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The nicotinic α7 receptor agonist GTS-21 improves cognitive performance in ketamine impaired rhesus monkeys

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ABSTRACT

The cognitive deficits associated with schizophrenia are recognized as a core component of the disorder, yet there remain no available therapeutics to treat these symptoms of the disease. As a result, there is a need for establishing predictive preclinical models to identify the therapeutic potential of novel compounds. In the present study, rhesus monkeys were trained in the object retrieval-detour task, which is dependent on the prefrontal cortex, a brain region implicated in the cognitive deficits associated with schizophrenia. The NMDA receptor antagonist ketamine significantly impaired performance without affecting measures of motor or visuospatial abilities. Pre-treatment with the nicotinic α7 agonist GTS-21 (0.03 mg/kg) significantly attenuated the ketamine-induced impairment, consistent with reports from clinical trials suggesting that nicotinic α7 receptor agonism has pro-cognitive potential in clinical populations. In contrast, pretreatment with the acetylcholinesterase inhibitor donepezil failed to reverse the ketamine-induced impairment, consistent with studies showing a lack of pro-cognitive effects in patients with schizophrenia. These data suggest that the ketamine-impaired object retrieval-detour task could provide a model with improved predictive validity for drug development, and confirm the need for additional efforts in back-translation.

This article is part of a Special Issue entitled 'Cognitive Enhancers'.

1. Introduction

Schizophrenia affects approximately seven individuals per 1000 (McGrath et al., 2008), and although the diagnostic criteria include a variety of symptoms, cognitive deficits impacting attention, executive function, and memory have become increasingly recognized as key components of the disorder (Elvevag and Goldberg, 2000; van Os and Kapur, 2009; Burdick et al., 2011; Goff et al., 2011). The importance of cognitive impairment has led to highly collaborative scientific movements such as the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) and the subsequent Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS), to guide research and therapeutic development, including an increased focus on improving the predictability of preclinical models (Marder et al., 2004; Buchanan et al., 2005; Carter et al., 2008).

In the present series of experiments, the object retrieval-detour (ORD) task was characterized in the rhesus monkey for its sensitivity to putative cognition enhancers for schizophrenia. The ORD task has been demonstrated to primarily rely on the prefrontal cortex (PFC) (Diamond and Goldman-Rakic, 1985; Diamond et al., 1989; Diamond, 1990; Dias et al., 1996; Wilkinson et al., 1997; Jentsch et al., 1999a,b, 2000), a brain region implicated in the cognitive disturbances associated with the disease (Minzenberg et al., 2009), and is dependent on cognitive functions such as strategy formation, attention, and response inhibition. Specifically, the task assays these domains by requiring the subject to ignore visual and tactile stimuli, recall the previous failed reach, and develop a revised reach strategy to obtain a food reward. The direct neuroanatomical evidence that the ORD task relies on PFC-mediated circuitry springs from studies demonstrating that lesions to the prefrontal cortex, but not the hippocampus, impaired performance on this task (Diamond et al., 1989; Wilkinson et al., 1997). Other brain regions might also be involved in ORD task performance, as treatment with MPTP (Taylor et al., 1990a,b; Schneider and Roeltgen, 1993), phencyclidine (Jentsch et al., 2000; Jentsch et al., 1999a; Jentsch et al., 1999b), and striatal excitotoxic lesions (Roitberg et al., 2002) have also shown to impair performance on the ORD task. Evidence that N-methyl-d-

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aspartate (NMDA) receptor hypofunction might underlie schizophrenia (Goff et al., 2011) is founded in reports that NMDA antagonists such as ketamine and phencyclidine exacerbate symptoms in schizophrenic patients and induce schizophrenic-like symptoms (including cognitive impairment) in healthy individuals (Lahti et al., 1995; Rowland et al., 2005). Thus, the effects of ketamine in the ORD task were first characterized.

