Original Paper

Dopamine dysregulation in the prefrontal cortex relates to cognitive deficits in the sub-chronic PCP-model for schizophrenia: A preliminary investigation

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Samantha L McLean[1], Michael K Harte[2], Joanna C Neill[2] and Andrew MJ Young[3]

Abstract

Rationale: Dopamine dysregulation in the prefrontal cortex (PFC) plays an important role in cognitive dysfunction in schizophrenia. Sub-chronic phencyclidine (scPCP) treatment produces cognitive impairments in rodents and is a thoroughly validated animal model for cognitive deficits in schizophrenia. The aim of our study was to investigate the role of PFC dopamine in scPCP-induced deficits in a cognitive task of relevance to the disorder, novel object recognition (NOR).

Methods: Twelve adult female Lister Hooded rats received scPCP (2 mg/kg) or vehicle via the intraperitoneal route twice daily for 7 days, followed by 7 days washout. In vivo microdialysis was carried out prior to, during and following the NOR task.

Results: Vehicle rats successfully discriminated between novel and familiar objects and this was accompanied by a significant increase in dopamine in the PFC during the retention trial ($p < 0.01$). scPCP produced a significant deficit in NOR ($p < 0.05$ vs. control) and no PFC dopamine increase was observed.

Conclusions: These data demonstrate an increase in dopamine during the retention trial in vehicle rats that was not observed in scPCP-treated rats accompanied by cognitive disruption in the scPCP group. This novel finding suggests a mechanism by which cognitive deficits are produced in this animal model and support its use for investigating disorders in which PFC dopamine is central to the pathophysiology.

Keywords

Dopamine, prefrontal cortex, cognition, phencyclidine, object recognition

Introduction

The novel object recognition (NOR) task was developed by Ennaceur and Delacour and is based on the natural propensity of rats to explore novel objects (Ennaceur and Delacour, 1988). It is a non-rewarded, ethologically relevant test of visual object recognition memory (Puma et al., 1998). Indeed, NOR has been listed by the Measurement and Treatment Research to Improve Cognition in Schizophrenia initiative as relevant for studying visual learning and memory deficits in schizophrenia (Young et al., 2009). Such tests of visual recognition memory are increasingly being used to detect novel drugs for improvement of cognitive dysfunction in schizophrenia and other human disorders, including Alzheimer's disease, Parkinson's disease, and Autism Spectrum Disorder (Grayson et al., 2015).

The brain regions thought to be involved in object recognition memory depend on the length of the inter-trial interval (ITI). We have recently shown that normal unimpaired animals lose the ability to discriminate objects following an ITI of 6 h (McLean et al., 2016). Rats with hippocampal lesions exhibit impairments in object recognition following long ITIs (>15 min), but not short intervals of <15 min (Clark et al., 2000). Although much of the evidence indicates a critical role for the perirhinal cortex in object recognition memory following short ITIs (Brown and Aggleton, 2001; Ennaceur et al., 1996; Gaffan and Murray, 1992; Hannesson et al., 2004; Meunier et al., 1993), research also suggests that the prefrontal cortex (PFC) may also contribute to recognition memory. PFC neurons have been shown to relay information concerning the relative familiarity of individual stimuli (Xiang and Brown, 2004), and damage to this area has been shown to impair recognition memory (Kolb et al., 1994; Ragozzino et al., 2002). More recently, fMRI studies have demonstrated that disruption of mPFC activation is correlated with impairments in recognition memory (Zanto et al., 2011). However, there is also conflicting evidence showing that cytotoxic lesions of the mPFC spared object recognition performance following a 10 min ITI (Yee,

[1]School of Pharmacy and Medical Sciences, University of Bradford, Bradford, UK
[2]Division of Pharmacy and Optometry, School of Health Sciences, University of Manchester, Manchester, UK
[3]Department of Neuroscience, Psychology and Behaviour, University of Leicester, Leicester, UK

Corresponding author:
Samantha McLean, School of Pharmacy and Medical Sciences, University of Bradford, Richmond Road, Bradford, BD7 1DP, UK.
Email: s.l.mclean@bradford.ac.uk

2000); this further highlights the need to further investigate the role of the PFC in this behavioural task.

