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Dopamine D1 receptor activation improves PCP-induced performance disruption in the 5C-CPT by reducing inappropriate responding

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Abstract

Attentional deficits contribute significantly to the functional disability of schizophrenia patients. The 5-choice continuous performance test (5C-CPT) measures attention in mice, rats, and humans, requiring the discrimination of trial types that either require a response or the inhibition of a response. The 5C-CPT, one version of human continuous performance tests (CPT), enables attentional testing in rodents in a manner consistent with humans. Augmenting the prefrontal cortical dopaminergic system has been proposed as a therapeutic target to attenuate the cognitive disturbances associated with schizophrenia. Using translational behavioural tasks in conjunction with inducing conditions relevant to schizophrenia pathophysiology enable the assessment of pro-attentive properties of compounds that augment dopaminergic activity. Here, using a repeated phencyclidine (PCP) treatment regimen and the 5C-CPT paradigm, we assess the pro-attentive properties of SKF 38393, a dopamine D1 receptor agonist, in rats. We show that repeated PCP treatment induces robust deficits in 5C-CPT performance indicative of impaired attention. Pre-treatment with SKF 38393 partially attenuates the PCP-induced deficits in 5C-CPT performance by reducing false alarm responding and increasing response accuracy. Impaired target detection was still evident in SKF 38393-treated rats however. Thus, augmentation of the dopamine D1 system improves PCP-induced deficits in 5C-CPT performance by selectively reducing aspects of inappropriate responding. These findings provide evidence to support the hypothesis that novel therapies targeting the dopamine D1 receptor system could improve aspects of attentional deficits in schizophrenia patients.

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Keywords

Schizophrenia; attention; phencyclidine; cognition; dopamine D1 receptors

Introduction

Cognitive deficits in schizophrenia remain an unmet clinical need that contribute significantly to long-term functional and occupational impairments [1, 2]. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative identified seven cognitive domains that are dysfunctional in schizophrenia patients; one of which was attention/vigilance [3, 4]. Improving attention is an important therapeutic target for schizophrenia, as impairments in attention impact other cognitive domains [5, 6] and are associated with higher costs of care-giving [7]. If pro-attentive therapies are to be developed, animal models that consist of inducing conditions relevant to the pathophysiology of schizophrenia and cross-species translational procedures are required [8].

The Continuous Performance Test (CPT) is commonly used to assess attention in humans [9] and schizophrenia patients exhibit CPT deficits [10–13]. Although several variants exist, all CPTs include target and non-target trials that require either a response or the inhibition of a response, respectively [14]. As subjects must discriminate between two trial types, generating either hits, misses, correct rejections or false alarms, signal detection theory (SDT) can be used to quantify signal sensitivity and response bias. Using an animal task that generates the same response outcomes as human CPTs will be advantageous in the assessment of novel therapeutics designed to improve attention. Several attentional tasks exist in rodents. Widely used since 1983, the 5-choice serial reaction time task [5-CSRTT; 15, 16] has significantly improved our understanding of the neural substrates that underlie attentional processing [16, 17]. However, while assessing sustained attention, the 5-CSRTT differs from human CPTs in that it does not include non-target trials that must be correctly rejected. As a result, the 5-CSRTT was modified to include both target and non-target trials, the latter requiring the inhibition of a response. As responding in this task, termed the 5-choice continuous performance task (5C-CPT), results in hits, misses, correct rejections or false alarms, SDT analyses can be performed in a manner similar to human CPT analysis. The 5C-CPT was originally described in mice [18–20] and subsequently validated in rats by us [21–24] and others [25]. This test has also been reverse-translated for use in humans and performance involves neural activation in brain regions consistent with other CPTs [26], sleep deprivation causes similar deficits in mice and man [27], and importantly, is clinically sensitive since schizophrenia patients exhibit deficits in the human 5C-CPT [28]. Accordingly, the 5C-CPT had been proposed as a potential cross-species test of attention by the cognitive neuroscience-based NIMH-initiative Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia [CNTRICS; 29]. Using the 5C-CPT may provide a method to assess putative pro-attentive compounds with cross-species translational relevance to human testing [8].

Glutamatergic dysfunction is a prominent hypothesis of schizophrenia pathogenesis [30, 31]. Indeed, blockade of the *N*-methyl-D-aspartate (NMDA) glutamate receptor generates a

schizophrenia-like state in humans [32, 33] and exacerbates symptoms in stabilized patients [34, 35]. Consequently, NMDA receptor antagonists (e.g., phencyclidine [PCP] or ketamine) are widely used in preclinical research when investigating various aspects of schizophrenia [36]. Repeated or sub-chronic administration of NMDA receptor antagonists to experimental animals induces cognitive impairments, aspects of negative symptoms and neuropathological changes observed in schizophrenia patients [37–40]. Disruption in attentional performance is evident after NMDA receptor antagonism. Repeated [41] or chronic intermittent PCP-treatment [42] impaired 5-CSRTT performance. Furthermore, 5-CSRTT deficits induced by repeated PCP-treatment were attenuated by clozapine [41], but not quetiapine [43] treatment. Repeated PCP treatment also replicates some of the neuropathological alterations observed in schizophrenia [44]. In addition, after a one week washout period, sub-chronic PCP treatment induces 5C-CPT deficits when task difficulty is increased [24] reminiscent to 5C-CPT deficits exhibited by schizophrenia patients [28]. PCP treatment may, therefore, reflect a relevant inducing condition to test pro-cognitive agents to treat the attentional disruption observed in schizophrenia.