In order to further characterize the ORD task, we next examined whether the ketamine-induced deficit could be attenuated by a pro-cognitive agent relevant to schizophrenia. Unfortunately, positive controls for establishing translatable predictive models are lacking as there are no marketed treatments targeting the cognitive deficits associated with the disease. As such, we chose to evaluate the effects of the nicotinic α7 receptor agonist GTS-21 (DMXB-A; 3-[(3E)-3-[(2,4-dimethoxyphenyl) methylidene]-5,6-dihydro-4H-pyridin-2-yl]pyridine], as data exists indicating its therapeutic potential. Schizophrenics are reported to have smoking rates dramatically higher than the general population (Ripoll et al., 2004), leading to the theory that patients utilize nicotine as a form of self-medication (Dalack et al., 1998; Ripoll et al., 2004). Schizophrenics also have decreased nicotinic α7 receptor levels in various brain regions associated with cognition, including the hippocampus and cingulate cortex (Freedman et al., 1995; Marutle et al., 2001; Severance and Yolken, 2008). Preclinically, GTS-21 has demonstrated effects in rodent and non-human primate (NHP) measures of learning and memory (Arendash et al., 1995; Buccafusco and Terry, 2009). However, the predictive validity of the preclinical assays used to demonstrate pro-cognitive effects of GTS-21 is a matter of debate, given the concern around the number of compounds that demonstrate efficacy in preclinical models which then fail clinically (Geyer and Markou, 1995; Markou et al., 2009; Young et al., 2009; Millan et al., 2012). Nevertheless, clinical reports also suggest that activation of the nicotinic α7 receptor with GTS-21 might improve performance in various cognitive domains (Olincy et al., 2006; Freedman et al., 2008), increase inhibition of the P50 response (Olincy et al., 2006), and alter default network activity in schizophrenic populations (Tregellas et al., 2011). While these data speak to the compound's therapeutic potential, the ultimate clinical efficacy and relevance of GTS-21 is unclear and remains matter of ongoing investigation (Freedman et al., 2008). Given these circumstances and the lack of a clinically validated positive control, we chose to evaluate the effects of GTS-21 in the presence of ketamine in the ORD task to assess this model's sensitivity to cognitive enhancers and further characterize the potential therapeutic value of this compound.

Finally, to examine the specificity and validity of the ketamine-impaired ORD task for identifying schizophrenia-specific cognitive enhancers, the acetylcholinesterase (AChE) inhibitor donepezil was tested as a negative control. Although AChE inhibitors are the clinical standard for treating cognitive impairment associated with Alzheimer's disease, they have generally been reported as ineffective for treating the cognitive impairment associated with schizophrenia (Friedman et al., 2002; Akhondzadeh et al., 2008; Dyer et al., 2008; Keefe et al., 2008; Lindenmayer and Khan, 2011), particularly in terms of affecting measures of executive function (Chouinard et al., 2007). Therefore, we predicted that GTS-21, but not donepezil, would improve the ketamine-induced deficit in the ORD task.

2. Methods

2.1. Subjects

Seven single-housed, male rhesus macaques (*Macaca mulatta*), 4–6 years old, ranging 6.5–9.5 kg, participated as subjects in this series of experiments. Subjects were maintained on a 12 h light cycle (6300–1830 h) with room temperatures sustained at 22 ± 2 °C. Testing was performed in each subject's home cage, between 1200 and 1500 h. Subjects were fed their full daily regimen of food (Purina High Protein Monkey Diet no. 5045) post-test at 1500 h, and water was available ad libitum. In addition to their chow, monkeys were given a variety of fresh fruits and vegetables daily. Principles from the *Guide for the Care and Use of Laboratory Animals*, National Institute of Health, and USDA were followed, and all protocols were approved by the Merck Institutional Animal Care and Use Committee.

2.2. The ORD task

The ORD task was conducted in the same manner as described in previous literature (Diamond et al., 1989; Taylor et al., 1990a,b). The task requires subjects to retrieve a food object (diced apple square, ~1 × 1 in.) from a clear acrylic box with a single open plane. Sessions consisted of a fixed arrangement of "easy" ($n = 8$) and "difficult" ($n = 9$) trials. In easy trials, the reward was positioned either (1) inside the box, with the open plane directly in the line of sight of the subject, (2) slightly protruding from the box with the open plane to the left or right of the subject, or (3) just inside the box with the open plane either to the left or right of the subject (see Fig. 1). Although performance on easy trials is not considered a measure of executive function, it was used to detect potential adverse events under drug conditions, such as drug-related motor or visuospatial impairment. For difficult trials, the reward was placed deep inside the box, opposite the open plane with the open plane to the left or right of the subject. Difficult trial performance was used as the dependent measure for assessing executive function.

