impair performance during the third block of trials (no distractor).

Fig. 2.

Illustration of the AMPH-pretreatment regimen developed by Robinson et al. (Robinson and Camp 1987; Robinson et al. 1988; Paulson et al. 1991; Paulson and Robinson 1995) and employed in our experiments on the cognitive and neuronal consequences of AMPH pretreatment and on the attenuation of these effects by low-dose treatment with antipsychotic drugs (Martinez et al. 2005; Kozak et al. 2007; Martinez and Sarter 2008). The pretreatment regimen consists of twice daily administration of AMPH in accordance with an escalating-dosing regimen over 40 days. While not producing neurotoxic effects, this AMPH-pretreatment regimen results in long-term sensitization of the mesolimbic dopamine system, impairments in behavioral and cognitive functions (see text), and in a hypersensitivity of these functions to AMPH challenges. Animals are on-task during the pretreatment regimen, although they cease to perform after doses >2 mg/kg. During weekends, vehicle is administered to model the crashes that are typically observed in AMPH abusers and are known to foster AMPH-induced psychosis (see text). Additionally, attentional performance recovers partially during the drug-off days. Our evidence indicates that the long-term consequences of repeated, escalating AMPH treatment on cortical cholinergic neurotransmission cannot be reproduced in animals that underwent such pretreatment but did not perform the task. Attentional performance recovers during a 10–15-day post-pretreatment period, after which the effects of distractors, AMPH challenges, and putative therapeutic treatments are assessed

Fig. 3.

Effects of distractor challenges on the performance of AMPH-pretreated animals (Young et al. 2007) as indicated by $VI_{500,50}$ (see legend of Fig. 1 for an explanation of this overall measure of attentional performance). AMPH-pretreated animals performed equally to control animals during block 1. The distractor impaired the performance of all animals, with AMPH-pretreated animals exhibiting significantly greater impairments and incomplete performance recovery in block 3. Importantly, omissions do not enter the calculation of VI and remained generally low, suggesting the animals' continued motivation to stabilize and recover performance and achieve normal rates of reward delivery (see also Fig. 1g). Thus, in the absence of AMPH challenges,

demands on attentional effort and associated recruitment of top-down mechanisms (see text)
reveal robust impairments in attentional performance

Fig. 4.

Circuitry models describing the regulation of the prefrontal (*PFC*) cholinergic input system mediating the performance of the standard sustained attention task (*SAT*) by healthy subjects (**a**), the disrupted *SAT* performance during acute illness periods (**b**), and the “normal” *SAT* performance (**c**) and the augmented detrimental effects of distractors during remission periods (**d**). The models explain key findings discussed in the main text and incorporate hypotheses concerning the mesolimbic regulation of prefrontal acetylcholine (*ACh*) release, as well as the abnormal top-down control of the basal forebrain and afferent mesolimbic systems during different disease states. **a** In intact subjects, standard *SAT* performance requires increases in *PFC* *ACh* release by about 100–140% over baseline (see *insert*); such increases in cholinergic activity specifically are required for the detection of signals (e.g., Parikh et al. 2007). As top-down control of the basal forebrain and its afferent mesolimbic systems [projections from prefrontal regions to the basal forebrain and to mesolimbic regions (nucleus accumbens, *NAC*, and ventral tegmentum, *VTA*), which in turn innervate the basal forebrain] is assumed to play an only minimal and perhaps negligible role for *SAT* performance by healthy subjects, standard-task performance-associated increases in *PFC* *ACh* release is thought to be based primarily on bottom-up mechanisms, meaning that the signal per se evokes cholinergic activity via local mechanisms in the *PFC*. We demonstrated that in the *PFC*, increases in cholinergic activity require glutamate (*Glu*) release and glutamatergic ionotropic receptor stimulation (Parikh et al. 2008). Such glutamate release originates from thalamic, mediodorsal (*MD*)

afferents and is thought to “import” information about the signal to the PFC. This information does not concern the primary sensory representation of the signal but rather a signal-evoked “attentional searchlight”, a term that refers to a preattentive narrowing of the “place demanding attention”. The topographic projections from sensory cortical regions to the thalamic reticular nucleus (*TRN*), that in turn contacts MD neurons, underlie this preattentive processing of signals. The finding that attentional orienting is impaired following lesions of the *TRN* corresponds with this model (Weese et al. 1999). The *TRN* also receives cholinergic and non-cholinergic (not illustrated) inputs from the basal forebrain. The positive glutamatergic modulation of prefrontal cholinergic activity is necessary for normal signal detection and thus attentional performance. **b** As discussed in the main text, acute illness periods are associated with a severe disruption of attentional performance. The freezing of PFC ACh release at baseline causes such disruption. As the collective evidence is consistent with the hypothesis that mesolimbic dopaminergic (*DA*) activity is abnormally reactive during acute disease periods, and as NAC manipulations preferably affect PFC ACh release (e.g., Zmarowski et al. 2005, 2007), we hypothesize that basal forebrain cholinergic activity is robustly attenuated in part as a result of abnormally active dopaminergic afferents from the VTA and, indirectly, GABAergic afferents from the NAC. The basal forebrain may be further dysregulated by abnormal prefrontal output to mesolimbic regions and directly to the basal forebrain (not shown; Zaborszky et al. 1997). As a result of such freezing of basal forebrain activity, prefrontal ACh release remains at baseline and fails to support attentional performance. **c** During remission periods, standard (unchallenged) SAT performance is normal but mediated via abnormally high levels of PFC ACh release. The mechanisms underlying this finding remain unclear but are likely a result of abnormal levels of top-down control of the basal forebrain and its afferent mesolimbic systems (note that in contrast to the scenario described in **b**, in **c** such abnormal top-down activity does not interact with a hyper-responsive mesolimbic dopamine system). As discussed in the text, levels of prefrontal ACh release correlate with demands for top-down control, consistent with the hypothesis that during periods of remission, standard SAT performance requires abnormally high levels of top-down control. **d** During remission periods, attentional performance is extremely vulnerable to additional demands for top-down control, such as the presentation of distractors. The severity of the distractor effect allows the prediction that performance-associated ACh release levels will be close to baseline, similar to the scenario in **b**; however, this aspect of the model requires substantiation. As even standard SAT performance requires top-down control during remission periods, the additional challenge by distractors is speculated to reveal the abnormal interplay between dysregulated prefrontal output systems and abnormally reactive mesolimbic systems, yielding a result that may approach the freezing of the basal forebrain similar to the scenario described in **b**. The severity of the distractor-induced impairment in attentional performance, in patients and animals modeling remission periods (see main text), is consistent with an attenuated responsivity of the prefrontal cholinergic input system

