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The five choice serial reaction time task: Comparison between Sprague–Dawley and Long–Evans rats on acquisition of task, and sensitivity to phencyclidine

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ABSTRACT

The 5-choice serial reaction time task (5-CSRTT) allows examination of multiple aspects of cognition/executive functions (attention/impulsivity/ perseveration). Most 5-CSRTT studies are performed with pigmented (i.e. Long–Evans: LE) rats; however, albino strains (i.e. Sprague–Dawley: SD) are more commonly used in behavioural pharmacology experiments. Hence, we compared 5-CSRTT performances of SD and LE rats and their sensitivity to acute phencyclidine (PCP, 1–2.5 mg/kg). SD required significantly fewer sessions (35 versus 50) than LE rats for task acquisition, especially at shortest stimulus light duration (1 s). However, once trained, under vehicle conditions, both strains performed similarly. In contrast, PCP treatment differentially affected the two strains. Thus, whilst percentage of accuracy was decreased for both strains, in SD rats number of premature responses was more markedly decreased, whereas omissions and latency time to correct responses were more notably increased. In addition, PCP monotonically diminished in SD, but augmented (1–1.5 mg/kg) in LE rats compulsive responding. To summarize, under our experimental conditions, the SD offer advantages over LE strain for speed of acquisition of 5-CSRTT. Once trained, basal performances of both strains were equivalent and stable enough for challenge with pharmacological compounds. However, PCP differentially affected the strains on several parameters considered.

1. Introduction

The five choice serial reaction time task (5-CSRTT) was originally described by Carli et al. (1983). It is considered to be an analogue of the Continuous Performance Test (Beck et al., 1956; Mirski and Rosvold, 1960), in which schizophrenic patients show impaired performance (Robbins, 2002), and/or of the Leonard's 5-choice serial reaction time task for humans, a model for selective attention that measures accuracy and speed of responding (Leonard, 1959). The 5-CSRTT allows for the simultaneous examination of multiple aspects of cognition and executive functions. In particular, it gauges sustained and divided attention abilities of rodents in a task requiring localization and retention of spatial cues (correct detection of a brief visual stimulus presented across one of five locations). In addition, it can also measure premature responding (i.e., responses before the onset of the light stimulus), a marker of impulsivity (i.e. the inability to inhibit a motor response in the anticipation of food reward) (Dalley et al., 2004; Robbins, 2002). Attentional impairment and impulsivity constitute core elements of clinical disorders such as attention deficit/hyperactivity disorder (ADHD) (Sagvolden et al., 1998; Sagvolden and Sergeant, 1998), schizophrenia (Laurent et al., 1999; Nuechterlein and Dawson, 1984), fibromyalgia (Young and Redmond, 2007), depression (Solanto, 2000; Taylor Tavares et al., 2007), Parkinson's disease (Walitza et al., 2007) and post-traumatic stress disorders (Kotler et al., 2001; Southwick et al., 1999), to cite the main ones. As such, the 5-CSRTT constitutes a useful tool to explore dysfunctions of cognition and executive function of a type commonly found in ADHD and schizophrenia (Robbins, 2002).

The 5-CSRTT also permits assessment of perseverative responding (i.e. additional responses performed after a correct one but before collection of the reward), a marker of compulsive behaviour. Finally, the latency time to respond correctly constitutes a measure of speed of processing, whereas the latency time to retrieve food pellets is a putative measure of motivation (Carli and Samanin, 1992; Harrison et al., 1997; Robbins, 2002).

The majority of experiments with this task have used Hooded Lister (LH) or Long–Evans (LE) rats as subjects, both types having pigmented retinas. However, these strains are less commonly used for most other behavioural tasks, which complicates comparison between tests (in terms, for example, of pharmacological reactivity). Indeed, albino rats (Sprague–Dawley: SD, and Wistar) are most frequently used in behavioural pharmacology experiments. However, the visual performance of these rats has been questioned (Paine et al., 2007; Searle, 1968), which might explain the paucity of studies that use albino rats in a task (5-CSRTT) that calls upon the ability of subjects to correctly detect and report visual stimuli (Amitai et al., 2007; Blondel et al., 1999, 2000; Jin et al., 1997; Le Pen et al., 2003; Mirza and Bright, 2001; Nakamura and Kurasawa, 2000; Paine et al., 2007). Also, in a

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study that compared the learning abilities of several rat strains in memory tasks with a strong spatial component, albino, and in particular SD rats, performed less well than their pigmented (LE) congeners (Harker and Whishaw, 2002).

