Disruption of Performance in the Five-Choice Serial Reaction Time Task Induced By Administration of *N*-Methyl-D-Aspartate Receptor Antagonists: Relevance to Cognitive Dysfunction in Schizophrenia

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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 five-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.

Key Words: 5-Choice serial reaction time task, animal model, cognition, NMDA receptor antagonists, schizophrenia

This article reviews the various measures provided by the five-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 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 in 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 might 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 might 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, 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 enhances 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 might be ineffective in tests assessing different cognitive functions. For instance, acute administration of agonists at Group II metabotropic glutamate

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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 might 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, whereas "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) although not in all cases (66,71,78,101,117,119,120,140). There are reports of lasting cognitive deficits in humans chronically using PCP 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 preexisting 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, although 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 and not during withdrawal or postdrug (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) might 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 might 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 rechallenge 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 might 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 seems to produce robust impairment of cognitive flexibility and disinhibition of impulsive responding, whereas its effects on attentional performance seem less consistent (see following text). These differential effects are likely due to distinct neurochemical effects induced by the various NMDA antagonist administration regimens.

Of note, although numerous studies report the effects of single acute administrations of NMDA antagonists, many of these studies administer several doses of NMDA antagonists with a within-subjects design. Although 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 for PCP (26,71,121,122). Thus, the cognitive effects reported in many studies nominally using a "single acute administration" design might be most reflective of the effect of repeated although discontinuous administrations of NMDA antagonists.

Finally, different species and strains might differ substantially in their sensitivity to NMDA antagonists. Therefore, treatment doses might vary significantly between studies using different experimental animals. Although 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.

Five-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 analogue of the continuous performance task (CPT) that is used to quantify attention in humans (155); however, certain key differences to the CPT exist (see following text). Numerous