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Disruption of Performance in the 5-Choice Serial Reaction Time Task Induced by Administration of NMDA Receptor Antagonists: Relevance to Cognitive Dysfunction in Schizophrenia

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Abstract

Schizophrenia patients suffer from cognitive impairments that are not satisfactorily treated by currently available medications. Cognitive dysfunction in schizophrenia encompasses deficits in several cognitive modalities that can be differentially responsive to different medications and are likely to be mediated by different neurobiological substrates. Translational animal models of cognitive deficits with relevance to schizophrenia are critical for gaining insights into the mechanisms underlying these impairments and developing more effective treatments. The 5-choice serial reaction time task (5-CSRTT) is a cognitive task used in rodents that allows simultaneous assessment of several cognitive modalities, including attention, response inhibition, cognitive flexibility, and processing speed. Administration of *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonists disrupts multiple 5-CSRTT performance measures in a way that mirrors various cognitive deficits exhibited by schizophrenia patients. Some of these disruptions are partially attenuated by antipsychotic medications that exhibit partial effectiveness on cognitive dysfunction in schizophrenia, suggesting that the model has predictive validity. Examination of the effects of pharmacological manipulations on 5-CSRTT performance disruptions induced by NMDA antagonists have implicated a range of brain regions, neurotransmitter systems, and specific receptor subtypes in schizophrenia-like impairment of different cognitive modalities. Thus, disruption of 5-CSRTT performance by NMDA antagonists represents a valuable tool for exploring the neurobiological bases of cognitive dysfunction in schizophrenia.

Introduction

This article reviews the various measures provided by the 5-choice serial reaction time task (5-CSRTT) and discusses the cognitive constructs to which these measures correspond, their relevance to cognitive dysfunction in schizophrenia, and the effects of *N*-methyl-D-aspartate (NMDA) receptor antagonists on these measures. This review further addresses convergent and divergent findings from other cognitive tests assessing the same cognitive constructs. An overview of the evidence for the involvement of various neurotransmitters and brain circuits in NMDA antagonist-induced deficits in the 5-CSRTT is provided in Supplement 1. The focus of this review is on experimental findings from animal studies, with some discussion of relevant

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human studies to clarify the significance of the findings in animals to schizophrenia. Where not otherwise specified, the text refers to studies using rats as the experimental subject. A glossary of experimental procedures is provided in Table S1 (see Supplement 1); these terms appear in italics in the text.

Cognitive deficits in schizophrenia

Cognitive impairment is recognized as a core deficit of schizophrenia [1] and is highly correlated with functional impairment [2–4]. Currently available treatments often do not improve cognitive deficits in schizophrenia patients and may even aggravate them [5–7]. The newer atypical antipsychotic medications are widely considered to show greater promise for the improvement of cognition in schizophrenia than the older typical antipsychotics [6,8–10]. However, recent clinical trials suggest that both typical and atypical antipsychotics may confer limited cognitive benefits [11]. In any case, it is clear that all currently available medications produce at best a partial amelioration of symptoms that falls short of restoring normal functioning [3,11,12]. Improved understanding of the etiology of cognitive dysfunction in schizophrenia is needed to allow the development of more effective treatments for these deficits. For this purpose, the development and validation of translational animal models of cognitive deficits in schizophrenia, a shortage of which still exists [13], are crucially important.

Importantly, accrued evidence suggests that “cognition” cannot be treated as a unitary concept when investigating cognitive dysfunction in schizophrenia [14]. Schizophrenia patients exhibit deficits in a wide range of cognitive modalities, including attention [15], response inhibition and impulse control [16], cognitive flexibility [17], and processing speed [18]. Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), an interdisciplinary initiative by the National Institute of Mental Health aimed at developing new interventions for cognitive deficits in schizophrenia, compiled a list of cognitive performance dimensions affected in schizophrenia that includes at least eight separable cognitive domains [14]. Clinical studies indicate that antipsychotic medications differ in their effects on the various aspects of cognition in schizophrenia patients. For example, the atypical antipsychotic clozapine improves attention but has fewer or no effects on working memory [8,19]. The atypical antipsychotic risperidone, in contrast, improves working memory function in schizophrenia patients [4,8,19,20], as well as enhancing attention [21–23]. Moreover, animal studies assessing schizophrenia-like cognitive deficits revealed that novel compounds with potential procognitive effects show efficacy in tests of one cognitive modality but may be ineffective in tests assessing different cognitive functions. For instance, acute administration of agonists at Group II metabotropic glutamate receptors ameliorated working memory deficits induced by the psychotomimetic phencyclidine (PCP) [24] but did not improve or even exacerbated PCP-induced attentional deficits [25,26], preattentional gating [27–31], and verbal memory [32]. These observations emphasize the need for assessing a broad range of cognitive domains when examining potential treatments for cognitive dysfunction in schizophrenia.

NMDA receptor antagonists as an inducing condition in animal models of cognitive deficits with relevance to schizophrenia

Dysfunction of NMDA glutamate receptors has been suggested to be a likely contributor to schizophrenia pathophysiology, specifically to cognitive dysfunction in schizophrenia [33, 34]. Blockade of NMDA receptors by noncompetitive NMDA antagonists produces a schizophrenia-like state in healthy humans [35–46], and exacerbates the symptoms of schizophrenia patients [38,47–50]. Exposure to NMDA antagonists has emerged as a well-accepted inducing condition in tests of various aspects of schizophrenia-like deficits. Importantly, and most relevant to this review, administration of NMDA antagonists, such as PCP or ketamine, to healthy humans also induces profound disruptions of cognition [51],

including attentional deficits [52–57], cognitive inflexibility [56,58], and slowed processing speed [59]. Similarly, the exacerbation of schizophrenia symptoms after NMDA antagonist administration includes worsening of cognitive symptoms [50]. NMDA antagonist administration also disrupts cognitive performance in experimental animals, including rats, mice, and monkeys [25,60–108,109–137].