Few studies have compared albino versus pigmented retina rats in the 5-CSRTT. Mirza and Bright (2001) reported that nicotine improved attention in SD but not in LH rats, thus showing that SD were more appropriate than LH for studying the impact of nicotine on attentional processes using this task (due to their lower level of performance under basal condition). Higgins et al. (2007) have shown that (1) under control (vehicle) conditions, LE performed the 5-CSRTT better than SD rats and with a shorter latency time; (2) caffeine did not modify these differences. Finally, Didriksen and Christensen (1993) have reported that Wistar and LE rats performed with the same accuracy.

The purpose of the present study was three-fold: first, to compare the ability of LE and SD rats (the strain most commonly used in behavioural pharmacology experiments), to acquire the 5-CSRTT, i.e. to reach pre-determined learning criteria. Second, to assess their stability of performance after acquisition, as this parameter is crucial for long-term pharmacological experiments. Third, to assess their sensitivity to the disruptive effects of phencyclidine (PCP), a glutamate/NMDA receptor non-competitive blocker, frequently used to induce deficits in various memory/cognition models. Indeed, glutamatergic/NMDA receptor antagonists disrupt cognitive function in both humans (Adler et al., 1999; Allen and Young, 1978; Bakker and Amini, 1961; Javitt and Zukin, 1991; Krystal et al., 1994) and animals (Handelmann et al., 1987; Jentsch and Roth, 1999; Krystal et al., 1994; Paine et al., 2007; Stefani and Moghaddam, 2005), producing deficits paralleling those present in schizophrenia (Pradhan, 1984). Hence, phencyclidine should be a useful agent to induce schizophrenia-like cognitive deficits such as attentional impairments and deficits in executive functions (Amitai et al., 2007; Baviera et al., 2008; Greco et al., 2005; Le Pen et al., 2003; Moghaddam and Adams, 1998) in animal models, especially in 5-CSRTT.

2. Materials and methods

2.1. Animals

11 Sprague–Dawley (Charles River, l'Arbresle, France) and 7 Long–Evans (Janvier, Le-Genest-St-Lisle, France) male rats, weighing 180±20 g upon arrival, were group-housed (n=5/cage), in stainless steel cages with grid flooring (26×42×18 cm; W×L×H). They were kept in an environmentally-controlled room (temperature 21±1 °C and relative humidity 55±5%) on a 12 h:12 h light:dark cycle (lights on at 7:00 a.m.). Before starting the experiment, subjects were held in quarantine for 4 to 8 days, with free access to standard laboratory food (A04, Scientific Animal Food and Engineering, Epinay sur Orge, France) and filtered water (0.22 µm pores; in bottles). One week before the beginning of the experiment, rats were housed individually in plastic hanging cages (31×11×18 cm, L×W×H) with metal grid floors. Access to standard food was restricted to 15 g per day to progressively reduce body weight to 85% of that under free-feeding conditions. Behavioural testing took place between 8.00 and 12.00 h.

Animals were handled and cared for in accordance with the Guide for the Care and Use of Laboratory Animals (National Research Council). Animals were housed and tested in an Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC)-accredited facility in strict compliance with all applicable regulations, and the protocol was carried out in compliance with French regulations and with local Ethical Committee guidelines for animal research.

2.2. Apparatus

Rats were tested in one of six identical operant conditioning boxes (29×25×32 cm, W×L×H, Coulbourn Instruments, Lehigh Valley, PA, USA), enclosed in ventilated and sound-attenuated chambers (54×40×45 cm, W×L×H). Each box was fitted with 5 holes disposed on the front panel, in a linear horizontal array. Holes were 2.5 cm in diameter, with their centre positioned 2.5 cm above the grid floor, and were 4.8 cm (centre to centre) apart. A food pellets magazine positioned in the middle of the opposite panel delivered 45 mg dustless precision pellets (BIOSERV, Frenchtown, NJ, USA). A house light was located 17 cm above the top edge of the food magazine. Infrared beams enabled detection of nose-pokes (NP) into holes or head entries into the magazine. All events were controlled and recorded by the Med-PC software (SOF-700W version 1.15, Med Associates Inc., St. Albans, VT, USA).