Dysfunction in the glutamatergic system is a prominent hypothesis for the pathogenesis of schizophrenia (Olney et al., 1999). As a result of this hypothesis, many pre-clinical animal models for schizophrenia are now based on the administration of NMDA receptor antagonists such as phencyclidine (PCP), MK-801 and ketamine (Neill et al., 2014). The non-competitive NMDA receptor antagonist PCP has been shown to produce enduring cognitive deficits similar to those observed in schizophrenia in rodents (Javitt and Zukin, 1991; Meltzer et al., 2013), particularly when administered sub-chronically (sc) (Janhunen et al., 2015; Jentsch and Roth, 1999; Neill et al., 2010; Rajagopal et al., 2014). Indeed, we have consistently shown in our laboratory that a sub-chronic phencyclidine (scPCP) treatment regimen produces long-lasting and robust cognitive impairments in several cognitive domains of relevance to schizophrenia, including visual learning (McLean et al., 2011; Neill et al., 2016), reasoning and problem solving (McLean et al., 2010, 2012; Neill et al., 2016), executive function (McLean et al., 2012) and attention/vigilance (Barnes et al., 2012, 2016).

While newer compounds for cognition and negative symptoms, the major unmet clinical needs in schizophrenia, targeting mechanisms such as the metabotropic glutamate receptor 2/3 subtype, phosphodiesterase subtype 10, glycine transporter subtype 1 and the α7 nicotinic acetylcholine receptor have been the subject of intense drug discovery and development efforts; there is still a lack of success in phase III clinical trials (Dunlop and Brandon, 2015). Dopamine hypofunction in the PFC is thought to have a major role in the aetiology of negative symptoms and cognitive dysfunction in schizophrenia (Abi-Dargham and Moore, 2003; Goldman-Rakic et al., 2004; Jentsch and Roth, 1999; Stone et al., 2007). scPCP has been shown to reduce dopamine utilisation in the PFC and nucleus accumbens (Jentsch et al., 1997). Furthermore, it has been shown that the atypical antipsychotics sertindole and risperidone increase extracellular dopamine in rat mPFC and nucleus accumbens (Mork et al., 2009) and improve a scPCP-induced deficit in NOR memory (Grayson et al., 2007; Idris et al., 2010). We have also previously shown that targeting dopamine D_1 receptors ameliorates the effects of scPCP treatment in NOR, reversal learning and the 5-choice continuous performance test (Barnes et al., 2016; McLean et al., 2009), further implicating the role of dopamine in prefrontal-based cognitive tasks.

As yet, the role of dopamine in scPCP-induced cognitive disruption remains to be fully established. Therefore, the aim of this study was to investigate the interaction between the NOR deficit induced by our scPCP treatment regime and levels of PFC dopamine. This was achieved by combining in vivo microdialysis in freely moving behaving animals to assess the changes in PFC dopamine at the same time as observing a cognitive deficit.

Materials and methods

Subjects and drug treatment

Twelve adult female Lister Hooded rats (Charles River, UK) were housed in groups of 2–3 and weighed 220–250 g at the start of the dosing regimen and 240–270 g at the time of surgery and behavioural testing. Animals were housed under standard laboratory conditions at a temperature of 20°C (±1°C) and humidity of 50 ±5%. They were maintained on a 12-h/12-h light/dark cycle (lights on at 0700 h) and experimental procedures were performed during the light phase. Rats had free access to food and water at all times, except during NOR testing and habituation. Rats were treated with 2 mg/kg PCP (PCP hydrochloride, Sigma, UK; $n = 5$) or vehicle (0.9% saline; $n = 7$), twice daily for 7 days; this was followed by a 7-day washout period. All experiments were performed according to the Animals (Scientific Procedures) Act 1986, and with approval from the University of Leicester Animal Ethics Committee.