Table 1

Cognitive effects of repeated AMPH administration

Species	Pretreatment regimen		Test time following pretreatment	Test	Challenge dose?	Results	Study
	Dose	Frequency	Duration				
Rhesus monkeys	0.1–1.0 ;mg/kg; i.m.; escalating	Twice daily; weekends off	6 or 12 ;weeks	>6 ;months	Delayed response; delayed non-match to sample	In selected cases; 0.4 ;mg/kg	Casner et al. (2005)
Rat	4.0 ;mg/kg; s.c.	Once daily	5 ;days	Immediately after	Associative blocking/selective attention	Testing took place on days 4 and 5 of the pretreatment	Crider et al. (1982)
Rat	1.0–5.0 ;mg/kg; i.p.	3× daily	6 ;days	Immediately after	Operant sustained attention	On day 7; 1.0 ;mg/kg	Kondrad and Burk (2004)
Rat	1.0–3.0 ;mg/kg; i.p.	3× per week	3 or 5 ;weeks	22 ;days	Prepulse inhibition	No	Tenn et al. (2003)
Rat	1.0–5.0 ;mg/kg; i.p.	3× per week	5 ;weeks	4 ;weeks	Attentional set shifting	No	Fletcher et al. (2005)
Rat	1.0–5.0 ;mg/kg; i.p.	3× per week	5 ;weeks	Testing took place during 5 ;weeks withdrawal	5-Choice serial reaction time	No	Fletcher et al. (2007)
Rat	1.0–10.0 ;mg/kg; i.p. escalating	Twice daily; weekends off	40 ;days	20 ;days	Operant sustained attention	None, 0.5 or 1.0 ;mg/kg	Martinez et al. (2005)
Rat	1.0–10.0 ;mg/kg; i.p. escalating	Twice daily; weekends off	40 ;days	>50 ;days	Operant sustained attention	None or 1.0 ;mg/kg	Kozak et al. (2007)
Rat	1.0–10.0 ;mg/kg; i.p. escalating	Twice daily; weekends off	40 ;days	35–55 ;days	Operant sustained attention	None or 1.0 ;mg/kg	Young et al. (2007)
Rat	1.0–10.0 ;mg/kg; i.p. escalating	Twice daily; weekends off	40 ;days	10–20 ;days	Operant sustained attention	None or 1.0 ;mg/kg	Martinez and Sarter (2008)

Data from studies involving neurotoxicity-inducing pretreatment regimen are not listed. Likewise, studies that explicitly addressed the cognitive correlates of psychostimulant withdrawal were not considered for this synopsis (except of studies that generated measures at >4 weeks since completion of the pretreatment regimen).

Table 2

Modeling the cognitive status during acute illness versus remission: attentional performance, performance-associated prefrontal ACh release, distractor challenges, and effects of low-dose treatment with clozapine or haloperidol

Measure/manipulation	AMPH challenge/acute illness period	Remission period
Level of attentional performance	Complete loss of cognitive control (responding not controlled by presence or absence of cues) ^{a,b,c}	Normal performance at baseline level ^{a,b,c}
Performance-associated ACh release in prefrontal cortex	Remains “frozen” at pretask baseline ^b	Abnormally high; augmented release levels mirror those in controls coping with distractors ^b
Effects of semi-chronic low-dose haloperidol on standard-task performance	Partial restoration ^c	No effects (irrespective of pretreatment condition) ^c
Effects of semi-chronic low-dose haloperidol on standard-task performance-associated ACh release	Performance effects predict partial restoration of performance-evoked increase in cortical ACh release ^d	No effects on performance; therefore, ACh release remains abnormally high to support normal performance ^d
Effects of semi-chronic low-dose clozapine on standard-task performance	Robust restoration of performance ^c	No effects (in contrast to impairments in vehicle-pretreated animals) ^c
Effects of semi-chronic low-dose clozapine on standard-task performance-associated ACh release	Predicted to restore performance-associated increases in cortical ACh release ^d	As (normal) performance remains unaffected in AMPH-pretreated animals, no effects on (abnormally high) levels of ACh release ^d
Distractor manipulation: effects on performance	No further impairment possible	Robust disruption of performance, comparable to distractor effects in animals with prefrontal cholinergic deafferentation ^e
Distractor manipulation: effects on performance-associated ACh release	No further attenuation possible; ACh release remains at pretask baseline	Performance effects predict attenuation of ACh release to levels close to pretask baseline ^d
Performance and cholinergic effects of semi-chronic low-dose antipsychotic treatment on distractor-induced challenges	No data, no basis for hypothesis	Partially attenuate the performance effects of distractor challenges by restoring recruitment of the cortical cholinergic input system ^d

^a Martinez et al. (2005)

^b Kozak et al. (2007)

^c Martinez and Sarter (2008)

^d Hypothesis (no evidence)

^e Young et al. (2007)