Trials were scored "correct" if subjects successfully reached into the open plane of the box and retrieved the reward on their first attempt. Reaches were scored "incorrect" if the subject contacted one of the solid planes of the box on their initial attempt to retrieve the reward. Subjects were not punished for incorrect reaches and all subjects eventually retrieved all rewards. If a subject ceased to perform the task, the session was terminated after 3-min had elapsed from the most recent attempt. A newly cleaned box was presented for every trial to eliminate any potential visual cues from previous handling. Prior to each trial, a barrier was placed in front of the acrylic box to prevent the subject from observing the position of the reward prior to the commencement of each trial.

2.3. Drug preparation

Ketamine (Ketaset HCl, Fort Dodge Animal Health) was diluted with sterile, injection-grade saline. GTS-21 (CAS # 156223-05-1), synthesized as described by Zoltewicz et al (Zoltewicz et al., 1993), was formulated with 0.01 M Na acetate buffer. Donepezil (Sequoia Research Products) was prepared with sterile saline. All drug formulations were prepared on the day of testing.

2.4. Drug testing

To avoid the potential confound of carryover effects, subjects were tested under vehicle conditions on Mondays and under drug conditions (GTS-21 and ketamine) on Thursdays, allowing 7 days for compound washout. In addition, order or carry over effects were statistically analyzed by examining the main effect of treatment session and the session × treatment interaction. Neither of these effects were significant ($p = 0.48$ and 0.69, respectively). Subjects were first tested under vehicle conditions (saline in the case of ketamine and 0.01 M Na acetate buffer for GTS-21) until their performance stabilized (defined as SEM ≤ 10 on easy and difficult trials for the 3 previous sessions). Next, subjects were characterized on ketamine to demonstrate sufficient impairment compared to their vehicle baseline. Due to individual differences in sensitivity to ketamine, each subject's "best dose" (the dose that produced a ~25% deficit on difficult trials, yet did not significantly impact easy trial performance) was identified and replicated at least once per subject. Ketamine characterization followed a pattern that our other non-human primate cognition impairment models have consistently demonstrated—doses used to impair performance need be individually titrated to produce a deficit that provides sufficient dynamic range for reversal with a cognitive enhancer, while at the same time not impairing aspects of performance that confound the interpretation of the results (e.g., effects on motivation or perception as measured by trial completion and/or performance on easy trials). For example, some subjects demonstrated impairment on difficult, but not easy trials at relatively low doses (i.e., 0.75 and 1 mg/kg), but failed to complete the task or were impaired on easy trials if the dose was increased. Alternately, one subject demonstrated no impairment at doses sufficient for other animals in the group and required a 3 mg/kg dose to produce a deficit on difficult trials. Table 1 presents the seven animals whose data were utilized in the study and their respective best doses of ketamine.

Once vehicle and ketamine baseline performance were stabilized, and after a week washout period, GTS-21 characterization was initiated. Utilizing a Latin square study design, ketamine and GTS-21 (0.01, 0.03, and 0.1 mg/kg) were administered intramuscularly 30-min and 1-hr prior to testing, respectively. The doses of GTS-21 that were examined were similar to a study in which GTS-21 was shown to be effective in a different NHP cognition task, delayed matching-to-sample (DMS) (Buccafusco and Terry, 2009). Upon completion of the GTS-21 study and a one week washout period, the donepezil study began. Donepezil (0.3 and 1 mg/kg) was administered PO (OG) 4-hrs prior to testing and ketamine was again dosed 30-min