2.3. Experimental procedure

The procedure was based on that described by Carli et al. (1983). All sessions lasted for 30 min and were conducted daily (5 days/week). The house light was switched on during the entire length of all sessions (except during time-out periods). At the beginning of the very first session, five pellets were delivered into the food magazine, and the stimulus light in each of the five holes was turned on for 60 s (referred to as the limited-hold period: L-H). A NP into any of the five holes during this 60 s L-H resulted in the extinction of all five lights and the delivery of a pellet. Another 60 s cycle was automatically initiated, with this time only four stimulus lights turned on (the one in which the rat nose-poked stayed turned off). If the rat nose-poked into any of the four remaining lit holes, a food pellet was delivered, and all stimulus lights switched off. In the next cycle, 4 holes were lit (not the one in which there had been a NP in the immediately preceding cycle). A NP into the "dark" hole was inconsequential. In the absence of a NP (omission) during this 60 s L-H, a pellet was still automatically delivered, and the next 60 s cycle initiated, again with 4 stimulus lights switched on. This cycling was implemented until the end of the first 30 min session. During consecutive daily sessions (corresponding to the first pre-training period, PTR1), the protocol was similar, except for the five pellets that were not delivered at the start of each session. Once a rat performed at least 20 NP into any lit hole, there was no more free pellet automatically delivered every min. Furthermore, rats were moved to the second pre-training period (PTR2) once they performed at least 100 NP in a single PTR1 session.

In the PTR2, rats were restricted to 10 g of chow/day: this was implemented to compensate for the increased number of pellets earned during daily sessions. During PTR2 sessions, a single hole, randomly chosen, was lit up for 60 s. A NP into the lit hole (correct response) resulted in the delivery of a pellet, followed by a 5 s inter trial interval (ITI), during which the stimulus light was switched off. The next cycle was initiated when the rat collected the pellet. As before, a NP into a dark hole (incorrect response) was without consequence. If a rat did not respond at all (omission) within the 60 s L-H period, there was a 5 s time-out period during which both the stimulus and the house lights were turned off. After an incorrect response or an omission, the next cycle was automatically initiated after the L-H. Once a rat performed at least 100 NP into lit holes (i.e. 100 correct responses) during a single session, it progressed to the training schedule.

During this third step, the period during which the stimulus light was presented was reduced progressively (i.e. 60, 10, 5, 3, 2.5, 2, 1.5 and finally 1 s). Each time a rat performed at least 100 NP and greater than 80% accuracy (i.e. (number of correct responses×100)/(number of correct+incorrect responses) was above 80) during a training session, the length of stimulus presentation was sequentially reduced during following sessions. Moreover, incorrect responses (NP in dark holes) or failures to respond (omission) during the L-H were now punished with a 5 s time-out (with the house light turned off), and the next trial was automatically initiated, with the same hole lit again. After a correct response, collection of the food pellet started a new

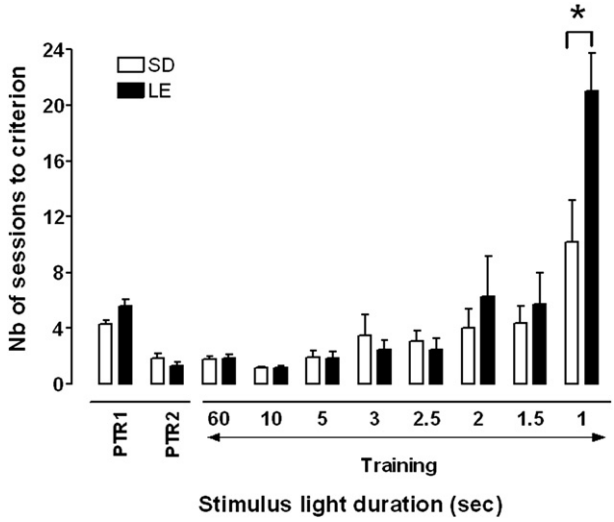

Fig. 1. Number of sessions required to reach criteria as a function of the duration of the stimulus light: Comparison between Sprague–Dawley (SD) and Long–Evans (LE) rats. Symbols are means+SEM. *$p<0.05$, Dunnett's post-hoc tests following significant two-way ANOVA. $N=11$ rats for SD, $n=7$ rats for LE. PTR: pre-training.

trial: another single hole, randomly chosen, was lit up for the considered stimulus duration. Premature/impulsive responses (responses in one of the holes during the ITI) and compulsive responses (repetitive responding after a correct NP, in the "correct" hole before collection of the reward) were recorded but not punished. Premature/impulsive responses were not punished as we were interested in having a 5-CSRTT with high basal levels of premature/impulsive responding, with the aim of subsequently studying the pharmacological sensitivity of this parameter in the context of a ADHD model (a pathology characterized by a high level of compulsivity and impulsivity).