The best exposure regimen for inducing cognitive deficits with NMDA antagonists in experimental animal models has been a subject of some debate. Acute administration of NMDA antagonists has been successfully employed to induce schizophrenia-like cognitive deficits [25,60,61,64–67,69,83,84,96,100,109,111]. However, acute administration can also result in profound general behavioral disruption, such as ataxia and sedation, and motivational deficits that may confound cognitive test results [101,117,138,139].

Some studies avoid these problems by exposing animals to a subchronic regimen of NMDA antagonists, followed by a period of drug washout and measurement of cognitive effects in the drug-free state. (For the purposes of this review, the term “subchronic administration” is defined as a limited number, usually 5–15, of discrete administrations of a drug, given 1–2 times daily, while “chronic administration” is reserved for continuous delivery of a drug for several days, e.g. via an osmotic minipump.) Cognitive deficits have been observed after such NMDA antagonist treatments [62,63,68,70,78,86,87,89–93,105,107,108,110,118], though not in all cases [66,71,78,101,117,119,120,140]. There are reports of lasting cognitive deficits in humans chronically using phencyclidine or ketamine even after cessation of drug-taking [38, 43,141–145; but see 146,147]. However, the results of such studies are confounded by several factors, such as potentially pre-existing cognitive deficits in persons likely to abuse NMDA antagonists, as well as concurrent abuse of other psychoactive drugs by virtually all users of NMDA antagonists. For example, while Cosgrove and Newell observed cognitive deficits in chronic PCP users after 12 hours of abstinence from PCP, the PCP user group also reported significantly higher levels of alcohol drinking than the control group [145]. In studies where NMDA antagonists were administered under controlled conditions, both the schizophrenia-like state evoked in healthy subjects and symptom exacerbation induced in schizophrenia patients by NMDA antagonists were typically observed only during acute intoxication, not during withdrawal or post-drug [35,36,40,50–53,56–59,148–151]. Nevertheless, the possibility remains that long-term frequent administration of high doses of NMDA antagonists to humans (which cannot ethically be performed in controlled experimental settings) may result in enduring neuronal changes that lead to lasting cognitive impairments.

An alternative approach involves repeated treatment with an NMDA antagonist, followed by a drug-free period and then assessment of cognitive performance upon repeated re-exposure to the NMDA antagonist, with the drug on board (for the purposes of this review, this regimen will be referred to as “repeated administration”). Repeated PCP administration reduces or even eliminates ataxia and other behaviorally disruptive effects that are seen after the first PCP administration [101,117,138], and may also allow the development of a degree of tolerance to initial profound cognitive deficits induced by acute PCP, such that the animal can perform the cognitive task, thereby permitting the quantification of deficits. Upon re-challenge with additional PCP injections, selective cognitive impairments are observed [71,101,117,138]. This administration regimen therefore permits investigation of the schizophrenia-like cognitive deficits induced by the acute actions of NMDA antagonists, while avoiding the confounding effects of nonspecific behavioral disruption and excessive cognitive disruption induced by the first NMDA antagonist administration.

Different NMDA antagonist administration regimens may be better suited for modeling deficits in certain cognitive domains and less suited for other cognitive deficits. For example, subchronic NMDA antagonist administration followed by washout and testing in the drug-free

state appears to produce robust impairment of cognitive flexibility and disinhibition of impulsive responding, while its effects on attentional performance seem less consistent (see below). These differential effects are likely due to distinct neurochemical effects induced by the various NMDA antagonist administration regimens.

Of note, while numerous studies report the effects of single acute administrations of NMDA antagonists, many of these studies administer several doses of NMDA antagonists using a within-subjects design. While the experimental design of these studies generally includes several days of drug washout between drug administrations, profound carryover effects on cognitive performance after only 1–2 exposures even after washout periods of 10 days or more have been observed at least in the case of PCP [26,71,121,122]. Thus, the cognitive effects reported in studies nominally using a “single acute administration” design may be most reflective of the effect of repeated, though discontinuous, administrations of NMDA antagonists.

Finally, different species and strains may differ substantially in their sensitivity to NMDA antagonists. Therefore, treatment doses may vary significantly between studies using different experimental animals. While 5-CSRTT research has been conducted predominantly in rats, this review includes corroborating evidence from other species when such data are available, and discusses instances of strain differences in NMDA antagonist effects.

5-choice serial reaction time task

The 5-CSRTT was originally developed as a test of attention [152,153] based on Leonard’s choice reaction time task [154]. Some researchers have suggested that it constitutes a rodent analog of the continuous performance task (CPT) that is used to quantify attention in humans [155]; however, certain key differences to the CPT exist (see below). Numerous studies have demonstrated the construct validity of the 5-CSRTT as a test of attention [13]. Additionally, the 5-CSRTT provides measures of a number of other cognitive domains with relevance to schizophrenia, including response disinhibition/impulsivity, cognitive flexibility/compulsivity, and processing speed. Originally developed for rats, a mouse version of the 5-CSRTT has existed for some time [156,157].

The task requires the experimental animal to monitor five equidistant locations for the presentation of a visual stimulus (see Figure 1). The animal indicates detection of the stimulus by performing a nosepoke in the location where the light flash was presented. Trials are usually initiated by the animal via head entry into the reinforcer magazine. After the intertrial interval (ITI) elapses, a brief light is presented pseudorandomly in one of the apertures. Nosepokes performed in the location of the light stimulus during a fixed limited hold period (“correct responses”) are rewarded with a reinforcer, most commonly a food pellet for rats and liquid sweetened milk for mice. Nosepokes in a different aperture (“incorrect responses”) result in a brief timeout period, usually signaled by a change in lighting in the operant chamber (e.g., extinguishing the house light if the task is performed with lights on, or illuminating the house light if the task is performed with lights off), and no reinforcer delivery. Failures to make any nosepoke during the limited hold periods (“omissions”), nosepokes in any aperture made before presentation of the target stimulus (“premature responses”), continued nosepokes after a correct response but before collection of the reward (“perseverative responses”), or nosepokes during the timeout period (“timeout responses”) are also recorded and usually result in initiating or resetting of a timeout period. Finally, the latency of the animal to make a correct or incorrect response (“correct latency” and “incorrect latency”) and the time it takes the animal to retrieve the reinforcer (“reward latency”) are also recorded.