Dopamine transmission, mediated through the dopamine D1 receptor subtype, has been proposed as a promising target for the development of pro-cognitive agents in schizophrenia [45–47]. Indeed, decreased prefrontal dopamine D1 receptor binding [48] and a reduced capacity for cortical dopamine release [49] has been observed in schizophrenia patients. Thus, augmenting the cortical dopaminergic system may alleviate some of the symptoms associated with schizophrenia. Dopamine D1 receptor activation has been shown to improve attention/vigilance in a baseline-dependent manner [21, 50]. Other dopamine-related treatments also improve attention in a baseline-dependent manner, such as methylphenidate and atomoxetine [23], and dopamine releasing agents such as nicotine [19] further demonstrating the involvement of dopamine in attentional processing. Dopamine D1 receptor activation attenuates reversal learning and novel object recognition (NOR) deficits induced by sub-chronic PCP administration [51, 52]. In addition, asenapine, a newly licensed antipsychotic, recruits D1 receptor mechanisms to reverse sub-chronic PCP induced deficits in the NOR test [53]. Finally, results from a recent preliminary proof-of-principle study in a small number of un-medicated patients suggest that dopamine D1 receptor activation may improve schizophrenia-spectrum working memory deficits in humans [54]. Collectively, these findings highlight the importance of the dopamine D1 receptor system as a potential target to ameliorate cognitive dysfunction associated with schizophrenia. As a result, our aim here was to determine whether dopamine D1 receptor activation can overcome attention deficits induced by repeated PCP in the translational 5C-CPT in female rats.

Methods

Subjects

Female hooded-Lister rats (n=23; Charles River; approx 220 ± 10 g at the start of the experiment) were housed on a 12 hour reversed light cycle (lights on at 7:00 pm) in a temperature ($21 \pm 2^\circ\text{C}$) and humidity ($55 \pm 5\%$) controlled environment. Female rats were used as they have consistently demonstrated reliable performance in our laboratory in a

variety of cognitive tests [40] at all stages of the oestrus cycle [52, 55]. Furthermore, we have thoroughly validated the 5C-CPT in our laboratory using female rats and demonstrated impaired performance following sub-chronic PCP and effects of D1 receptor agonism in “normal” rats [20–23]. All experimentation was conducted in the animal's natural dark-cycle under red lighting. Animals had free access to food (Special Diet Services, UK) and water until one week prior to the beginning of training, when food restriction reduced their weight to 90% of their free-feeding body weight (approximately 14g rat chow/rat/day). Food restriction continued throughout training and testing, however water was available *ad libitum* in the home cage. All experiments were conducted in accordance with the UK Animals (Scientific Procedures) 1986 Act and local University ethical guidelines.

Drugs

Phencyclidine hydrochloride (PCP, Sigma-Aldrich, UK) was dissolved in 0.9% sterile saline, SKF 38393 (Sigma-Aldrich, UK) was dissolved in distilled H₂O. Drugs were administered in a volume of 1 ml/kg via the intraperitoneal (i.p.) route, where drug dose is expressed as free-base. PCP was administered at 2.5 mg/kg (i.p.). The D1 receptor agonist SKF 38393 was used at one dose only of 6 mg/kg, chosen as we have found it to be the most effective dose in our previous 5C-CPT experiments [21]. In addition, 6 mg/kg SKF 38393 has been investigated in other domains of cognition [56], and demonstrates efficacy to attenuate PCP-induced cognitive impairments in other tests [51, 52].

Apparatus

The test apparatus consists of eight 25 cm × 25 cm aluminium chambers, each enclosed within a sound attenuating box [21, 24]. The rear wall of the test chamber was concavely curved and contained nine individual apertures, four of which were occluded, leaving apertures 1, 3, 5, 7 and 9 free for exploration. Each aperture was 2.5 cm², 4 cm deep and set 2 cm above floor level. Located at the rear of each aperture was a white LED providing the visual stimulus. An infrared photocell beam fixed vertically at the entrance to each aperture registered nose-poke responses. Located on the front wall of the test chamber was a food magazine that allowed retrieval of the food reward (45 mg sucrose Rodent Pellet, Sandown Scientific). A hinged panel covered the food magazine and a micro-switch reported the collection of food rewards. In addition to the sound attenuating box, there was also a low-level fan that not only provided ventilation, but masked extraneous background noise. The floor of the test chamber consisted of a wire grid, under which was a removable tray covered with sawdust. All eight chambers were connected to a PC and data collection and initial analysis was controlled by K-Limbic software (Conclusive Solutions) which generated an Excel spreadsheet (Microsoft) containing the raw data.