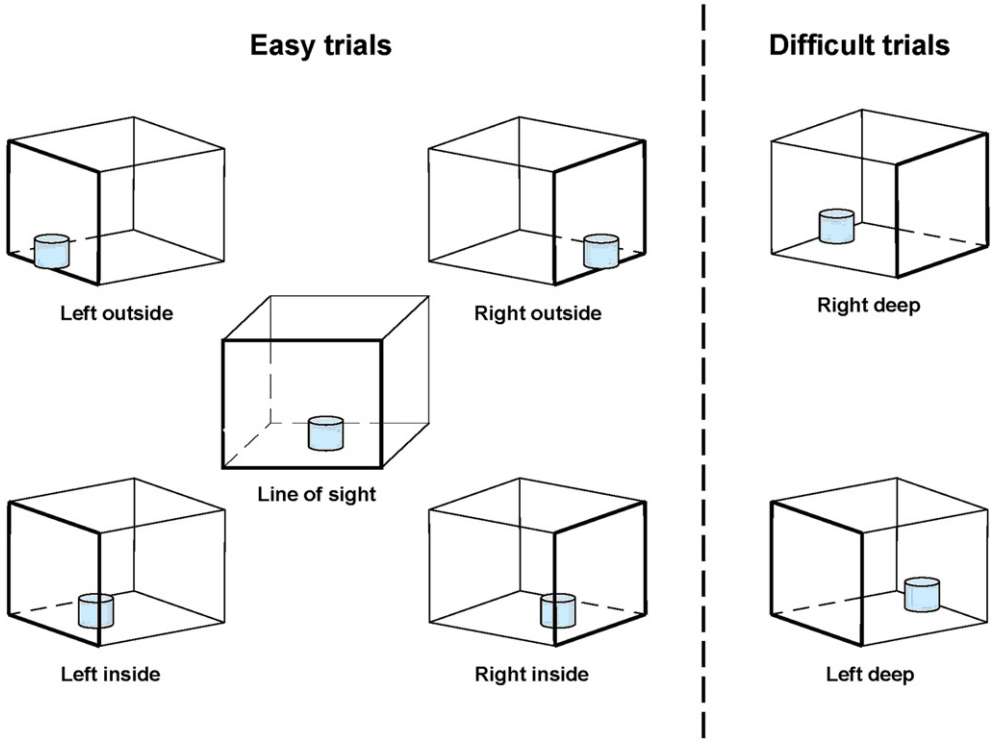

Fig. 1. A diagram of easy and difficult trials variants in the ORD task. The left segment illustrates the five variations of easy trials, the right segment illustrates the two variations of difficult trials. All illustrations represent the trials as viewed from the subject's perspective.

prior to testing. The doses of donepezil that were examined were based on in-house data demonstrating that these doses reliably reverse a scopolamine-induced deficit in the ORD task. Both lab care staff administering the compounds and the biologist conducting the assay were blind to treatment conditions. Vehicle performance was monitored and remained stable throughout the drug studies.

2.5. Data analysis

Both easy and difficult trial means were analyzed via one-way repeated-measures analysis of variance (ANOVA) and Dunnett's post-hoc tests were performed to compare differences between vehicle and drug-treated groups. Furthermore, in order to better characterize the dose-effect function of GTS-21, we used a within subjects *t*-test to compare the effects of the highest dose tested (0.1 mg/kg) to the middle dose (0.03 mg/kg).

3. Results

The influence of ketamine and GTS-21 on the ORD task is shown in Fig. 2. Within-subjects ANOVA revealed a main effect of group for difficult trials ($F_{(4,\ 24)} = 4.44$, $p < 0.01$). This was because 1) ketamine impaired performance on difficult trials in animals treated with only vehicle ($p < 0.01$) and 2) animals given 0.03 mg/kg GTS-21 prior to ketamine demonstrated improved performance relative to the group receiving vehicle prior to ketamine ($p < 0.05$). In order to better characterize the shape of the GTS-21 dose-effect function, the response to the effective dose of GTS-21 (0.03 mg/kg) was directly compared to the highest dose of GTS-21 (0.1 mg/kg). Difficult trial performance was significantly higher when animals received 0.03 mg/kg as compared to 0.1 mg/kg ($p < 0.05$). For easy trials, the main effect of group was significant ($F_{(4,\ 24)} = 2.86$, $p = 0.045$), however Dunnett's post-hoc test failed to demonstrate significant differences between treatments (see Table 2).