By allowing the simultaneous examination of multiple aspects of cognition, the 5-CSRTT offers a valuable tool for efficiently assessing the effects of various manipulations thought to

induce schizophrenia-like disruptions in different cognitive domains, as well as the effectiveness of various treatments on these disruptions. While the predictive validity of the 5-CSRTT for potential therapeutics for cognitive deficits in schizophrenia remains difficult to assess in the absence of well-established positive controls that treat cognitive symptoms, numerous studies have documented robust predictive validity of the 5-CSRTT for manipulations impairing or improving attentional performance across rodents and humans [13]. Moreover, a variety of manipulations can further extend the versatility of this task. For example, in addition to divided spatial attention, assessed by the requirement for the subject to simultaneously monitor five different potential stimulus locations, researchers can gauge sustained attention by increasing the number of trials in a challenge test session and comparing performance on earlier *vs*. later trials. Additionally, attentional load can be increased by using a variable ITI. This modification prevents the use of mediating strategies based on time estimation, which is possible with a fixed ITI duration, because the animal must attend to the apertures throughout the ITI instead of only during the short time window when the stimulus is expected to occur.

A recently developed modification of the 5-CSRTT addresses a major difference between the 5-CSRTT and the human CPT, namely, the absence in the 5-CSRTT of “non-signal” stimuli after whose presentation the subject needs to withhold responding to receive a reward. The newly developed 5C-CPT adds a condition in which all apertures are simultaneously illuminated; in these trials, the animal is required to withhold responding in any aperture to receive the reward [158]. The 5C-CPT therefore allows the assessment of inhibition of responding to irrelevant stimuli, a key component of the human CPT.

Attention: accuracy, correct and incorrect responses, and omissions

Attentional function is severely disrupted in schizophrenia [15]. Schizophrenia patients perform well below healthy controls in the CPT, a human attention task with some analogies to the 5-CSRTT [159–163]. The main measure of attentional performance in the 5-CSRTT is accuracy (sometimes also referred to as “percent correct responses”), defined as the total number of correct responses divided by the sum of correct and incorrect responses. Accuracy is a conservative measure of attention because it is independent of omissions. Consequently, this measure is relatively impervious to potential confounds such as sedation, locomotor impairment, or motivational changes.

In some cases, the stringency of the accuracy measure may preclude detection of attentional changes resulting from pharmacological or other manipulations. Animals with greater entrainment to respond to the light stimulus are more likely to withhold responding after failure to attend to the visual stimulus instead of ‘guessing’ which hole was lit, thus making an omission error instead of an incorrect response. Such omissions are particularly likely to occur when using mice as the experimental subjects, because mice appear to have better entrainment to the light stimulus compared to rats [13,164]. An increase in omissions, typically accompanied by a decrease in total correct responses, can therefore reflect a deficit in attention, even if accuracy is unaltered. Of course, such a pattern can also result from non-cognitive disruptions, such as sedation, locomotor impairment, or reduced motivation. However, inspection of other 5-CSRTT measures can often rule out these confounds. Reduced motivation for the food reward (e.g., because of feeding prior to testing in the task) reduces the total number of trials completed by the animal and the number of head entries into the collection magazine [165], as well as the latency to retrieve the reward [166]. Sedation or locomotor impairment would tend to increase response latencies and reward collection latencies in the task. Therefore, if 5-CSRTT omissions are increased and/or total correct responses are decreased without concomitant decreases in head entries into the magazine, decreases in completed trials, or

slowed latencies, it is likely that the disruptions reflect a true attentional deficit instead of motivational deficits, sedation, or locomotor impairment.

The above considerations illustrate a crucial point about the 5-CSRTT. It is critically important to consider the various parameters measured by the task in combination. While this review addresses different 5-CSRTT measures separately in the interest of clarity, the final interpretation of the effects of any manipulation on the 5-CSRTT should only be made after taking into account how *all* of the task measures are affected.

Administration of NMDA antagonists induces attentional deficits in the 5-CSRTT. Accuracy in the 5-CSRTT was decreased in rats after acute [67,96] or repeated administrations [71] of PCP (see Figure 2A), or acute administration of dizocilpine, another NMDA antagonist also referred to as MK-801 [83,167], at moderate doses (0.05–0.06 mg/kg). Acute low doses of dizocilpine (≤0.03 mg/kg) were without effect [84,168], and acute higher doses led to a significant increase in omissions without affecting accuracy, indicating a general, nonspecific behavioral suppression that affected correct and incorrect responses equally [123,168; but see 66,100]. Repeated administration of high doses (0.25 mg/kg) of dizocilpine did not produce attentional deficits in the 5-CSRTT when testing was conducted 24 h after drug administration [66]. This negative finding may indicate that attentional performance is less sensitive than other cognitive modalities to disruption by NMDA antagonist pretreatment in the absence of acute drug exposure, and is more robustly disrupted while the drug is on board. DBA, but not C57/BL6, mice also exhibited decreases in 5-CSRTT accuracy after acute PCP administration (see Figure 3A, D) [25]. However, 5-CSRTT accuracy was unaffected by acute ketamine administration in mice [124], mirroring the observation that ketamine does not reliably disrupt attention in humans [51,58,148,149,151], possibly because it has lower affinity and less selectivity for the NMDA receptor than PCP [169]. Chronic clozapine, an atypical antipsychotic with some effectiveness against attentional deficits in schizophrenia [8,19], attenuated disruptions in 5-CSRTT accuracy induced by repeated PCP [71] (see Figure 2A), indicating that this model may have predictive validity [170]. Further supporting this possibility, acute administration of haloperidol, a typical antipsychotic that is less effective against attentional deficits in schizophrenia [171–173], did not affect 5-CSRTT accuracy disruption induced by acute dizocilpine, while acute clozapine attenuated the deficit [66]. In contrast, chronic treatment with a different atypical antipsychotic, quetiapine, did not attenuate 5-CSRTT deficits induced by repeated PCP [122]. As discussed above, cognitive impairments respond differentially to different antipsychotic medications [8,19]. NMDA antagonist-induced disruptions in 5-CSRTT performance may be similarly differentially sensitive to different therapeutics. However, recent reports suggest that quetiapine may in fact improve attentional deficits in schizophrenia patients, although relatively few studies are available so far [174]. As stated above, conclusive assessment of the predictive validity of a model for cognitive schizophrenia deficits is complicated by the fact that documented ameliorative effects of any medication on these deficits remain limited and controversial.