Behavioural Procedure

The 5C-CPT is similar to the 5-CSRTT in that animals must detect and respond to a visual stimulus presented during target trials. The 5C-CPT differs, however, as animals must differentiate between target and non-target stimuli and inhibit a response when presented with non-target trials. Briefly, rats were trained to detect and respond to a brief visual stimulus presented pseudo-randomly in one of the five available response apertures after a

variable (4.0, 4.5, 5.5, and 6.0 seconds) inter-trial interval (ITI). If the animal correctly responded ('correct responses') during the two second limited hold (LH) period following stimulus presentation in which the animal can respond, it was rewarded with a food pellet. Collecting the food pellet triggered a micro-switch and initiated the next trial. The latency to collect the reward (reward latency, RL) was recorded. Failure to respond to the stimulus ('error of omission') or responding in an aperture where the stimulus was not presented ('incorrect response') resulted in a 5 second time-out (TO) period, whereby the house light was illuminated, apertures were non-responsive and no food reward was delivered. Responses during the ITI were recorded as 'premature response' and initiated a TO. A TO period also occurred when the animal made a single inappropriate repeat response following a correct response ('perseverative response'). In previous 5-CSRTT studies, accuracy is sometimes referred to as percent correct responses and the terms are often interchangeable. However, an important distinction exists and one that is often overlooked; accuracy is calculated independently from omissions, whereas percent correct responding is calculated from the total number of target trial responses within the session (correct, incorrect and omissions) [57]. We have adopted this method of calculating accuracy and percent correct responses, as previously described by others [41, 43]. During non-target trials all apertures are illuminated and the animal must inhibit its response to obtain the food reward ('correct rejection'). Responses made during the LH of non-target trials were deemed false alarms and resulted in a TO. Each session consisted of 120 trials and lasted no longer than 30 minutes. In addition to the measures typically reported in the 5-CSRTT literature, described above, signal detection theory (SDT) can be employed in experiments utilising the 5C-CPT as the task contains both target and non-target trials. The SDT indices used in the current investigation were originally described by Frey and Colliver [58] and were utilised in previous 5C-CPT experiments [18, 21, 24]. Therefore, using the hit rate (HR) and false alarm rate (FA), the sensitivity (S1) and responsivity indices (RI) can be calculated. The calculations used to derive these measures are described below.

$$p[HR] = \frac{Correct}{Correct + Incorrect + Omission} \quad p[FA] = \frac{FA}{FA + CR}$$

$$SI = \frac{p[HR] - p[FA]}{2(p[HR] + p[FA]) - (p[HR] + p[FA])^2}$$

$$RI = \frac{p[HR] + p[FA] - 1}{1 - (p[FA] + p[HR])^2}$$

Training Schedule

The training schedule used is described in detail elsewhere [21]. Briefly, animals were assigned to an operant chamber and habituated for two days, during which the response apertures were baited to encourage exploration. Initial training consisted of a target to non-target ratio of 100:20. Once a rat reliably responded to the target trials, a greater emphasis

was placed on the presentation of the non-target trials and the number presented per session was increased (77:43) to encourage response inhibition. Once rats could reliably discriminate between trial types and respond appropriately (i.e. hit rate > false alarm rate) the ratio was again altered (84:36). This last ratio was used throughout the remainder of training and testing. Training began with a stimulus duration (SD) of 10 seconds and was progressively reduced (10, 8, 4, and 2, 1.5 s) for individual rats as they reached criterion (>75% accuracy, <30% omission and >65% correct rejections of non-target trials, for 3 consecutive days). Training was conducted until animals achieved a stable performance at the desired criteria (1 s SD, 5 s TO, variable ITI with mean of 5 s, and 2 s LH) over three consecutive days. Training was conducted 5-days per week taking approximately 5 months to complete.

Treatment Regimen

The repeated PCP treatment regimen (see figure 1) was adapted from that originally described by Amitai et al. [41]. All animals were injected with vehicle (0.9% saline) for three days (days 1 to 3) followed by two days (days 4 and 5) where all animals received PCP (2.5 mg/kg i.p.). Animals were then treated with vehicle for 5 days (days 6 to 10). Rats were tested in the 5C-CPT on each day 30 minutes following drug administration. The next 5 days (days 11 to 15), animals were pre-treated with either vehicle (0.9% saline, n = 11, Fig. 1A) or SKF 38393 (6.0 mg/kg i.p.; n = 12, Fig. 1B). Thirty minutes after the first treatment (saline or SKF 38393), all animals were then administered PCP (2.5 mg/kg i.p.). Thirty minutes later 5C-CPT testing was initiated.

Group Matching

It is known that there is individual variability in PCP sensitivity, resulting in some animals having a more profound reaction to PCP treatment than others [41]. Animals were counter-balanced to the two groups using a stratified randomisation so that performance in the two groups was matched in response to saline (days 1 to 3) and initial PCP (days 4 and 5) treatment. Performance was matched according to the following parameters; sensitivity index, hit rate, false alarm rate, responsivity index, correct latency and reward latency. The group-matching procedure limited the possible differences in baseline PCP treatment response between treatment groups, ensuring a meaningful comparison of SKF 38393 effects compared to that of vehicle in PCP-treated rats.