2.4. Pharmacological treatments

Once rats attained a stable level of performance (i.e.: NP>100 and 80% of accuracy, during 3 consecutive training sessions with a stimulus duration of 1 s), they were subjected to the pharmacological treatment phase, which lasted for 5 weeks. From Monday to Thursday, rats were administered twice with vehicle 60 min (i.p. or s.c., alternatively) and 45 min (s.c.), before being subjected to a training session. Note: rats were injected with a first injection of vehicle, as some of them were subsequently subjected to pharmacological interaction studies (not reported here) requiring double injection procedures. After each injection, animals were returned to their home cages until testing. On each Friday, rats that were stable (see above) received a vehicle administration 60 min, and a s.c. injection of vehicle or phencyclidine (PCP, 1.0, 1.5, 2.0 or 2.5 mg/kg), administered in an unsystematic order, 45 min before being tested. Every rat received, as the second injection, each dose of PCP and one vehicle treatment.

2.5. Data analysis

The dependent variables analysed were:

- Percentage of accuracy: (number of correct responses)×100/(number of correct+incorrect responses)
- Percentage of omissions: (number of omissions/number of total trials)×100
- Number of premature responses
- Number of compulsive responses
- Number of trials completed (sum of correct and incorrect responses)
- Latency time to make a correct NP: time elapsed between stimulus onset and a NP into the correct (i.e. lit) hole
- Latency time to collect the pellet: time elapsed between a NP into the correct hole and pellet collection from the food magazine.

During pharmacological treatment sessions, the above parameters were taken into account only if the number of correct and incorrect responses totalled ten or more.

For acquisition of the task, data (number of sessions to reach successive learning criteria) were analysed with a two-way ANOVA with the stimulus light duration as the within-subjects factor, and the strain as the between-subjects factor, followed, when appropriate, by Dunnett's post-hoc tests for multiple comparisons. For the PCP treatment experiment, data were subjected to a two-way ANOVA, with the dose of PCP as the within-subjects factor, and the strain as the between-subjects factor, followed, when appropriate, by Dunnett's post-hoc tests for multiple comparisons.

2.6. Drugs

An injection volume of 10 ml/kg was used throughout and doses refer to the weight of the free base. PCP hydrochloride was obtained from Francopia (Paris, France) and was dissolved in distilled water and administered s.c.

3. Results

3.1. Comparison of the number of sessions to criteria for each training phase for SD and LE rats

Overall, the strains significantly differed ($F(1,154)=4.71$, $p<0.05$) in the number of sessions to reach successive learning criteria (Fig. 1); there was also a significant strain×session interaction factor ($F(9,154)=3.17$, $p<0.01$). Moreover, shorter stimulus light durations were associated with longer time of training, as evidenced by a significant session factor ($F(9,154)=18.79$, $p<0.001$). Indeed, there was a significant (post-hoc test) tendency for LE rats to require a higher number of sessions (21.0±2.8) than SD rats (10.2±3.0) to reach criterion in the sessions with the shortest (1 s) stimulus light duration (last pair of bars, Fig. 1).

When summing the number of sessions to reach criteria across all training phases, statistical analysis (*t*-test: $t=2.52$, $df=16$, $p<0.05$) confirmed that LE rats required significantly more sessions before being testable with pharmacological challenges (49.6±4.6 versus 35.4±3.4).

3.2. Comparison of baseline performance between SD and LE rats

Whatever the parameters considered, basal performance (i.e. during a test session following a vehicle injection) of both strains was not significantly different (Table 1). LE rats presented a marginally higher number of premature and compulsive responses, but presented performances remarkably similar to those of SD rats for the other four parameters studied.

Table 1
Summary of basal (post training) performance of Long–Evans (LE) and Sprague–Dawley (SD) rats

	SD	LE	*t*-test
Percentage accuracy	84.6±1.6	83.1±1.9	$t=0.61$, $df=16$, $p>0.05$
Percentage omissions	0.04±0.04	0.08±0.08	$t=0.50$, $df=16$, $p>0.05$
Premature responses	210.0±29.3	258.4±44.5	$t=0.95$, $df=16$, $p>0.05$
Compulsive responses	18.4±7.1	23.0±5.6	$t=0.46$, $df=16$, $p>0.05$
Latency time to correct responses (s)	0.65±0.04	0.72±0.07	$t=0.94$, $df=16$, $p>0.05$
Latency time to collect pellets (s)	1.36±0.23	1.38±0.08	$t=0.07$, $df=16$, $p>0.05$

Values are expressed as means±SEM, and were obtained during a test session (Friday) following a vehicle injection.