Surgery and microdialysis

Rats were anaesthetised with isoflurane (1–3% isoflurane in O_2: 1 L/min) and stainless steel guide cannulae (o.d., 890 μm; i.d., 685 μm; length 10 mm: Coopers Needle Works, Birmingham, UK) were stereotaxically implanted into the brain, aimed at the PFC, Figure 1. Following recovery from surgery (⩾7 days), dialysis probes were inserted into the guide cannulae to lie in the PFC with stereotaxic co-ordinates (tip position mm from Bregma: H, +3.2; Tr, –0.5; V, –5.4; (Paxinos and Watson, 1998)). Microdialysis probes were constructed in-house and checked for flow rate integrity and leaks before implantation (Young et al., 1998). At least 1 h after implantation of the probe, animals were connected to the delivery system, and perfusion with artificial cerebrospinal fluid (mM: NaCl, 145; KCl, 3.3; $MgSO_4$, 2.4; KH_2PO_4, 1.25; $CaCl_2$, 1.85: 2 μL/min flow rate) commenced immediately. Following equilibration for 1 h, dialysate samples were collected consecutively for 10 min into 2 μL of 1.0 M H_3PO_4 (to minimise oxidation). The first four samples (40 min) were used to determine basal dopamine levels in the dialysates. Samples were then collected during the NOR test during the 10 min habituation to the box, acquisition, ITI and retention phases (all 10 min); in addition, three samples were collected post-testing (30 min). At the end of the collection period, animals were killed by anaesthetic overdose (sodium pentobarbitone, JML, Southampton, UK) and cervical dislocation. The brains were removed and stored in 4% formalin and placement of the probes confirmed using cresyl violet staining.

NOR testing

Rats were tested in the NOR task as described in detail previously (McLean et al., 2011), with the exception that 10 min trials were used with a 10 min ITI (not 3 min trials with a 1 min ITI, our usual protocol) in order to give enough time to collect the required sample for HPLC analysis. Rats were habituated to the test arena for 30 min for 3 days prior to the test day. Following a 10 min habituation session on the day of testing, each rat was placed in the NOR chamber and exposed to two identical objects for a period of 10 min. The rats were then returned to their home cage for an ITI of 10 min; the entire box was cleaned with 10% ethanol, both objects removed and one replaced with an identical familiar copy and one with a novel object. Following the ITI, rats were returned to explore the familiar and a novel object in the test arena for a 10 min retention trial. All experiments were video recorded for subsequent behavioural analysis by an experimenter blinded to the treatment. Locomotor activity (LMA) was also