Statistical Analysis

Performance on days 1 to 3 were averaged giving baseline 5C-CPT performance for each animal. To explicitly determine the disruptive effect of repeated PCP administration on 5C-CPT performance, a one-way repeated-measures mixed model was conducted on the group of animals receiving PCP and saline injections. Day served as the repeated factor. Performance was compared to baseline during the initial PCP exposure (days 4 and 5) and during the post-PCP recovery period (days 6 to 10). Assessment of the effect of SKF 38393 pre-treatment on PCP-induced performance impairment (days 11 to 15) was determined by a 2-way repeated-measures mixed model [59], with Pre-treatment (SKF 38393 or saline) as the between-subject factor and Day of administration as the repeated factor. In addition, both groups were subject to a within-subject comparison to their respective baseline performance.

To control the false discovery rate, the unadjusted p-values were adjusted using the Benjamini-Hochberg procedure [59], with $p < 0.05$ denoting a significant effect. Performance for each behavioural measure generated in the 5C-CPT was displayed as the observable mean $\pm$ SEM, graphically displayed in Graphpad Prism v 5.0 and analysed using InVivoStat [60]. The parametric assumptions of these analyses were assessed using the inbuilt diagnostic and normality plots in InVivoStat and outliers providing values greater than 2 standard deviations from the mean were removed.

Results

Effect of initial PCP exposure on 5C-CPT performance

Initial PCP exposure induced wide-ranging deficits in 5C-CPT performance. Response accuracy was significantly impaired [$F_{(2,20)}=8.92$, $p < 0.01$], and reduced after each dose of PCP ($p < 0.05$; Fig. 2A). Percent incorrect responding was also disrupted [$F_{(2,20)}=5.24$, $p < 0.05$] and was increased on each day ($p < 0.05$) (Fig. 2B). Both the hit rate (HR) [$F_{(2,20)}=16.38$, $p < 0.001$] and false alarm rate (FA) [$F_{(2,20)}=5.06$, $p < 0.05$] were disrupted by the initial PCP exposure (Figs 2C and D, respectively). While hit rate was reduced on both days ($p < 0.01$), increased false alarm rate was only observed on the second day ($p < 0.05$). The sensitivity index (SI) was reduced after initial PCP treatment [$F_{(2,20)}=20.83$, $p < 0.001$]. This effect was evident on both days ($p < 0.01$; Fig. 2E) but was not accompanied by a significant change in the responsivity index (RI) [$F_{(2,20)}=2.69$, ns] (Fig. 2F). Percent correct responding was also disrupted [$F_{(2,20)}=16.38$, $p < 0.001$]. Correct responses were reduced after each PCP dose ($p < 0.01$; Table 1). PCP-treatment also increased omissions [$F_{(2,20)}=14.28$, $p < 0.001$], an effect evident after each PCP dose ($p < 0.05$; Table 1). A reduction in completed trials was also evident [$F_{(2,18)}=4.45$, $p < 0.05$] that reached significance after the second dose of PCP ($p < 0.05$; Table 1). Correct latency was also affected [$F_{(2,20)}=8.56$, $p < 0.01$], increased on both days ($p < 0.01$; Fig. 2F). Reward latency was affected [$F_{(2,20)}=7.28$, $p < 0.01$], this was significantly increased after the second PCP dose ($p < 0.01$; Table 1). Inappropriate responding was also increased after the initial PCP exposure ($p < 0.05$; Table 1). This was revealed as increases in perseverative [$F_{(2,18)}=6.57$, $p < 0.01$], time out [$F_{(2,18)}=6.04$, $p < 0.05$] and premature responding [$F_{(2,18)}=6.51$, $p < 0.01$].

Recovery from initial PCP exposure

Response accuracy [$F_{(5,49)}=0.37$, ns] (Fig. 3A) and percent incorrect responding [$F_{(5,48)}=0.55$, ns] (Fig. 3B) returned to normal after the initial PCP exposure. Similarly, hit rate [$F_{(5,50)}=2.09$, ns] (Fig. 3C) and false alarm rate [$F_{(5,49)}=0.61$, ns] (Fig. 3D) were observed to be no different to baseline during days 6 to 10. An overall main effect of recovery from the initial disruptive effects of PCP was observed when sensitivity index was assessed [$F_{(5,50)}=2.90$, $p < 0.05$], however, individually none of the post-PCP recovery days were significantly different from baseline (Fig. 3E). The responsivity index was no different to baseline [$F_{(5,50)}=1.18$, ns] (Fig. 3F). Correct latency was altered overall [$F_{(5,50)}=3.25$, $p < 0.05$], where responses on days 9 and 10 were significantly lower than baseline ($p < 0.05$; data not shown). Percent correct responding [$F_{(5,50)}=2.09$, ns], percent omissions [$F_{(5,50)}=2.13$, ns] and completed trials [$F_{(5,50)}=0.79$, ns] all returned to baseline after the initial PCP treatment (data not shown). This occurred without alterations in reward latency

[$F_{(5,48)}=2.03$, ns]. In addition, perseverative [$F_{(5,45)}=0.82$, ns], time out [$F_{(4,45)}=2.02$, ns], and premature responding [$F_{(4,45)}=0.78$, ns] were not susceptible to long-term alterations (data not shown).