3.3. Effects of acute treatment with phencyclidine on performances of SD and LE rats

Analysis of the percentage of accuracy (Fig. 2A) did not show any significant difference between strains ($F(1,70)=0.003$, $p>0.05$), or for the strain×treatment interaction $F(4,70)=0.53$, $p>0.05$), but pointed to a significant decrease of accuracy as a function of the dose of PCP ($F(4,70)=18.84$, $p<0.001$). Indeed, post-hoc analysis showed a significant difference between percentage of accuracy obtained after treatment with 1.5, 2.0 and 2.5 mg/kg PCP, in comparison with vehicle treatment for both strains. The mean percentage of accuracy was circa 85% for LE and SD rats for vehicle treatment, and fell to circa 50% with 2.5 mg/kg PCP.

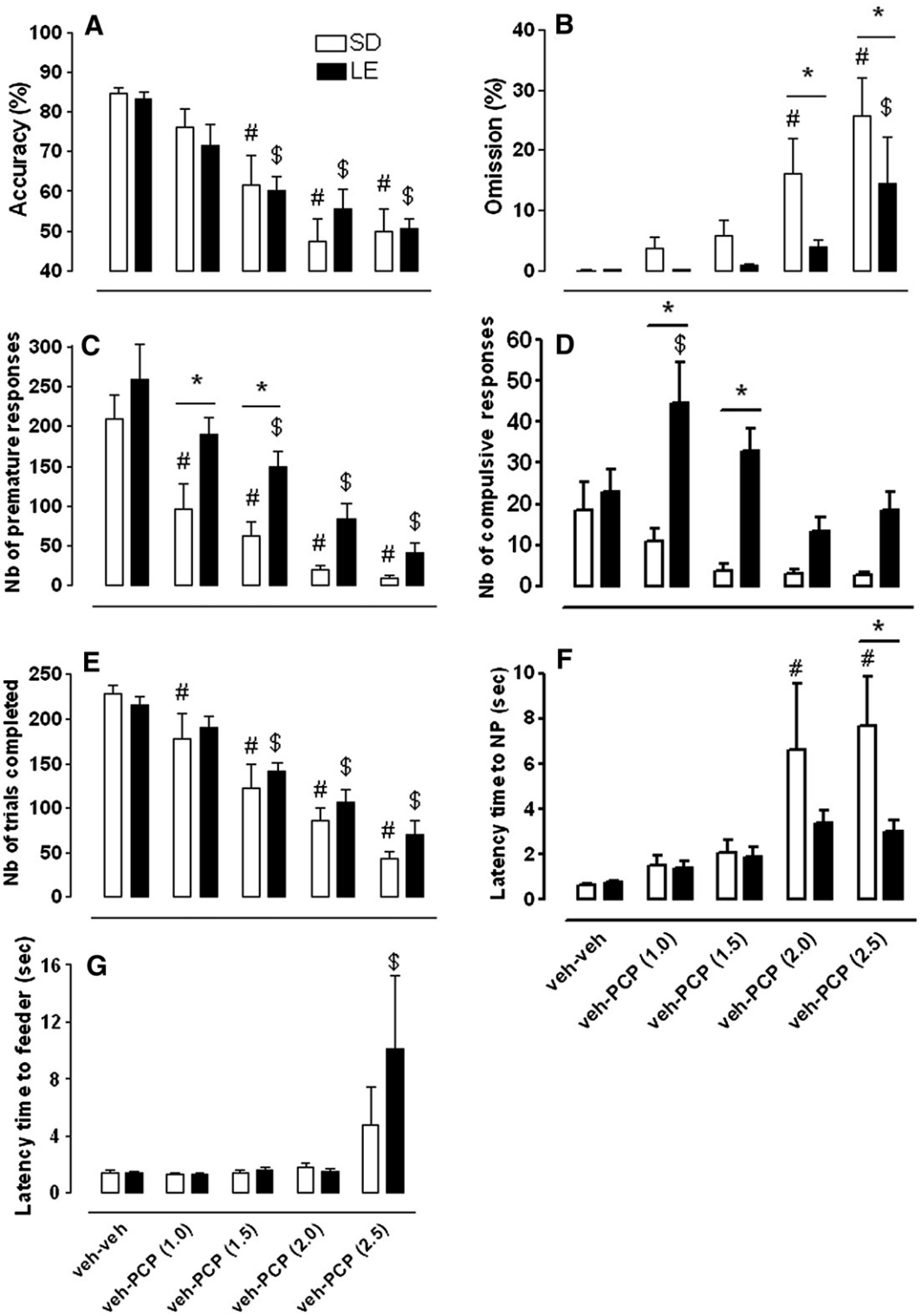

Fig. 2. Effects of treatment with phencyclidine on performance in the 5-CSRTT: comparison between Sprague–Dawley (SD) and Long–Evans (LE) rats. Symbols are means+SEM. Rats were injected twice, with vehicle (veh) 60 min before testing and with vehicle or phencyclidine (PCP) 45 min before testing. *$p<0.05$ for comparison between SD and LE rats, $^{\#}p<0.05$, compared with the vehicle control group for SD rats, $^{\$}p<0.05$, compared with the vehicle control group for LE rats, Dunnett's post-hoc tests following significant two-way ANOVA. NP: nose-pokes. $N=7$ (veh and PCP) for LE rats; $n=11$ (veh) and $n=6$–9 (PCP) for SD rats.

The percentage of omission (Fig. 2B) was significantly higher for SD than for LE rats ($F(1,70)=7.89$, $p<0.01$), and varied as a function of the dose of PCP ($F(4,70)=9.64$, $p<0.001$). Post-hoc analysis revealed that SD rats had significantly higher omission rates than LE rats at 2.0 and 2.5 mg/kg of PCP. There was however no interaction between the two factors ($F(4,70)=1.10$, $p>0.05$). The maximum percentage of omissions observed was 25.6%±6.4 at 2.5 mg/kg of PCP for SD rats.

LE and SD rats also significantly differed ($F(1,70)=16.08$, $p=0.0001$) in terms of the number of premature/impulsive responses (Fig. 2C), with values significantly higher for the former strain at 1 and 1.5 mg/kg of PCP. Moreover, the number of premature/impulsive responses significantly decreased when the dose of PCP was augmented ($F(4,70)=21.11$, $p<0.001$). Indeed, post-hoc analysis showed a significant difference for the number of premature responses between all doses of PCP and vehicle for SD rats, and at higher doses only (1.5 to 2.5 mg/kg) for LE rats. This parameter dramatically decreased from 258.4±44.5 (LE) and 210.0±29.3 (SD) for vehicle treated rats to 40.7±12.7 (LE) and 10.2±3.4 (SD), at the highest dose of PCP tested. The interaction factor did not reach the level of significance ($F(4,70)=0.51$, $p>0.05$).

The number of compulsive responses (Fig. 2D) was overall significantly different between strains ($F(1,70)=31.51$, $p<0.001$), and as a function of treatment ($F(4,70)=4.58$, $p<0.01$). However, each strain did not react in the same manner with increasing doses of PCP, as revealed by a significant interaction factor ($F(4,70)=2.91$, $p<0.05$). More specifically, the number of compulsive responses of SD rats tended to be monotonically reduced with increasing doses of PCP from 18.36±7.1 for vehicle treated rats to 2.5±0.67 at 2.5 mg/kg of PCP. In contrast, LE rats showed an increase in compulsive responding with PCP at 1.0 mg/kg (+194%), and returned towards control values at higher doses of PCP. Inter-strain statistical analysis confirmed that SD and LE rats significantly differed in their response to PCP at 1.0 and 1.5 mg/kg. Concerning the total number of trials completed, there was a significant effect of the treatment ($F(4,70)=34.16$, $p<0.001$), but no significant interaction or strain effects ($F(4,70)=0.71$, $p>0.05$ and $F(1,70)=1.47$, $p>0.05$). PCP significantly diminished the number of trials at all doses tested in SD rats, and from 1.5 mg/kg in LE rats (Fig. 2E).

The latency time to perform a correct NP (Fig. 2F) differed significantly between strains ($F(1,70)=4.40$, $p<0.05$) and as a function of the dose of PCP ($F(4,70)=5.86$, $p<0.001$). Latency time was significantly increased from 0.65±0.04 s for vehicle treated SD rats to 6.6±2.9 and 7.7±2.1 s for 2.0 and 2.5 mg/kg, respectively. Although there was no significant interaction ($F(4,70)=1.47$, $p>0.05$), post-hoc analysis detected significant differences between both strains at 2.5 mg/kg of PCP (latency time went up to 7.7±2.1 s for SD rats, but only to 3.0±0.5 s for LE rats).