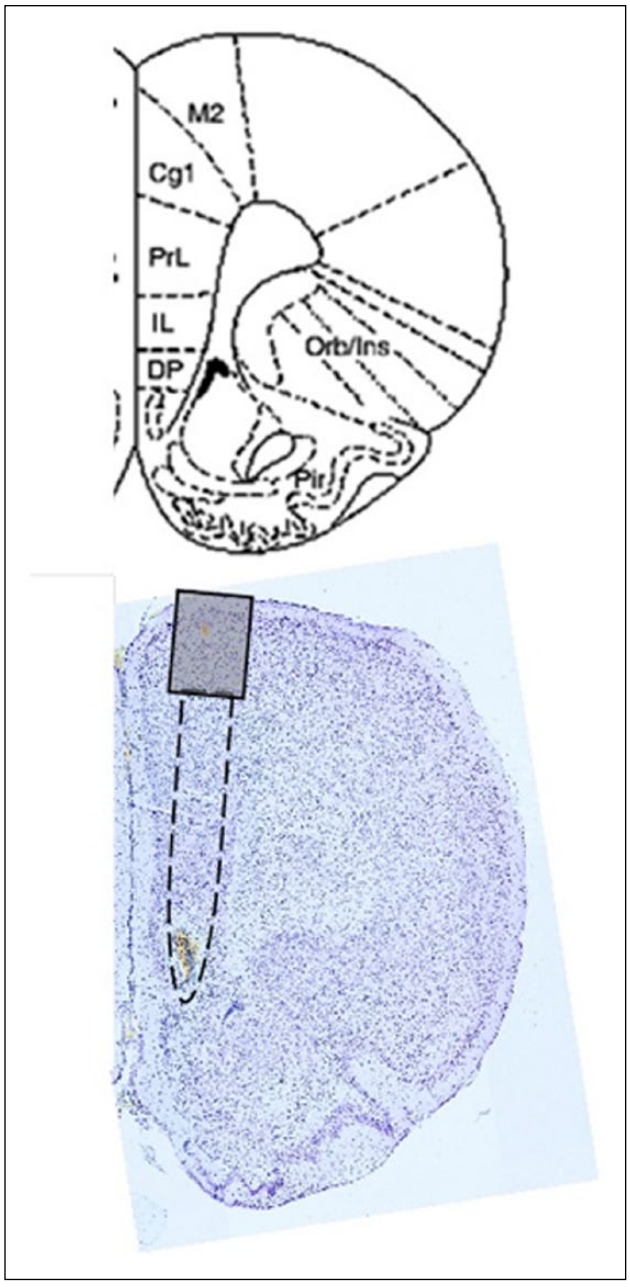

Figure 1. Microdialysis probe placement. Top: coronal image reproduced from Paxinos and Watson (1998) *The Rat Brain Atlas in Stereotaxic Coordinates with permission from Elsevier*, Bregma 2.7 mm showing PFC regions. Bottom: Photograph taken at ×4 magnification following cresyl violet staining. The solid shaded rectangle represents the position of the cannula; the dotted line represents the tip position.

recorded; this was evaluated by scoring the total number of sectors or line crossings by the animal in acquisition and retention trial. The exploration time (s) of each object in each trial was recorded manually using two stopwatches and the discrimination index (DI) was calculated: DI = (time exploring the novel object (s) – time exploring the familiar object) / total time exploring both novel and familiar objects. The DI represents the difference in exploration time expressed as a proportion of the total time spent exploring the two objects in the retention trial. A value of 1 would show that rats explored only the novel object; a value of –1 would show that rats only explored the familiar object and a value of 0 indicates exploration of both objects equally.

HPLC detection of dopamine

After collection, all dialysate samples (1–11) were analysed to determine the concentration of dopamine in each sample by HPLC with electrochemical detection. Samples (15 µL) were injected onto the column using a Spark Triathlon refrigerated autosampler (Presearch, UK). The mobile phase consisted of 75 mm NaH_2PO_4, 1.1 mm octanesulfonic acid, 1 mm EDTA, 10% methanol, pH 3.7 and was pumped at 110 µL/min using a Rheos 4000A pump (Presearch, UK), and separation was achieved using a 150 mm × 1.0 mm LUNA C18(2) 5 µm column (Phenomenex, UK). Dopamine (retention time of approximately 12 min) concentrations were calculated with reference to standards at 1, 10, and 100 nm. Data were collected and analysed using Chrom Perfect Analysis v5.5.4 (Justice Laboratories, NJ, USA) PC-based integrator. All chemicals were supplied by Sigma Chemicals (Poole, UK) and were HPLC grade.

Data and statistical analysis

The NOR data are expressed as mean exploration time ± S.E.M. Student's paired *t*-test was performed to compare time spent exploring the familiar versus the novel object. The DI values are expressed as mean ± S.E.M. LMA data are expressed as mean ± S.E.M of the total number of lines crossed during the acquisition and retention trials. Analysis of the DI values and total LMA were performed using independent *t*-tests, vehicle compared with the scPCP group.