SKF 38393 attenuates PCP-induced 5C-CPT disruption (days 11 to 15)

A Treatment $\times$ Day interaction on response accuracy was observed [$F_{(5,98)}=2.94$, $p<0.05$]. Compared to BL (Days 1 to 3), PCP treatment alone reduced response accuracy on all 5 treatment days ($p<0.01$), whereas a significant reduction in the SKF-treated animals, compared to BL, was only evident on days 11 ($p<0.05$) and 12 ($p<0.01$). Between-subject comparisons revealed a significant increase in accuracy in PCP animals pre-treated with SKF 38393 compared to animals pre-treated with saline on day 15 ($p<0.05$) (Fig. 4A). A Treatment $\times$ Day interaction was also evident for incorrect responding [$F_{(5,100)}=2.38$, $p<0.05$]. PCP treatment alone increased incorrect responding on each day ($p<0.05$) while incorrect responding was increased only on days 11 and 12, compared to BL, in the PCP + SKF 38393 treated group ($p<0.05$). Furthermore, a between-subject comparison indicated that SKF 38393 treatment reduced incorrect responding on days 13 to 15 ($p<0.05$) (Fig. 4B). An overall Day effect was evident when hit rate was analysed [$F_{(5,102)}=18.30$, $p<0.001$], without a Treatment [$F_{(1,21)}=0.14$, ns] or Treatment $\times$ Day interaction [$F_{(5,102)}=1.02$, ns] indicating that the hit rate was reduced compared to baseline in both groups ($p<0.001$) (Fig. 4C). In contrast, a significant Treatment $\times$ Day interaction was observed for false alarm responding [$F_{(5,102)}=5.52$, $p<0.001$]. Compared to BL, false alarm responding was increased in the PCP + saline group on day 15 ($p<0.05$), while in the PCP + SKF 38393 group false alarm responding was only elevated on day 11 ($p<0.05$). Moreover, a significant between-subjects difference was observed on day 15 ($p<0.05$) indicating that SKF 38393 pre-treatment attenuated the PCP-induced increase in false alarm responding (Fig. 4D). A Treatment $\times$ Day interaction for sensitivity index (SI) failed to reach statistical significance [$F_{(5,102)}=2.13$, ns]. An overall main effect of Day was evident [$F_{(5,102)}=40.64$, $p<0.001$] and, compared to BL, SI was reduced in both groups on days 11 to 15 ($p<0.001$) (Fig. 4E). Similarly, the Treatment $\times$ Day interaction for responsivity index (RI) did not reach statistical significance [$F_{(5,102)}=0.76$, ns] whereas the main effect of Day [$F_{(5,102)}=9.76$, $p<0.001$] was significant. Post-hoc comparisons demonstrated RI in both groups was significantly altered on day 12 only ($p<0.001$) (Fig. 4F).

For the following measures, a Treatment or Treatment $\times$ Day interaction was not present and so the main effect of Day only is reported (Table 2). Percent correct responding [$F_{(5,107)}=20.39$, $p<0.001$], percent omissions [$F_{(5,107)}=17.71$, $p<0.001$] and completed trials [$F_{(5,102)}=5.11$, $p<0.001$] were altered across the treatment regimen. Post-hoc analyses demonstrated that these measures were different from baseline on each day ($p<0.01$). Correct latency was disrupted in both groups [$F_{(5,100)}=14.30$, $p<0.001$] and was increased compared to baseline on each day ($p<0.001$). Reward latency [$F_{(5,104)}=10.75$, $p<0.001$] also displayed alterations. This effect was attributed to the first four days ($p<0.05$) as day 15 was not significantly different to baseline. Perseverative [$F_{(5,100)}=8.99$, $p<0.001$], time out [$F_{(5,100)}=10.39$, $p<0.001$], and premature responding [$F_{(5,100)}=10.09$, $p<0.001$] were also disrupted. These forms of inappropriate responding were elevated in both groups on each day ($p<0.05$).

Discussion

Repeated PCP administration produced robust deficits in attention. Impaired 5C-CPT performance resulted from a reduced ability to correctly identify target trials, and a diminished ability to correctly reject non-target trials. The PCP-induced deficits in 5C-CPT performance were partially attenuated by augmenting dopamine D1 receptor transmission. SKF 38393 treatment ameliorated select forms of inappropriate responding (i.e., false alarm responding and incorrect responding) induced by PCP treatment. Deficits in other behavioral processes necessary for vigilant performance, such as target detection, and other forms of inappropriate responding (i.e., premature, perseverative and time out responding) were not sensitive to SKF 38393-induced improvement. Interestingly, there was a delayed onset of action, with SKF 38393-induced improvements only emerging on repeated dosing. This is a particularly important observation given that any treatment developed for cognitive deficits in schizophrenia would be administered in the long-term.