The latency time to retrieve pellets (Fig. 2G) in the food magazine did not vary overall between LE and SD rats ($F(1,70)=1.08$, $p>0.05$; interaction factor: ($F(4,70)=0.99$, $p>0.05$). However, it was significantly longer ($F(4,70)=5.04$, $p<0.001$) as a function of the dose of PCP. In particular, 2.5 mg/kg of PCP produced a significant increase from 1.4±0.1 (under vehicle treatment) to 10.1±5.2 s for LE rats.

4. Discussion

The main findings of the present study are as follows: 1) There was a notable difference in the ability of the two strains to acquire the 5-CSRTT: indeed, the total number of sessions to reach the learning criteria was less for SD than for LE rats. However, this effect was manifest entirely for sessions with the shortest stimulus light duration. 2) Conversely, concerning basal performance once training has been achieved, both strains did not fundamentally differ, and showed robust stability of performance in-between pharmacological test sessions. 3) There were however differences in terms of the reactivity of the two strains to the disrupting effects of the psychotomimetic phencyclidine.

4.1. SD rats acquire the task more rapidly than LE congeners

SD rats acquired the task with, on average, 10 sessions fewer than their congeners. Both strains learnt equally fast for long to intermediate durations of light stimulus, but differed in sessions with 1 s stimulus duration. Indeed, during acquisition, SD were notably more efficacious than LE rats for short stimulus duration (i.e. significant difference at 1 s). Considering the visual nature of the stimulus, and that SD rats are albino, this finding may seem rather odd as one would have expected pigmented retina rats to outperform albino rats. Indeed, the intensity of the stimulus has been shown to influence performance in this task (Carli et al., 1983). However, it has been reported that albino rats have higher light sensitivity at lower light levels (Thomas et al., 2005). It can also be argued that shorter durations are more demanding on the attentional capacities of rats, implying that SD rats might have higher attentional capacities than LE rats, at least under the current experimental conditions. This is at variance with other findings with the 5-CSRTT (see below) showing that in general, LE rats perform better than SD rats on attentional parameters. However, this overall better aptitude of SD rats to acquire a 5-CSRTT might only apply to the present experimental conditions, and that variants in the protocol (such as criterion for accuracy, punishing or not premature responses, see below for more extended list) might greatly affect this outcome. It is unlikely that SD rats have a higher level of motivation to perform this task, because if that had been the case, one would have expected learning performances to be higher across all stimulus light durations.

4.2. Once trained, SD and LE rats do not fundamentally differ in basal performance of the 5-CSRTT

Following acquisition of the task, during test sessions under vehicle conditions, LE and SD rats exhibited similar levels of performance across all six parameters recorded. Overall, this comparative analysis of baseline performance allows one to conclude that both strains are suitable for conducting long-term pharmacological experiments.

Studies assessing performances of different strains of rats in the 5-CSRTT are scant, and results inconsistent between them. Hence, in some studies, pigmented rats performed better than albino rats (Higgins et al., 2007; Mirza and Bright, 2001), whilst in another one, albino rats were capable of learning the 5-CSRTT but were unable to reach the same level of accuracy than that of LE rats, despite more extensive training (Paine et al., 2007). In contrast, Didriksen and Christensen (1993) did not observe differences between three strains (Wistar, Long–Evans and a mixed strain) in a comparative study. It must be added that comparisons on performances of various strains tested in different laboratories should be made prudently in view of numerous differences between experimental procedures, which are sometimes only partially described. Hence (non exhaustive list), some authors have used 9 hole chambers with only 5 of them active, whereas others have used 5 hole chambers; the type of light stimuli (LED versus incandescent light bulb) and its intensity differed; the location of the stimulus in the hole changed (at the bottom or at the rear); the final stimulus duration varied (1 or 0.5 s); the learning criteria was more or less stringent (>60% or 80% of correct responses and <15% or 20% of omissions), inter trial intervals were fixed or variable; the duration of training session greatly varied (15, 20, 30 or 60 min). Any one, or a combination of any number of these differences, might explain reported variations in performances in the 5-CSRTT.

4.3. Phencyclidine differentially affects SD and LE rats in performance of the 5-CSRTT

Overall, the two strains responded differentially to the effects of PCP. This could either stem from differential pharmacodynamic or

pharmacokinetic properties (or a subtle combination of the two) of PCP between SD and LE rats. However, assessing the pharmacokinetic profile of PCP, under the present experimental conditions, was both out of the scope of the present study, and not feasible for reasons of lack of dedicated resources for pharmacokinetic analysis.