At doses that decrease accuracy in the 5-CSRTT, PCP and dizocilpine induce hyperlocomotion in rats and mice [84,96,123,175]. These findings raise the question whether 5-CSRTT performance may have simply been disrupted by locomotor hyperactivity rather than a true attentional deficit. However, other manipulations that increase locomotor activity, such as amphetamine, leave accuracy in the 5-CSRTT unaffected [176]. Moreover, in most studies discussed here, latency to reward retrieval was unchanged and latency to correct response actually increased after NMDA antagonist exposure [71,84,96,100,167,168]. These findings suggest that potential increases in locomotor activity were not severe enough to lead to indiscriminate, rapid responding that disrupted performance. Importantly, the deficit in 5-CSRTT accuracy after intracerebral injection of 3-(*R*)-2-carboxypiperazin-4-propyl-1-phosphonic acid (CPP), a competitive NMDA antagonist, was significantly reduced when the

attentional load in the task was lowered by increasing the duration of the visual stimulus [177], suggesting that the observed decrease in accuracy was indeed attributable to impaired attention.

Disruption of attentional performance in the 5-CSRTT induced by NMDA antagonists mirrors the observation of similar disruptions in other attentional tasks after the same manipulation. Decreased attentional performance after acute administration of PCP or dizocilpine was observed in the *open-field stimulus object test* [76], *two-lever and three-lever choice tasks* [94,98], *lateralized reaction time task* [88], *lateralized visual signal detection task* [60,103, 104], and *operant ratio discrimination task* [64,65]. However, performance in the *lateralized visual signal detection task* was not altered after a period of withdrawal from repeated dizocilpine administration [120], again suggesting that attentional performance is less affected in the drug-free state after NMDA antagonist treatment than during acute drug exposure. Similar to the 5-CSRTT, single acute or repeated administration of ketamine did not affect attentional performance in the *lateralized visual signal detection task* up to doses that produced profound nonspecific performance disruptions [99], again pointing toward less reliable effects of ketamine on attentional performance.

Impulsivity: premature responses

Premature responses (sometimes also called “anticipatory responses”; i.e., nosepoke responses performed before presentation of the visual stimulus) are widely accepted as a measure of impulsivity in the 5-CSRTT [152,178–181], and reflect loss of impulse control and disinhibition of inappropriate responding. Some controversy exists regarding whether this type of impulsivity is strictly an aspect of cognition, or should be more properly considered a type of motor impulsivity [180,182]. Schizophrenia patients do exhibit impulsivity characterized by response disinhibition, exemplified by increased errors of commission on Go/No Go tasks or similar tests of response inhibition [16,183–186]. This disinhibition of impulsive responding correlates with impaired overall cognitive performance and other clinical symptoms [186–188], and exhibits similarities to premature 5-CSRTT responding. It should be noted, however, that 5-CSRTT premature responding constitutes failure to inhibit inappropriate responding before the presentation of any stimulus, while errors of commission on Go/No Go tasks or the human CPT reflect failure to inhibit inappropriate responding after the presentation of an irrelevant stimulus when responding should be inhibited. Recent findings suggest that these two types of response inhibition may be differentially mediated [J. W. Young, personal communication].

Most versions of the 5-CSRTT “punish” premature responses with a timeout period, during which the animal is unable to initiate a new trial or otherwise perform the task [152]. Some researchers, however, use a version of the task in which premature responses are merely recorded and have no consequences for the animal [189,190]. This alteration of the task changes the nature of premature responses, because it decreases the incentive for the animal to withhold premature responding. However, a literature overview shows very similar effects of NMDA antagonist administration on both punished or unpunished premature responses. Furthermore, while the original version of the 5-CSRTT requires the animal to initiate each trial through a head entry into the reward magazine [152], some studies employ a version of the task in which new trials start automatically; that is, the ITI begins directly after a correct or incorrect response or at the end of the limited hold period [189,190]. This version of the task does not allow a distinction between premature responses and another 5-CSRTT measure, perseverative responses (discussed below). Instead, any responses that occur during the ITI (which, in this version of the task, encompasses any time period other than stimulus presentation or limited hold) are recorded as “anticipatory responses” or “inappropriate responses.” This lack of distinction is not optimal for the assessment of the effects of NMDA antagonists because

evidence suggests that premature and perseverative responses reflect different aspects of response inhibition that have been shown to be dissociable by pharmacological and other manipulations (see below).