Repeated PCP administration resulted in a robust impairment in 5C-CPT performance. Impairments in response accuracy, reduced correct responding, increased incorrect responding and increased omissions were observed. In addition, repeated PCP-treatment increased premature, perseverative and timeout responding. Moreover, speed of processing was decreased after PCP, and persisted throughout the treatment-regimen even when the reward latency was no longer different from baseline. These findings are largely in agreement with previous studies that assessed the disruptive effects of systemic administration of PCP [41–43, 61], ketamine [62] or MK-801 [63], or central injections of an NMDA receptor antagonist [64, 65], on 5-CSRTT performance. In addition, NMDA receptor blockade impaired signal discrimination in the sustained attention task (SAT) [66–69], another preclinical attentional task that requires the discrimination between target and non-target trials [70]. However, as both trial types in the SAT require an active response, a correct rejection does not require the inhibition of a response and may not accurately reflect the non-target trials that are presented in human CPTs [18]. The current investigation demonstrates that repeated PCP treatment impaired not only the ability to correctly respond to target trials, but also impaired the ability to correctly inhibit a response when presented with non-target trials. Correctly responding to relevant stimuli and rejecting irrelevant stimuli are two vital components of vigilance assessment in human CPTs [14]. Hence, assessing 5C-CPT deficits after the repeated PCP-treatment regimen may serve as an appropriate model for assessing efficacy of potential pro-cognitive compounds to attenuate attentional deficits associated with schizophrenia.

An interaction between NMDA receptor activation and dopamine D1 activation has been demonstrated [71]. This synergistic interaction may contribute to the SKF 38393-induced attenuation in PCP-induced 5C-CPT deficits. By the final treatment day, while the deficit in target detection remained, the PCP-induced increase in false alarm responding was attenuated. The sensitivity index is used to provide a measure of vigilance. As the Treatment $\times$ Day interaction for this measure failed to reach statistical significance, we cannot conclude that SKF 38393 improved the PCP-induced deficit in vigilance. However, the sensitivity index is calculated from the hit rate and false alarm rate. If SKF 38393 treatment had improved the hit rate, in addition to the false alarm rate, a more robust improvement in

signal sensitivity would have been detected. Nonetheless, a significant improvement in one aspect of vigilant performance was observed after dopamine D1 receptor activation. Additional measures can provide insights into attentional processing. Repeated PCP treatment impaired accuracy, correct responding and omissions, which may also be indicative of impaired attention [57]. Accuracy is a conservative measure, with alterations occurring independently of omissions, whereas percent correct responding is sensitive to increased omissions [57]. Interestingly, while activating the dopamine D1 receptor completely reversed the PCP-induced deficit in accuracy, deficits in correct responding and omissions remained. SKF 38393 treatment attenuated the PCP-induced increase in incorrect responding. This led to an improvement in response accuracy while deficits in correct responding and omissions persisted. It is possible that the PCP-induced disruptions in correct responding and omissions were initially mediated by non-specific effects, as they were also accompanied by an increase in reward latency. However, by the final treatment day, the elevation in reward latency was no longer different from baseline, yet the PCP-induced alterations in correct responding and omissions remained. Interestingly, attentional deficits induced by NMDA receptor blockade are improved by clozapine treatment [41, 67]. Notably, clozapine improved 5-CSRTT performance by reducing incorrect responding and not increasing correct responding [41]. Clozapine has a rich pharmacology [72] acting, in part, as a dopamine D1 receptor partial agonist [73]. It has been suggested that clozapine treatment improves PCP-induced deficits by normalizing cortical dopamine levels [74]. Repeated exposure to clozapine treatment normalized cortical dopamine transmission [74] and chronic clozapine treatment improved PCP-induced 5-CSRTT deficits [41]. These findings are consistent with our observations, suggesting that the delayed onset of action may result from the gradual normalization of cortical dopamine transmission in SKF 38393 treated rats. Taken together, it appears that activation of the dopamine D1 receptor attenuated PCP-induced attentional deficits by ameliorating specific forms of inappropriate responding (i.e., false alarms and incorrect responding) confirmed in this cross-species translational 5C-CPT.