The basal concentration of dopamine was calculated from the four samples taken prior to behavioural testing; subsequent samples were then expressed as percent of basal. Microdialysis data were analysed using a repeated measures two-way ANOVA with stage of task as a within-subjects factor (habituation, acquisition, ITI, retention, three post-test) and treatment (vehicle or scPCP) as a between-subjects factor. This was followed by planned pairwise comparisons with Bonferroni adjustment. All statistical analyses were performed using SPSS (version 22).

Results

Initially the groups consisted of seven vehicle-treated and five scPCP-treated rats; however, two vehicle-treated rats were excluded due to technical problems with HPLC. These rats were removed from all analyses, therefore the final treatment groups were both $n = 5$. Following cresyl violet staining, the locations of the probes were verified. All probes were located within the PFC at Bregma 2.7–3.2 mm. An example image of probe location is shown in Figure 1.

Paired *t*-tests revealed that there was no significant difference between the time spent exploring the two identical objects during the acquisition trial in either vehicle or scPCP-treated rats (data not shown). In the retention trial, vehicle-treated rats explored the novel object more than the familiar object, although this effect was not significant ($p = 0.11$; Table 1); there was no significant

Table 1. The effect of treatment with vehicle or scPCP on exploration times of objects in the NOR task. The effect of treatment with vehicle or scPCP (2 mg/kg, twice daily for 7 days, i.p. followed by 7 days drug free) in the NOR task. Data are shown as mean exploration times ± S.E.M (n = 5 per group). There were no significant differences between time spent exploring the novel and familiar object in either treatment group.

Group	Exploration time (s)			
	Acquisition		Retention	
	Left	Right	Novel	Familiar
Vehicle	20.7 ± 6.6	19.8 ± 5.1	24.7 ± 11.4	6.0 ± 2.3
PCP	24.8 ± 3.6	24.2 ± 3.5	27.0 ± 6.2	17.2 ± 4.0

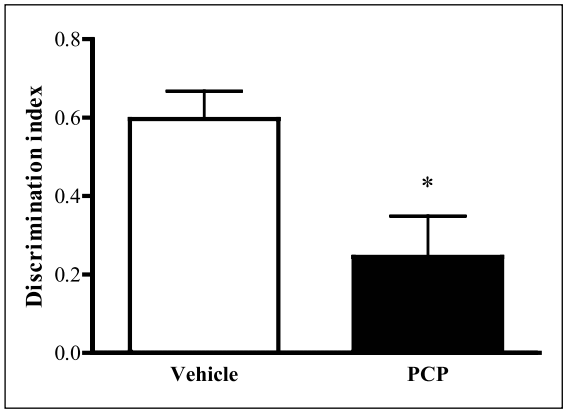

Figure 2. The effect of treatment with vehicle or scPCP (2 mg/kg, twice daily for 7 days, i.p. followed by 7 days drug free) in the NOR task. Data are shown as mean DI ± S.E.M (n=5 per group). The DI for the scPCP-treated group was significantly reduced compared to the vehicle group (*p < 0.05).

difference in exploration of the novel and familiar object in scPCP-treated rats (Table 1). However, an independent t-test revealed a significant difference in the DI (t[9] = 2.87; p = 0.018). The DI for the scPCP-treated group was significantly reduced from 0.60 in the vehicle-treated group to 0.25 (Figure 2). Moreover, one-sample t-tests showed that the DI was significantly different from zero (no discrimination) in the saline treated animals (t[5] = 8.41; p < 0.001), but not in the scPCP pre-treated group (t[4] = 2.34; p = 0.78). Independent t-tests showed no significant effect on LMA assessed by the total number of line crossings in the acquisition and retention trials (76.5 ± 19.6 in vehicle-treated rats compared with 97 ± 16.9 in scPCP-treated rats; data not shown).