Premature responding in the 5-CSRTT is increased by exposure to NMDA antagonists. Single or repeated administration of PCP increased premature responses in the 5-CSRTT in rats (see Figure 2B) [71,96; but see 67] and mice (see Figure 3B, E) [25]. At doses that disrupted accuracy (0.05–0.06 mg/kg), acute administration of dizocilpine also increased premature responses in the 5-CSRTT [83]. Decreases in accuracy and increases in premature responding sometimes co-occur in the 5-CSRTT [179], and it may be argued that the decreases in attention observed after these doses of PCP and dizocilpine were secondary to disruption of task performance by excessive premature responding. However, a number of studies have shown that effects on accuracy and premature responding can be dissociated [25,176,189,190]. Increases in premature responding without concurrent effects on accuracy have been observed after acute administration of a low dose of dizocilpine (0.03 mg/kg) in some studies [84; but see 83,123]. Higher doses induced general, nonspecific behavioral disruption [123,168; but see 66,100]. Increases in premature responses were also observed after acute ketamine administration in CD1, but not C57/BL6, mice [124]. Similar to PCP-induced decreases in accuracy, chronic or acute clozapine, but not acute haloperidol, attenuated the increase in premature responses induced by repeated PCP [71](see Figure 2B) or single acute administrations of dizocilpine [66] in the 5-CSRTT.

Increases in impulsive responding were also observed after single acute or repeated PCP administration, as well as acute dizocilpine administration, during *differential reinforcement of low rates (DRL)* in rats [75,84,85,109,123,125–131] or mice [81,132,133]. Acute administration of PCP also increased impulsive responding in the *lateralized reaction time task* in rats [88]. Subchronic administration of PCP, followed by several days of drug washout, delayed *extinction of operant responding* and increased *responding for a conditioned reinforcer* in rats [91], and increased impulsive responding in the *object retrieval/detour task* in monkeys [89,90,92,118], indicating that impulsivity may be more reliably observed in the drug-free state after NMDA antagonist treatment than attentional deficits. Acute ketamine administration did not affect *DRL* performance in rats [134]. It is possible that impulsivity, like attentional disruption, is less reliably induced by ketamine than by PCP or dizocilpine; however, the paucity of studies investigating ketamine effects on impulsive responding does not permit definite conclusions.

Cognitive flexibility: perseverative responses

Perseverative responses, defined as continued nosepokes after a correct response has been performed, are considered an indicator of compulsivity. Cognitive inflexibility, i.e. the inability to alter behavior in reaction to changing situational demands, is hypothesized to contribute to compulsivity [191]. Because perseverative responses constitute persistence in an initially rewarded behavior (nosepoke) despite the fact that it is no longer rewarded, they are often considered a measure of cognitive inflexibility [192]. Cognitive inflexibility is a characteristic deficit in schizophrenia [193–199; but see 200].

The interpretation of perseverative responses as an indicator of cognitive inflexibility assumes that perseverative nosepokes occur in the same aperture as the initial correct responses, thus constituting repeated maladaptive enactment of a previously rewarded action. Unfortunately, 5-CSRTT studies do not typically record the actual aperture in which perseverative responses occur. However, informal observations in the authors' laboratory suggest that, indeed, perseverative responses are usually made in the same aperture as the original correct response. Different versions of the 5-CSRTT either record perseverative responses without consequences

for the animal or punish them with a timeout. The latter option means that only one perseverative response can be recorded per trial, even if the animal performs a large number of repetitive nosepokes, because the initial perseverative response triggers the timeout period and any remaining nosepokes are recorded as timeout responses. This may lead to underestimation of perseveration.

Acute administration of PCP or dizocilpine increased 5-CSRTT perseverative responses in rats [83,84,96,123]. Acute administration of PCP also increased perseverative responses in DBA, but not C57/BL6, mice (see Figure 3C, F) [25], while acute ketamine increased perseverative responses in C57/BL6, but not CD1, mice [124]. Increases in perseverative responding sometimes coincided with decreases in 5-CSRTT accuracy [25,83,96,123], but were also observed at doses that did not affect accuracy, omissions, or response latencies [84,96,124]. Importantly, although NMDA antagonists often increased both premature and perseverative responding [83,84,96,123], effects on the two types of disinhibited responding could be dissociated. For example, while acute PCP did not affect perseverative responses in C57/BL6 mice in a study by Greco and coworkers, the same doses increased premature responses (see Figure 3C, F) [25], suggesting that different mechanisms of inhibitory response control may be implicated. Similarly, although acute administration of ketamine increased perseverative responses in C57/BL6 mice, premature responses remain unaffected in these mice; conversely, acute ketamine increased premature responses, but not perseverative responses, in CD1 mice [124].

In other tasks assessing compulsivity and cognitive flexibility, NMDA antagonists also induced performance disruption indicative of increased perseveration. Such deficits were observed in the *reversal learning task* in rats after single or repeated administration of PCP [61,69,77,87], or during the drug-free state following subchronic PCP [68,70,72,86,91,108] or ketamine [140] administration. However, it should be noted that one study using acute dizocilpine found impairments in *reversal learning* only at doses that also disrupted simple odor discrimination [82]. The *extradimensional shift* phase of the *set shifting task* was likewise disrupted during the drug-free state after PCP administered subchronically [62,63,105,107,110,115], chronically [116], once 24 hours before testing [79], or postnatally [114,115], though not after withdrawal from subchronic ketamine treatment [140]. Similar deficits were seen in the *set shifting task* in rats given an acute administration of dizocilpine [111] and mice given repeated PCP [95]. Perseverative errors were also observed in the *repeated acquisition task* after acute administration of PCP or dizocilpine to rats [74,113] or monkeys [73,80], and in the *object retrieval/detour task* after a period of withdrawal from subchronic PCP administered to monkeys [89,90,92].

The persistent increase in perseverative errors in a variety of tasks in the drug-free state after NMDA antagonist treatment in both rats and monkeys [62,63,68,70,[72],[79],[86],[89–92],[105],[107],[108],110,115,116,140] suggests that this administration regimen reliably induces some types of cognitive inflexibility, and may be expected to increase perseverative responding in the 5-CSRTT also. However, one study found no impairment of *reversal learning* after a period of withdrawal from subchronic PCP exposure in mice [119], possibly indicating that this species is less sensitive to this manipulation. A similar PCP regimen also produced no disruption in the *fixed/variable goal location task* in rats [78]; this task may be less suited to detect cognitive deficits induced by subchronic NMDA antagonist treatment. Increases in perseverative errors in both the 5-CSRTT [124] and other tasks [140] after ketamine treatment suggest that cognitive flexibility may be more susceptible to disruption with ketamine than attention.