Repeated PCP-treatment resulted in a robust increase in premature, perseverative and TO responding, these effects were not improved by dopamine D1 receptor activation. NMDA receptor blockade in the medial prefrontal cortex (mPFC) increased premature and perseverative responding [64]. Blockade of dorsal striatal dopamine D1 receptors attenuated premature, but not perseverative, responding, while activation of dopamine D1 receptors has been shown to increase premature responding [64, 75]. SKF 38393 treatment in the current investigation had no effect on PCP-induced increases in premature responding. A potential limitation of the current investigation is the use of a single dose of SKF 38393. Previous investigations have indicated that 6 mg/kg was the most effective dose in not only improving 5C-CPT performance [21], but also other domains of cognition [56], and demonstrates efficacy in attenuating PCP-induced cognitive impairments in other tests assessing recognition memory or reversal learning [51, 52]. However, it is possible that 6 mg/kg SKF 38393 may not be the most efficacious dose to improve repeated PCP-induced deficits in the 5C-CPT. Indeed, the role of the dopamine D1 receptor in alterations in discrete aspects of 5-CSRTT performance has been shown to be dose-dependent [76]. A wider dose-response curve may have revealed a broader profile of attenuation rather than the

selective profile of SKF 38393-induced attenuation observed in the current investigation. Accurate attentional performance requires activity of a diverse network of brain regions [13]. Functional changes in the dorsolateral PFC, parietal cortices, basal ganglia, insular cortex, and supplementary motor cortex are involved in 5C-CPT performance [26]. In addition, anterior cingulate [77], limbic and temporal regions [14, 78, 79] have shown involvement in the myriad of CPTs used to assess vigilance in humans. Interestingly, many of these structures are compromised in schizophrenia [80, 81], and several overlap with volumetric deficits observed after sub-chronic PCP treatment in the rat [82]. Moreover, several of these regions also express dopamine D1 receptors [83, 84] and regulate aspects of inhibitory control and/or error detection [85]. The involvement of these structures in regulating aspects of behavioural inhibition, their sensitivity to PCP-induced structural deficits, and expression of dopamine D1 receptors may account for the profile of PCP-induced impairment in the 5C-CPT and the selective SKF 38393-induced attenuation of inappropriate responding observed here.

In summary, we have identified robust deficits in 5C-CPT performance as a result of repeated PCP treatment. Impairments in target detect and inhibitory control have been demonstrated. Repeated activation of the dopamine D1 receptor attenuated discrete aspects of this deficit and improved attentional performance. In conclusion, these results provide further evidence that the dopamine D1 receptor remains a suitable candidate for improving certain cognitive deficits observed in schizophrenia patients.

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Highlights

- Repeated PCP administration induced robust deficits in 5C-CPT performance.
- Pre-treatment with dopamine D1 receptor partial agonist, SKF 38393, partially attenuated PCP-induced deficits.
- Augmenting dopamine D1 receptors improved PCP-induced deficits by reducing inappropriate responding

Fig. 1.

Diagram summarising the treatment regimen used in the two test groups. All animals were administered PCP on days 4, 5 and 11 to 15, however, on days 11–15 one group was pre-treated with saline (**A**) while the other group was pre-treated with the dopamine D1 receptor agonist, SKF 38393 (**B**). Arrows indicate PCP injection (2.5 mg/kg i.p.). On days 1 to 3 and 6 to 10, all animals received saline (0.9%) injections. During the period of assessing the efficacy of SKF 38393, (days 11 to 15), animals were pre-treated with either saline (0.9%, i.p., n=11) or SKF 38393 (6 mg/kg i.p., n=12) 60 min before testing. PCP was administered to all animals 30 minutes before 5C-CPT testing.

Fig. 2.

Initial PCP administration disrupted 5C-CPT performance (n=11). Initial PCP treatment (days 4 and 5): (A) reduced signal discrimination without a significant effect on response bias (B). impaired target detection on both days and (C) increased false alarm responding on the second day (D). Response accuracy was reduced (E) and correct latency (F) was increased after initial PCP exposure. * denotes a significant effect of PCP alone compared to baseline (BL) (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$). Data presented as mean $\pm$ SEM.

Fig. 3.

Performance in the 5C-CPT test for 5 days after the initial two PCP injections (days 6 to 10) ($n=11$). Performance deficits after the initial PCP exposure (days 4 and 5) were transient. Sensitivity index (A), responsivity index (B), hit rate (C), false alarm rate (D) and response accuracy (E) were no different to baseline. During recovery, correct latency was faster compared to baseline on days 9 and 10 (F). * denotes significant effects of PCP alone compared to BL (baseline) (*, $p<0.05$). Data are presented as mean $\pm$ SEM.

Fig. 4.

5C-CPT performance in animals treated with PCP + saline (filled circles, n=11) or PCP with SKF 38393 (open circles, n=12). Signal sensitivity was impaired on days 11–15 in both groups. SKF 38393 partially attenuated PCP deficits on day 15 (A). Responsivity index (B) and hit rate (C) were reduced in both treatment groups on days 11–15. False alarm responding was increased in the PCP + saline group on day 15. This effect was absent on day 15 in the PCP + SKF 38393 group and the only increase in false alarm responding in this group was transient and only evident on day 11 (D). Response accuracy was impaired in

the PCP + saline group on days 11–15 and in the PCP + SKF 38393 group on days 11 and 12. The PCP-induced deficit in accuracy was attenuated in the SKF 38393 group by day 15 (**E**). Correct latency was increased in both groups on days 11–15 (**F**). # denotes a significant effect of PCP alone compared to baseline (BL) (# - $p < 0.05$, ## - $p < 0.01$, ### - $p < 0.001$). \$ denotes a significant effect of PCP + SKF 38393 compared to BL (\$ - $p < 0.05$, \$\$ - $p < 0.01$, \$\$\$ - $p < 0.001$). & denotes a significant effect of both groups collapsed and compared to BL (&&& - $p < 0.001$). * denotes between-subject effect between groups on days 11 to 15 (* - $p < 0.05$, ** - $p < 0.01$). Data are presented as mean $\pm$ SEM.