Table 1
Each of the seven subjects are listed with their corresponding non-impairing, best, and behaviorally impairing (i.e., significantly disrupted easy trial performance or caused the subject to be unable to complete the task) dose of ketamine. Not all doses were characterized in each subject, and generally once the criteria for impairment had been met, higher doses were not explored.

Subject ID	Non-impairing doses tested	Best dose	Doses disrupting easy trials or task completion
1 (884)	0.1, 0.18, 1, 1.8 mg/kg	2.4 mg/kg	3 mg/kg
2 (896)	1 mg/kg	1.8 mg/kg	1.8 mg/kg was the highest dose tested
3 (899)	0.1, 0.18, 1 mg/kg	1.8 mg/kg	1.8 mg/kg was the highest dose tested
4 (106)	0.1, 0.18, 1, 1.8 mg/kg	2.4 mg/kg	3 mg/kg
5 (107)	0.1, 0.18, 1 mg/kg	1.8 mg/kg	1.8 mg/kg was the highest dose tested
6 (109)	0.1, 0.18 mg/kg	1.0 mg/kg	1.8 mg/kg
7 (115)	0.1, 0.18, 1.8 mg/kg	3.0 mg/kg	3 mg/kg was the highest dose tested

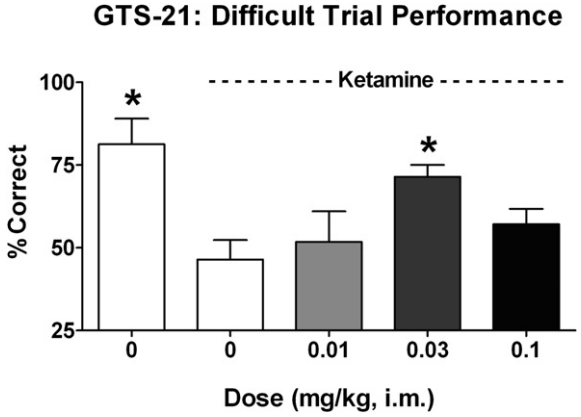

Fig. 2. The influence of ketamine and GTS-21 on difficult trials in the ORD task. Difficult trial performance was significantly impaired by ketamine pretreatment. GTS-21, when dosed at 0.03 mg/kg, significantly attenuated the ketamine deficit (asterisks indicate statistical significance from ketamine impairment). Ketamine and GTS-21 were administered intramuscularly at 30-min and 60-min prior to testing, respectively.

Table 2
The total group averages and SEM for easy trial performance according to treatment.

GTS-21 study (mg/kg)						Donepezil study (mg/kg)			
Treatment	0	0-Ket	0.01	0.03	0.3	0	0-Ket	0.3	1.0
Average	87.2	76.2	74.6	79.4	90.2	89.4	82.5	82.6	69.3
SEM	4.7	5.6	6.3	5.6	3.8	2.3	3.3	4.1	6.4

The effects of ketamine and donepezil on the ORD task are shown in Fig. 3. ANOVA revealed a main effect of group for difficult trials ($F_{(3,\ 21)} = 4.51$, $p < 0.02$), caused by the ketamine-impaired performance on difficult trials, compared to animals given vehicle ($p < 0.05$). Neither dose of donepezil improved performance compared to the animals given ketamine pretreated with vehicle. For easy trials, the ANOVA revealed a main effect of group ($F_{(3,\ 21)} = 5.24$, $p < 0.01$), caused by the negative impact on easy trial performance associated with the highest dose of donepezil ($p < 0.01$). Animals given vehicle prior to ketamine did not significantly differ on easy trial performance from animals given only vehicle (Table 2).

4. Discussion

We report three novel findings. First, ketamine dose-dependently impaired performance on difficult, but not easy trials in the ORD task. This pattern of effects is consistent with previous research showing that NMDA receptor antagonists disrupt neuronal activity in the PFC and PFC-mediated tests of cognition (Lewis and Moghaddam, 2006). Second, the nicotinic α7 receptor agonist GTS-21 attenuated the ketamine impairment in the ORD task, consistent with the pro-cognitive effects of GTS-21 observed in several preclinical and clinical studies (Arendash et al., 1995; Olincy et al., 2006; Buccafusco and Terry, 2009). Finally, donepezil, an acetylcholinesterase inhibitor effective for treating the cognitive deficits in Alzheimer's disease but not schizophrenia, failed to affect the ketamine-induced impairment on the ORD task. These data speak to the specificity of this model for identifying schizophrenia-specific cognitive enhancers. The doses of donepezil tested in the present study are able to attenuate a scopolamine-induced deficit in the ORD task (data not shown), indicating that the lack of effect in the present study should not be attributed to lack of target engagement, but rather due to the nature of the impairing agent used.