Cognitive flexibility/stimulus control: timeout responses

Timeout responses (i.e., nosepokes made during the timeout interval) are not as well studied as other 5-CSRTT parameters. Unfortunately, most studies do not even report this measure. Timeout responses constitute continued responding past the point when responding is no longer rewarded, and thus may represent an additional measure of compulsivity related to cognitive inflexibility. Indeed, as outlined above, when perseverative responses are punished by a timeout period, the majority of perseverative responses may be recorded as timeout responses. This may explain why, in studies performed in our laboratory, repeated PCP administration did not increase perseverative responding but significantly increased timeout responding [26, 71,121,122]. In addition, the measure of timeout responses may record disorganized responses during the timeout that are not tied to stimulus presentation. Such responses may reflect a loss of stimulus control over responding. Timeout responses could therefore constitute a measure of stimulus control impairment, especially in studies that do not punish perseverative responding (thus reducing the influence of perseveration on the number of timeout responses recorded). To better assess this possibility, 5-CSRTT response patterns could be analyzed to determine whether timeout responses in a given experiment occur in close temporal and/or spatial proximity to the stimulus, or are largely unrelated to stimulus presentation.

Like perseverative responses, timeout responses appear to reflect a different aspect of response disinhibition than premature responses. Chronic clozapine treatment, at doses that successfully attenuated increases in premature responding induced by repeated PCP administration, did not affect the PCP-induced increases in timeout responding [71]. Conversely, chronic treatment with a metabotropic glutamate receptor antagonist attenuated increases in timeout responding induced by repeated PCP, but did not affect increases in premature responding [26] (see Supplement 1).

Speed of processing: response latencies

The average latency of the animal to make a correct response in the 5-CSRTT represents a measure of its processing speed in the task, as long as motor slowing or lack of motivation is ruled out. Increases in correct response latency in the absence of changes in another latency measure, the average latency to retrieve the reward, suggest that the animal's locomotor function and motivation for the reward are unaffected; such a pattern of effects is therefore likely to reflect a true slowing of processing speed. The average latency to make an incorrect response is rarely reported, because it is generally affected similarly to the latency to a correct response [26,71,121,122], despite exhibiting somewhat less reliable drug effects [176].

Increases in correct response latency in the 5-CSRTT, without alteration of reward latency, were observed after single or repeated PCP administration [67,71,96]. In contrast, one study found *decreases* in latency to a correct response after an acute low dizocilpine dose (0.03 mg/kg) [83] with no effect on other 5-CSRTT measures, suggesting that the decrease in correct response latency was not simply due to a gross increase in locomotor activity. These results may therefore indicate that the effects of NMDA antagonists on processing speed are dose-dependent, with low doses subtly enhancing processing speed. Indeed, increases in the latency to a correct response in the 5-CSRTT were found after administration of an acute high dose of dizocilpine (0.25 mg/kg), as well as in the drug-free state after subchronic dizocilpine administration [66]. However, during withdrawal from subchronic dizocilpine treatment, reward latencies were also significantly increased; therefore, nonspecific locomotor impairment cannot be ruled out in this case.

Single acute or repeated PCP administrations also increased response latencies in a number of other cognitive tasks, including the *three-lever choice task* [94] and the *reversal learning task* [77]. Acute administration of ketamine tended to increase response latency in a *simple*

reaction time task in monkeys [112]. Increases in response latency were also found after acute dizocilpine administration in the *lateralized visual signal detection task* [103,104].

Conclusion

In summary, NMDA antagonist administration induces a number of disruptions of performance in the 5-CSRTT with relevance to cognitive dysfunction in schizophrenia, including impaired attention, increased impulsivity, cognitive inflexibility, and slowed processing speed. These deficits are partially responsive to treatments that show some effectiveness in ameliorating cognitive schizophrenia symptoms, suggesting that NMDA antagonist-induced disruption of 5-CSRTT performance has predictive validity as an animal model of cognitive disruptions in schizophrenia.

Investigation of neurochemical changes after NMDA antagonist administration, and examination of the effects of various neurotransmitter manipulations on NMDA antagonist-induced disruption of 5-CSRTT performance, have implicated a number of brain areas and neurotransmitter systems in schizophrenia-like cognitive deficits as assessed by the 5-CSRTT. These findings are discussed in the Supplement 1, and summarized in Tables S2 and S3.