Table 1

PCP-induced disruption of 5C-CPT performance to initial exposure

Measure	Baseline	Day 4	Day 5
%Correct	67.71 ± 4.79	53.58 ± 6.30 **	39.67 ± 8.07 ***
% Omissions	27.26 ± 4.75	35.92 ± 6.15 *	49.14 ± 7.34 ***
CL	0.73 ± 0.04	0.87 ± 0.06 **	0.91 ± 0.07 **
RL	1.23 ± 0.06	1.51 ± 0.09	1.87 ± 0.19 **
Trials	120 ± 0.00	114 ± 3.77	108 ± 4.74 *
Persev	2.1 ± 0.5	9.4 ± 3.1 *	12.1 ± 4.3 **
TO	17.8 ± 5.7	35.3 ± 6.4 **	34.7 ± 7.0 **
Premature	7.4 ± 1.0	22.8 ± 6.2 *	26.4 ± 7.3 **

Behavioral measures are displayed as mean ± SEM. Performance on days 4 and 5 were compared to baseline.

* , p<0.05;

** , p<0.01;

*** , p<0.001.

Table 2

Effects of repeated PCP in animals pre-treated with either saline or SKF 38393

Measure	Pre-treatment	Baseline	Day 11	Day 12	Day 13	Day 14	Day 15
% Correct	Saline	67.71 ± 4.78	43.25 ± 7.31	*** 32.69 ± 6.60	*** 48.52 ± 7.64	*** 48.52 ± 7.09	*** 47.37 ± 4.89
	SKF 38393	70.30 ± 3.35	47.45 ± 4.11	24.36 ± 6.11	56.64 ± 4.98	48.39 ± 3.58	48.96 ± 4.73
% Omission	Saline	27.26 ± 4.75	45.76 ± 6.88	*** 55.44 ± 6.31	*** 39.11 ± 7.12	*** 40.82 ± 7.30	*** 38.98 ± 5.54
	SKF 38393	25.06 ± 3.17	43.26 ± 3.71	67.14 ± 5.64	37.83 ± 4.17	46.28 ± 3.36	45.09 ± 4.26
CL	Saline	0.73 ± 0.04	0.87 ± 0.07	*** 0.95 ± 0.04	*** 0.82 ± 0.05	*** 0.81 ± 0.05	*** 0.82 ± 0.04
	SKF 38393	0.68 ± 0.03	0.93 ± 0.06	0.91 ± 0.06	0.81 ± 0.05	0.84 ± 0.03	0.80 ± 0.03
RL	Saline	1.22 ± 0.05	1.75 ± 0.19	*** 1.84 ± 0.14	*** 1.43 ± 0.1	*** 1.36 ± 0.04	* 1.29 ± 0.03
	SKF 38393	1.17 ± 0.04	1.59 ± 0.09	2.19 ± 0.28	1.49 ± 0.07	1.60 ± 0.08	1.50 ± 0.09
Trials	Saline	120 ± 0.00	102 ± 5.25	*** 106 ± 5.07	*** 104 ± 5.40	** 105 ± 5.12	*** 105 ± 5.43
	SKF 38393	120 ± 0.00	112 ± 3.32	100 ± 5.86	116 ± 2.16	109 ± 3.54	107 ± 4.65
Persev	Saline	2.10 ± 0.49	13.90 ± 4.93	*** 15.33 ± 4.06	* 18.30 ± 4.4	*** 22.20 ± 5.08	*** 22.44 ± 4.65
	SKF 38393	2.06 ± 0.63	13.67 ± 3.42	6.08 ± 1.97	16.75 ± 4.32	16.17 ± 4.84	19.36 ± 5.83
TO	Saline	17.83 ± 5.73	32.50 ± 4.48	*** 32.78 ± 4.93	*** 40.70 ± 8.53	*** 64.90 ± 14.53	*** 59.22 ± 13.96
	SKF 38393	10.77 ± 1.38	44.33 ± 9.10	29.50 ± 6.22	30.75 ± 4.72	42.83 ± 5.30	40.64 ± 7.13
Premature	Saline	7.43 ± 1.03	24.88 ± 7.22	*** 34.11 ± 8.58	*** 40.2 ± 7.6	*** 40.4 ± 7.65	*** 48.11 ± 10.30
	SKF 38393	7.27 ± 1.67	26.66 ± 5.51	12.16 ± 3.65	29.16 ± 5.51	30.25 ± 7.01	34.9 ± 10.01

Behavioral measures are displayed as mean ± SEM. Performance on days 11 – 15 were compared to baseline.

* , p<0.05;

* , p<0.01;

*** , p<0.001.