The percentage of accuracy was dose-dependently diminished by acute treatment with PCP in very similar manners in the two strains. This finding is consistent with previous observations that systemic administration of PCP decreased accuracy in albino (Amitai et al., 2007; Jin et al., 1997; Le Pen et al., 2003) as well as in pigmented rats (Jentsch and Anzivino, 2004). A similar effect was also obtained with other NMDA receptor antagonists, such as CPP and dizocilpine (Baviera et al., 2008; Carli et al., 2006; Mirjana et al., 2004; Paine et al., 2007). This diminution could reflect an attentional deficit for both strains at lower doses of PCP (up to 1.5 mg/kg for SD rats and 2 mg/kg for LE rats), as it was not accompanied by a modification in the number of omissions and the latency times to nose-poke. However, at higher doses, the specificity of PCP on attentional performances might be questioned for SD rats (2 and 2.5 mg/kg), as it was concomitant with an increase in omission and in the nose-poke latency time. Hence, it might be the case that the observed decrease in accuracy in SD rats partly or mainly results from a non-specific motor impairment produced by high dose of PCP (Sams-Dodd, 1997; Takahashi et al., 2001). An implication of an effect of the highest dose of PCP on motivational processes is unlikely for SD rats, but possible for LE rats, considering that the latency time to collect food pellets, taken as an indicator of motivation (Carli and Samanin, 1992; Harrison et al., 1997; Robbins, 2002) was increased for the latter strain only. However, the exact impact of motivation cannot be accurately evaluated with our protocol, since initiation of a new trial was not controlled by the animal in case of an incorrect response or of absence of responding (cf Experimental procedure).

PCP treatment dose-dependently decreased premature responses, with a more marked effect in SD than in LE rats. This is in stark contrast with the literature, which generally reports an increase of premature responding following treatment with NMDA receptor antagonist in albino (Le Pen et al., 2003; Paine et al., 2007) as well as in pigmented rats (Baviera et al., 2008; Higgins et al., 2003, 2005; Mirjana et al., 2004). The sole exception being Amitai et al. (2007), who reported a decrease in the number of premature responses following acute (despite a low level of basal premature responding), but an increase following repeated administration of PCP (Amitai et al., 2007). However, under our training and testing conditions, premature responses were not punished, and as a consequence, were much higher than those reported in other 5-CSRTT studies in which those responses were usually punished. Hence, it might be the case that basal level of premature responding was too high to be further enhanced by PCP, at least at the doses tested herein. Therefore, the effects of NMDA receptor antagonists on this parameter might be highly dependent on the baseline level of premature responses, as argued by Paine et al. (2007) for psychostimulants.

Compulsive responding was differentially affected by PCP in the two strains. In fact, whereas PCP tended to monotonically decrease this parameter in SD rats, it augmented it, at 1 mg/kg (and less so at 1.5 mg/kg), in LE congeners. Several studies have described an increase of compulsive responses with pigmented (Baviera et al., 2008; Carli et al., 2006; Higgins et al., 2003, 2005; Mirjana et al., 2004) as well as albino rats (Le Pen et al., 2003). However, Amitai et al. (2007) have related an absence of effect of PCP on compulsive responses in albino rats. An increase in compulsive responding is usually ascribed to perseverative behaviour (i.e. loss of inhibitory response control or the inability to shift out of a behavioural pattern). Our data suggest that PCP, under our testing conditions, did not significantly affect this executive function in albino rats (although there was a trend to decrease it), whereas it did, at two doses (1.0 and 1.5 mg/kg), augment it in pigmented rats. It might be that a possible natural tendency, brought under control by training (vehicle values do not differ between the two strains), reappears following treatment with PCP. This characteristic of LE rats would warrant further investigation, in particular to assess if doses of PCP lower than those studied here can produce even higher levels of compulsive responding. Indeed, if low doses of PCP can increase compulsive responding without affecting other parameters, then LE rats might be advantageously used in 5-CSRTT to model pathologies characterized by high levels of perseverative behaviour, such as compulsive–obsessive disorders.

5. Summary and conclusions

When considering basal performances, either strain of rat studied here (SD or LE) seems to be appropriate for conducting studies on the 5-CSRTT. Although LE rats took longer for acquisition of the task, the two strains did not differ in terms of level and stability of performance once trained. There were however some notable differences concerning the sensitivity of these two strains to PCP, particularly on compulsive responding. Whether or not this differential pharmacological sensitivity would apply to other classes of psychotomimetic is unknown, but warrants further investigation. It may be surmised that the choice of the rat strain in the 5-CSRTT should therefore be influenced by the nature of the parameters one wishes to focus on.

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