Following the behavioural experiments, HPLC was carried out; therefore the groups for dopamine analysis were vehicle (n = 5) and scPCP (n = 5). The mean of the four baseline concentrations prior to behavioural testing was calculated. An independent t-test revealed no significant difference between basal levels in the two groups (vehicle, 3.3 ± 2.0 nm; scPCP, 2.9 ± 0.6 nm). Data were subsequently expressed as percent of basal (Figure 3). A two-way repeated measures ANOVA with stage of test as the within-subjects factor and treatment as the between-subjects

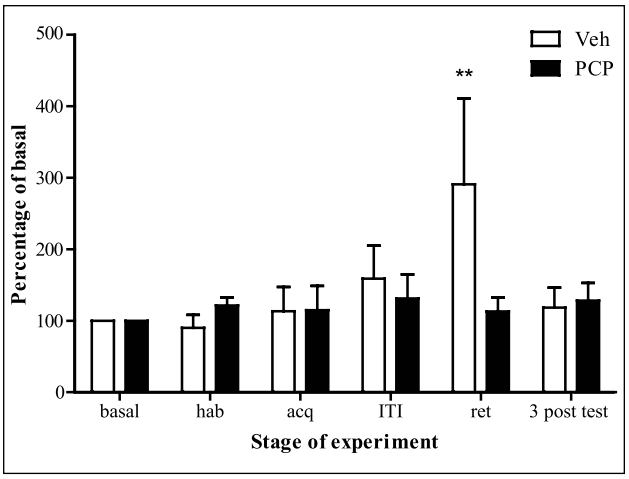

Figure 3. Relative concentrations of dopamine in the PFC expressed as percent basal in vehicle and scPCP-treated rats at each stage of the NOR task. Data are shown as mean percent of basal ± S.E.M (n = 5). **p < 0.01 significant increase in dopamine in the retention phase compared to basal level.

factor revealed no significant interaction ($F_{[4,32]}$ = 1.89; p = 0.13). However, planned pair-wise comparisons with Bonferroni adjustment revealed a selective and significant increase in dopamine levels in vehicle-treated rats in the retention phase compared with basal (290 ± 120% of basal; p < 0.01); however, this effect was not observed in scPCP-treated rats (113 ± 19% of basal).

Discussion

This study aimed to investigate the role of prefrontal dopamine in deficits in NOR task performance in the scPCP animal model for schizophrenia. The main findings suggest that an increase in dopamine in the PFC during the retention trial may be beneficial for NOR performance either by increasing the preference for the novel object or for aiding the recall of memory for the familiar object. During the acquisition trial of the NOR task there was no difference in the exploration time of the two identical objects in either vehicle or scPCP-treated rats. Conversely, in the retention trial, calculation of the DI revealed that vehicle-treated rats could discriminate the novel from familiar object in the retention trial, suggesting that they remembered the familiar object. However, this discrimination was not observed when comparing time spent at the novel versus the familiar object; this lack of discrimination is likely due to the low numbers and subsequent large variability within the group. In the scPCP-treated rats, however, the object exploration data and the DI revealed that rats could not discriminate between the novel and familiar objects, suggesting that scPCP-treated rats did not remember the familiar object. This scPCP-induced deficit in NOR (and its attenuation by dopamine/serotonin receptor antagonist drugs for schizophrenia and novel targets) is supported by many previous studies in our laboratory (McLean et al., 2011; Neill et al., 2010, 2016) and elsewhere. These results are also consistent with previous reports from others demonstrating scPCP treatment in rats impairs object recognition (Le Cozannet et al., 2010; Miyauchi et al., 2016; Redrobe et al., 2012). In addition, it has been shown that PCP, when given

in varying dosing regimens, produced deficits in object recognition in mice (Hashimoto et al., 2005; Horio et al., 2013; Nagai et al., 2009; Rajagopal et al., 2016).