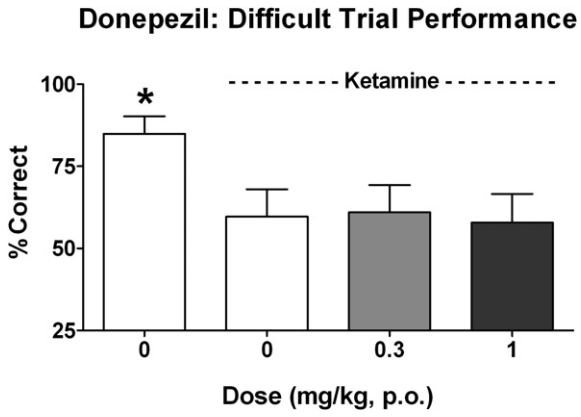

Fig. 3. The influence of ketamine and donepezil on difficult trials in the ORD task. Difficult trial performance was significantly impaired by ketamine pretreatment. Donepezil failed to reverse the cognitive deficit imposed by ketamine on difficult trial performance. Ketamine was administered intramuscularly 30-min prior to testing. Donepezil was administered PO (OG) 4-hrs prior to testing.

As far as we know, these results represent just the second demonstration showing the beneficial effects of a nicotinic α7 receptor agonist in a ketamine-impaired, NHP cognition task. Buccafusco and Terry (2009) elegantly showed that GTS-21 reversed a ketamine-induced impairment in the DMS task in pigtail monkeys, similar to what was observed following administration of the partially selective nicotinic α7 receptor agonist cotinine. Importantly, the efficacious dose in the ORD task (30 μg/kg) was very similar to the efficacious doses in DMS (20 and 40 μg/kg). Although Buccafusco and Terry (2009) did not observe an inverted U-shaped dose effect function, this is most likely because the highest dose of GTS-21 tested in DMS (40 μg/kg) was only slightly higher than the efficacious dose identified in the current study (30 μg/kg), whereas effects in the ORD task were absent at a much higher (~3-fold) dose (100 μg/kg). The shape of the dose-effect curve we observed is of particular significance due to its alignment with clinical studies, where an inverted U-shaped dose-effect function was observed with GTS-21 in schizophrenic patients (Olincy et al., 2006). Furthermore, it was reported that a different nicotinic α7 receptor agonist, MEM3454, improves cognition in Alzheimer's disease patients at low, but not high, doses (Wallace and Porter, 2011). These data indicate that inverted U-shaped dose-effect functions are important to characterize preclinically, are potentially vertically translatable, and should be considered when selecting doses to examine in clinical studies. Inverted U-shaped dose-effect functions appear frequently in NHP based assessments of putative cognitive enhancers in preclinical studies (Arnsten and Goldman-Rakic, 1990; Matsuoka and Aigner, 1996; Williams and Castner, 2006), yet all too often it appears that the maximum tolerated dose is examined in clinical studies, indicating a need for further harmonization between the stages of drug development.

The current results also indicate that subjects differ in terms of the ketamine dose that selectively impairs difficult trials, pointing to the importance of identifying individualized doses of ketamine for characterizing reversal agents. Buccafusco and Terry (2009) also noted the constraints of using a single fixed dose of ketamine when it was found the 2 mg/kg dose they used disrupted performance on easy trials in the DMS task. This complicated the interpretation of their results, as these trials are not meant to be cognitively challenging or heavily dependent on working memory. They observed that "some effect of ketamine on discrimination is suggested by the decrease in zero delay accuracy, though it is not possible to directly determine whether alterations in perception significantly contributed to the deficits" (pg 859) (Buccafusco and Terry, 2009). Therefore, building on these observations and the findings of the current study, we suggest that selecting the best dose of the impairing agent for each subject is a strategy that can successfully navigate this constraint, provide increased clarity in data interpretation, and should be considered for future efforts. It is worth noting, however, that while this methodology alleviates issues that arise with single-dose study designs, as described above, it might also impact the ability of reversal agents to accurately demonstrate therapeutic effects. Continued efforts in forward and backwards translation to address this topic are warranted.