Disruption of 5-CSRTT performance via NMDA antagonist administration therefore presents a promising model of cognitive dysfunction that may be used to: (*i*) explore the role of different brain circuits and neurotransmitter systems in the cognitive symptoms of schizophrenia, (*ii*) ensure benign cognitive profiles of novel antipsychotic medications, and (*iii*) investigate the effectiveness of proposed procognitive treatments for schizophrenia patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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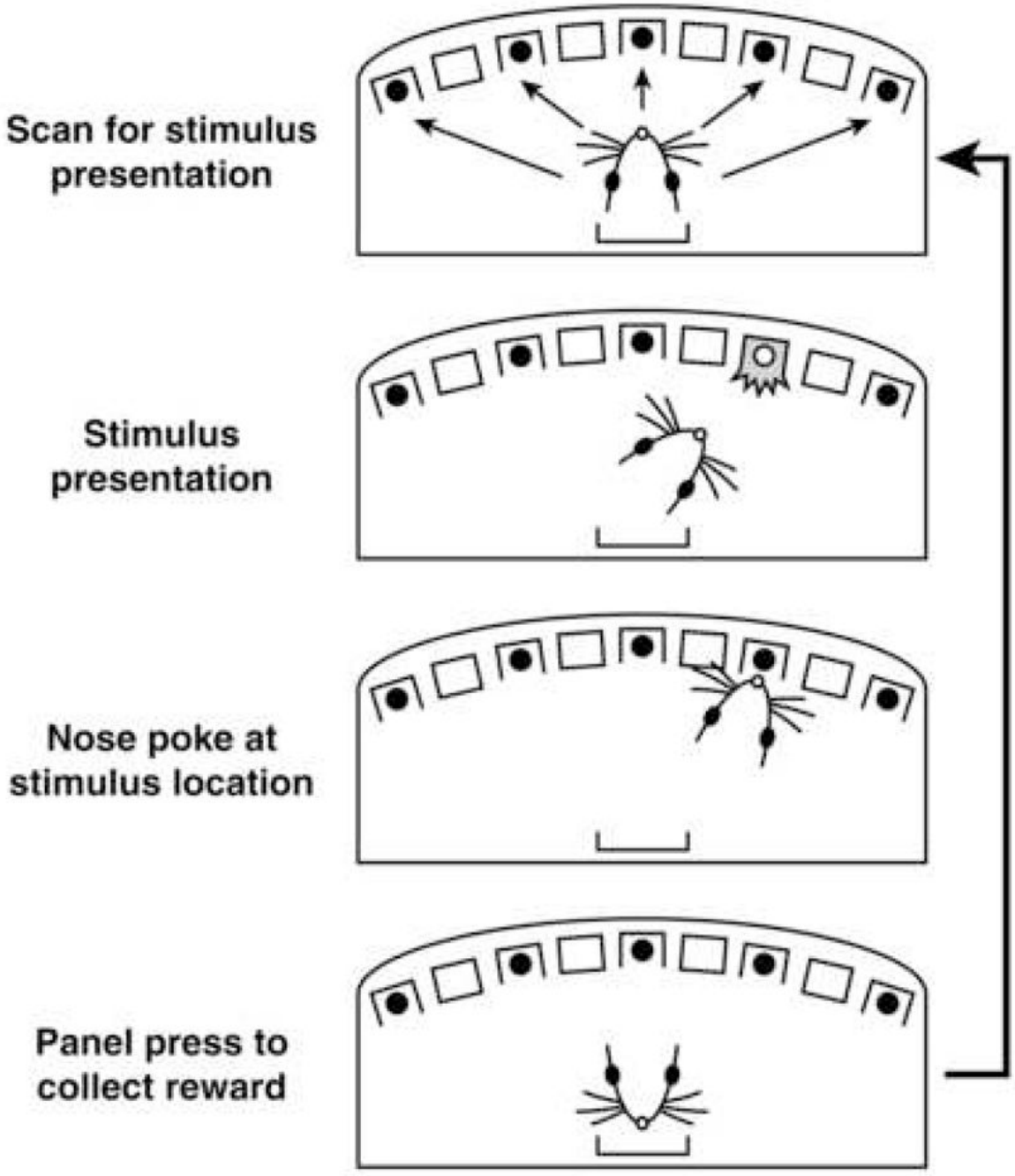

Figure 1.
Schematic of a rat's performance in the 5-choice serial reaction time task.