The concentration of dopamine in the PFC revealed that the basal levels in vehicle and scPCP-treated rats were similar. Concentrations were also comparable during all stages of the NOR task with the exception of the retention trial, in which a large increase in dopamine was observed in the vehicle-treated group. This suggests that dopamine in the PFC is important for retrieval of object recognition memory, not encoding or consolidation, as levels remained comparable with baseline during the acquisition trial and ITI. In contrast, this increase in prefrontal dopamine was absent in the scPCP-treated group. In collaboration with the Meltzer laboratory we conducted a similar study some years ago (published in abstract form only). There were some differences as in that study we used female Long Evans rats, 15 min time bins, also investigated hippocampus and did not include so many time points (Snigdha et al., 2008). However, our current findings confirm that early result and show impaired performance in retention accompanied by a lack of increase in dopamine in the PFC.

It has been shown that many dopamine/serotonin receptor antagonist drugs for schizophrenia such as sertindole and risperidone (Mork et al., 2009), and clozapine, olanzapine and quietapine (Tanda et al., 2015) increase extracellular dopamine in male rat mPFC. More specifically, we have shown that intracortical perfusion of the dopamine D_1-like receptor agonist, SKF-38393, in drug-naïve awake male rats decreased glutamate and increased GABA release in the mPFC, potentially restoring the balance between glutamate and GABA (Harte and O'Connor, 2004). We have also established that SKF-38393, when given systemically, can reverse the scPCP-induced deficit in NOR in female rats (McLean et al., 2009). This is supported by data reporting that microinfusion of the dopamine D_1-like receptor antagonist SCH-23390 into the rat mPFC produced a deficit in NOR (Clausen et al., 2011; Rossato et al., 2013). Conversely in a recent study, microinfusion of the D_1-like receptor agonist SKF81297 into the mPFC induced a dose-related impairment in object recognition encoding and retrieval (Pezze et al., 2015). Although these results appear conflicting, the authors propose that NOR memory requires an optimal level of D_1 receptor stimulation in the mPFC and may reflect an inverted U-shaped function (Pezze et al., 2015). The role of dopamine in the PFC has been further investigated using other selective dopamine receptor agonists and antagonists. Bilateral microinjection of the dopamine D_3 antagonist, S33084, into the rat PFC caused a dose-related improvement in NOR, while intra-striatal injection had no effect (Watson et al., 2012). In contrast, bilateral microinjection of the preferential D_2 antagonist, L741,626, into the PFC (but not striatum) caused a dose-related impairment in NOR in rats (Watson et al., 2012). Taken together, these results show that pharmacological manipulation of dopamine levels in the PFC can have either beneficial or detrimental effects on object recognition memory, in that they follow an inverted U-shaped relationship.

One limitation of the present study is low numbers, as two vehicle-treated rats had to be excluded from the final analysis due technical problems with the HPLC analysis; therefore, the final number of rats (five vehicle and five PCP) was low for a behavioural study. Previous studies in this laboratory have found a robust and reproducible deficit with scPCP in NOR when using 8–10 rats (Neill et al., 2010). Due to the low number of rats used here, the error within the groups is large; this is particularly apparent in the vehicle group during exploration of the novel object and may explain the lack of a significant difference in exploration times in the retention trial. However, this is a preliminary study and clearly requires verification with a larger sample size and more detailed analysis of other neurotransmitters.

In summary, these current results demonstrate recruitment of dopamine in the PFC when rats are exposed to two objects, one new and one familiar. As there was no increase in PFC dopamine in the acquisition trial, these new, but preliminary, data support the hypothesis that, for rats to recall information about the familiar object they must recruit PFC dopamine, an effect which is absent in scPCP-treated rats which may explain why they cannot discriminate the novel from familiar object. A link between dopamine and cognition has been observed in patients with schizophrenia, in that low dopamine turnover was associated with poor verbal recall (Oades et al., 2005), albeit dopamine was measured in plasma and not brain. In conclusion, our findings provide evidence that the scPCP model has considerable validity for investigating cognitive deficits in schizophrenia. Furthermore, the ability of novel compounds to restore this PFC dysfunction (and the NOR deficit) may well reveal compounds with good efficacy in the clinic to overcome cognitive disturbances observed in schizophrenia, a current unmet need.

Declaration of conflicting interests

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