The neural circuitry by which nicotinic α7 receptor activation improves ORD task performance remains speculative, but could depend on the ability of nicotinic α7 receptor agonists to influence dopamine levels in the PFC. GTS-21 administration has been found to increase extracellular dopamine in the PFC (Summers et al., 1997). This is important because dopamine in the PFC is heavily implicated in mediating performance on the ORD task. For example, low doses of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which destroys dopaminergic projections to the PFC, disrupts ORD task performance (Taylor et al., 1990a,b; Schneider and Roeltgen, 1993). These deficits were

attenuated by co-administering the dopamine precursor Levadopa and the nonselective nicotinic receptor agonist SIB-1508Y, further suggesting an important interaction between the cholinergic and dopaminergic systems (Schneider et al., 1998). Additionally, subchronic administration of PCP also impaired performance in the ORD task, and this deficit was found to significantly correlate with dopamine depletion in the PFC (Jentsch et al., 1999a,b). It is possible that the effects of GTS-21 in this study could result from its ability to enhance glutamate release by acting on α7 receptors at glutamatergic terminals (Marchi et al., 2002; Rousseau et al., 2005; Dickinson et al., 2008; Livingstone et al., 2010). Given that ketamine is an NMDA receptor antagonist and GTS-21 increases glutamate release, it is possible that the effects we have observed are due to (indirect) competition between ketamine and enhanced extracellular glutamate acting on the NMDA receptor. Receptor tautology is one of several issues virtually inherent to pharmacological models and that it could impact the interpretation of our results is worth noting (Geyer, 2006).

In contrast to the improvement in ORD task performance following treatment with the selective nicotinic α7 receptor agonist GTS-21, donepezil failed to improve performance in ketamine-impaired animals. Initially, this might seem surprising as donepezil should indirectly activate nicotinic α7 receptors by elevating synaptic acetylcholine. However, acetylcholine is not a potent agonist at the nicotinic α7 receptor, with EC50 values ranging from ~80 μM to 1.1 mM depending on the assay conditions and analytical methods (Alkondon and Albuquerque, 1993; Alkondon et al., 1994; Peng et al., 1994; Puchacz et al., 1994; Gopalakrishnan et al., 1995; Zhao et al., 2003). The affinity of acetylcholine for the nicotinic α7 receptor is also in the micromolar range, making it a much weaker binder for this receptor relative to its affinity for other nicotinic receptors (Gotti et al., 2006). Therefore, it is unclear whether donepezil (at biologically-relevant doses) indirectly activates the nicotinic α7 receptor, and if so, to what extent. Recent advances in identifying a PET ligand to measure nicotinic α7 receptor occupancy could possibly clarify this point (Ettrup et al., 2011; Maier et al., 2011). Alternatively, by elevating acetylcholine, donepezil might non-selectively influence other nicotinic and muscarinic receptors thereby countering the effects of nicotinic α7 receptor activation. These possibilities warrant future examination.

In conclusion, the current results demonstrate that a ketamine-induced impairment in the ORD task is dose-dependently attenuated by the nicotinic α7 receptor agonist GTS-21, but not donepezil. These findings provide a back-translation from what has been observed in schizophrenic populations to a NHP task relevant to the disease. Further, the shape of the dose-effect curve for GTS-21 observed in the current study is similar to what was observed clinically, suggesting that NHP models such as the ketamine impaired ORD task might act to improve the predictive validity of preclinical testing and potentially serve to inform dose selection in the clinic. This might be particularly relevant for tasks dependent on the PFC, for which the NHP is much more homologous to the human compared to less homogeneous species. Additional back-translation efforts are needed to further understand the utility of specific cognition tests and deficit models so that investment in forward-translation from preclinical species to humans continues, streamlining drug development and ultimately resulting in improved therapeutics.

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