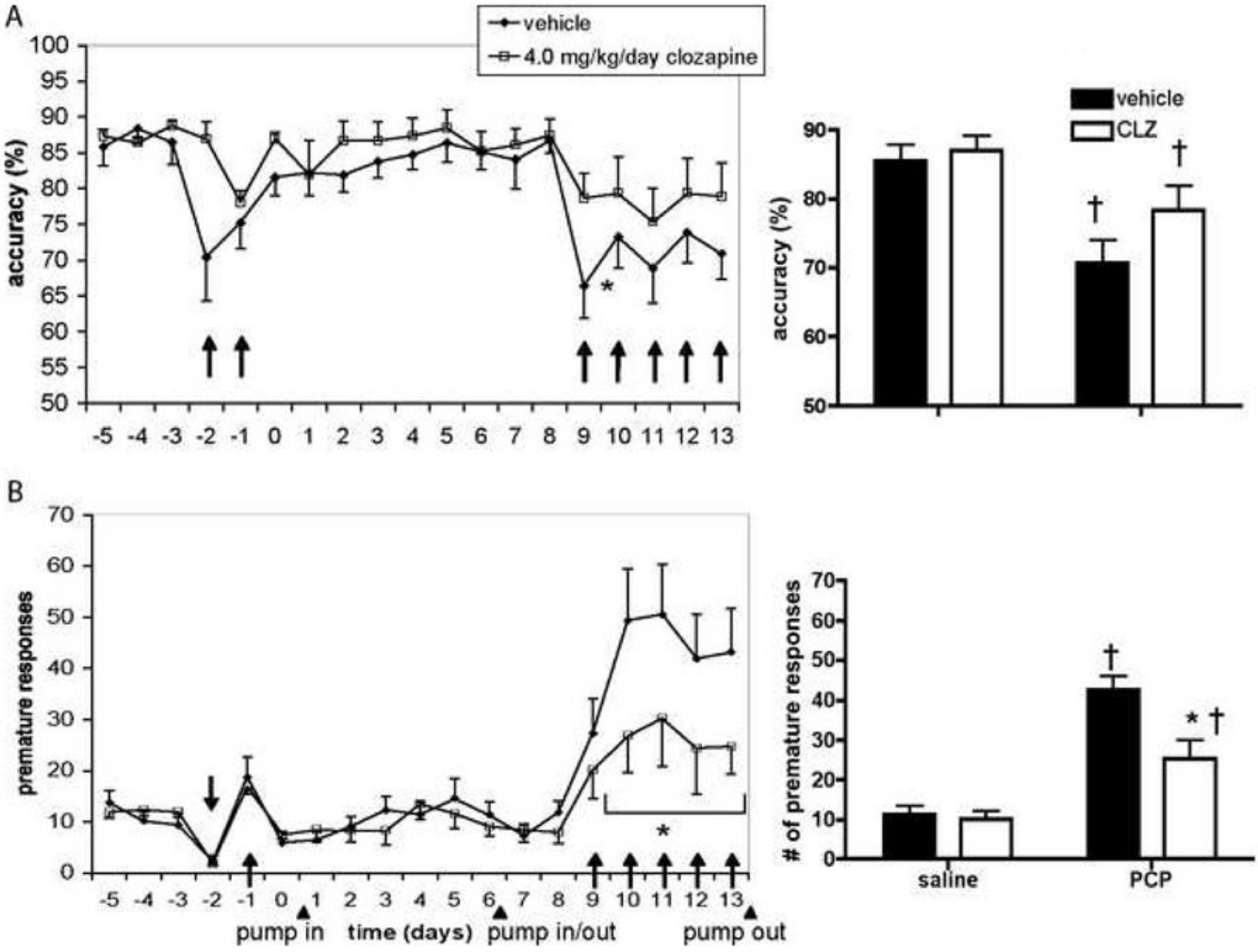

Figure 2.

Effects of chronic clozapine treatment on 5-CSRTT performance disruption induced by repeated PCP. Accuracy (A) and premature responses (B) are shown as mean±SEM. *P<0.05 vs. vehicle group; †P<0.05 vs. performance after saline injections; ↑ or ↓ indicates a PCP injection. CLZ = clozapine; pump in/out = beginning/end of chronic clozapine treatment via subcutaneous minipumps. Adapted from [71], © *Springer-Verlag 2007*, with kind permission from Springer Science+Business Media.

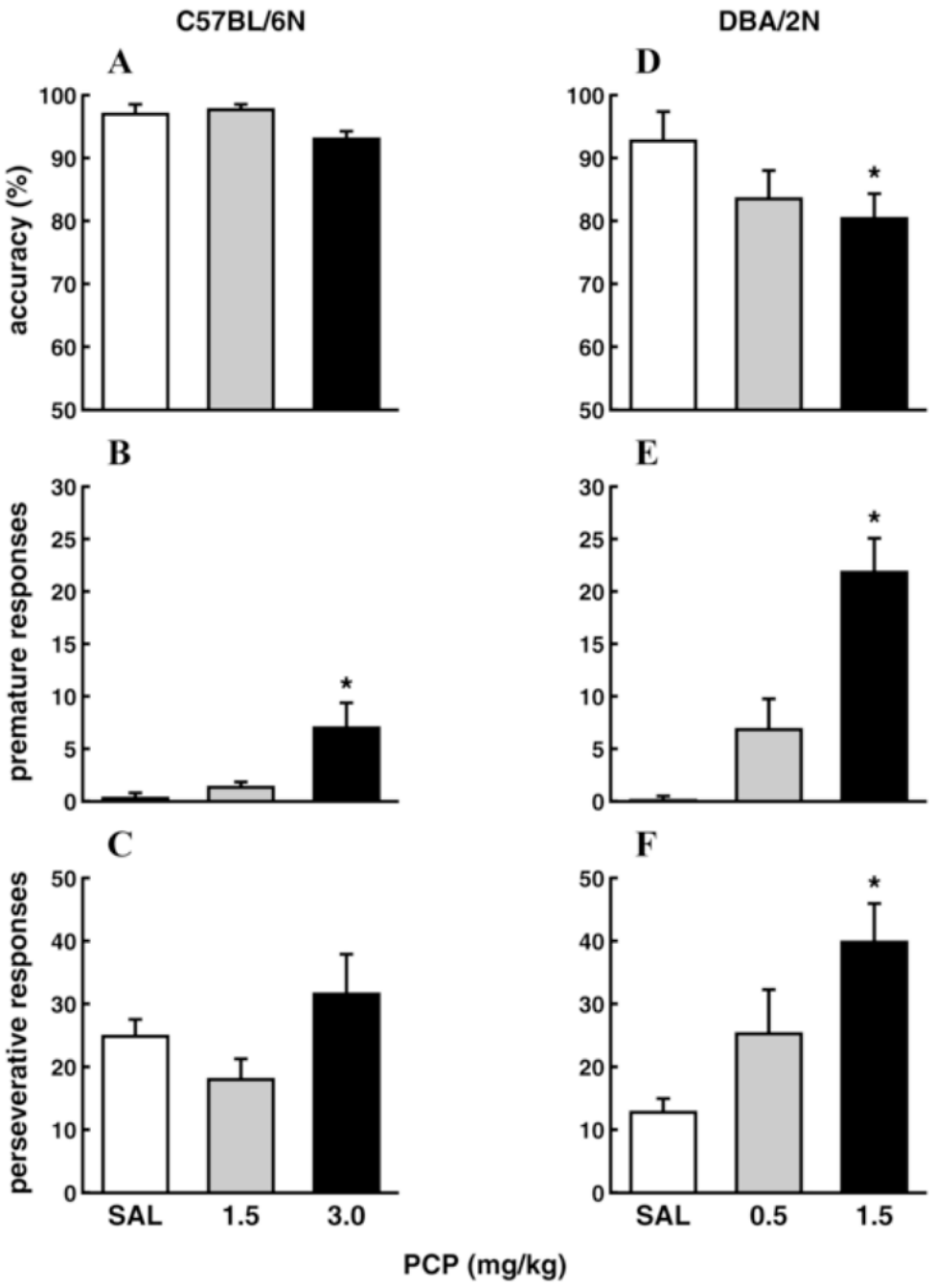

Figure 3.

Effects of PCP on 5-CSRTT performance of C57BL/6N and DBA/2N mice. Accuracy (A), premature responses, (B) and perseverative responses (C) of C57BL/6N mice are shown as mean±SEM; (D), (E), (F) same parameters in DBA/2N mice. *P<0.05 vs. saline group. SAL = saline. Adapted from [25], © *Springer-Verlag 2005*, with kind permission from Springer Science+Business Media.