MODAFINIL REVERSES PCP-INDUCED DEFICITS IN COGNITIVE FLEXIBILITY

R.J. Thompson[1,2], N. Dawson[1,3], A. McVie[1,2], D.M. Thomson[1,2], B.J. Morris[1,2] and J.A. Pratt[1,3]

[1]PsyRING, Glasgow, G12 8QQ, UK; [2]Faculty of Biomedical and Life Sciences, University of Glasgow, Glasgow, G12 8QQ, UK,
[3]Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, G4 0N, UK.
r.thompson.1@research.gla.ac.uk www.psyring.co.uk

INTRODUCTION

•Cognitive deficits such as impairments in cognitive flexibility, attention and working memory are a core feature of schizophrenia that are minimally responsive to current antipsychotic drugs.

•Impairments in cognitive flexibility, such as set-shifting and reversal learning are consistently found in schizophrenia and are attributed to disrupted prefrontal cortex function. In tests such as the Wisconsin Card Sorting test (WCST), patients show impairments in different rules or strategies, exemplified by impairments in the intra-/extra dimensional (ID/ED) task in a computerised version of the WCST. .

•We have previously demonstrated that subchronic intermittent phencyclidine (PCP) treatment in rats produces cognitive deficits as well as alterations in brain function and neurochemistry akin to those seen in schizophrenia (Pratt *et al*., 2008).

•Cognitive deficits in animal models can be assessed using the Attentional Set-shifting Task (ASST) (Figure 1.), an adapted version of the WCST for use in rodents (Birrel & Brown, 2008).

•Recently, clinical trials have shown that modafinil improves cognitive deficits in the WCST in schizophrenic patients (Turner *et al*., 2004).

Figure 1. ASST

AIM

• Here we further validate the subchronic PCP model as a translational model of schizophrenia by investigating the ability of modafinil to reverse PCP-induced cognitive deficits in the ASST.

METHODS

•Male Lister Hooded rats received either subchronic vehicle (saline, *i.p.*) or PCP (2.58mg.kg^{-1}, *i.p.*) 1 x daily for 5 days. 72 hours after the final treatment animals were tested in the ASST as previously described (Egerton *et al*., 2005)

•30 minutes prior to behavioural testing animals received either acute Modafinil (64 mg.kg^{-1}, *p.o.*) or vehicle (5% methylcellulose). Acute treatment was also repeated 30 minutes prior to the fourth discrimination in the ASST due to the short half-life of modafinil.

•During the test session rats performed a series of discriminations in the order outlined in Table 1. The identity of the exemplar combinations employed in the ASST, and their pairings, are outlined in Table 2.

•Data was analysed by ANOVA, Mann-Whitney U- or t-test. Bonferroni correction was applied for multiple comparisons as appropriate.

ASST discriminations

Table 1. Order of discriminations performed.

Discrimination	Relevant Dimension Exemplars	Irrelevant Dimension Exemplars
Simple (SD)	**M1**/M2	Non-dissociable
Compound (CD)	**M1**/M2	O1/O2
Reversal (REV1)	**M2**/M1	O1/O2
Intradimensional acquisition (ID)	**M3**/M4	O3/O4
Reversal (REV2)	**M4**/M3	O3/O4
Extradimensional shift acquisition (ED)	**O5**/O6	M5/M6
Reversal (REV3)	**O6**/O5	M5/M6

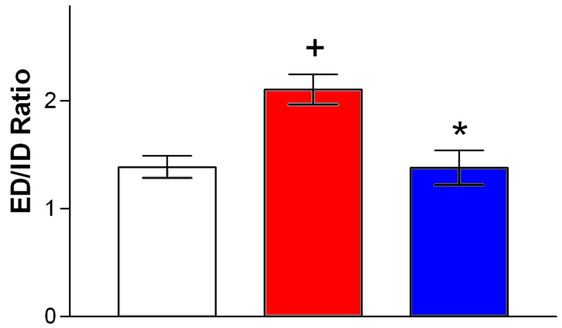
ASST Exemplar combinations

Table 2. Exemplar combinations employed.

Dimension	TrainingPairing	Pairing 1	Pairing 2	Pairing 3
Odour	09 – Mint O10 – Oregano	O1 Cinnamon O2 – Ginger	O3 – Sage O4 Paprika	O5 – Turmeric O6 – Cloves
Medium	M9 Polystyrene M10 – Confetti	M1 Coarse Tea M2 – Fine Tea	M3 – Sand M4 – Grit	M5 Coarse shavings M6 Fine Shavings

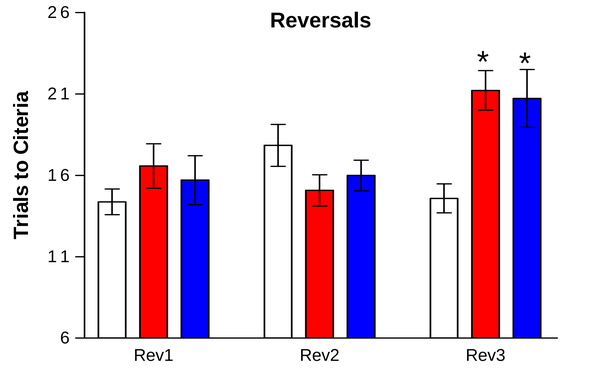
RESULTS

Figure 2. PCP-induced impairment of set-shifting is reversed by acute modafinil.



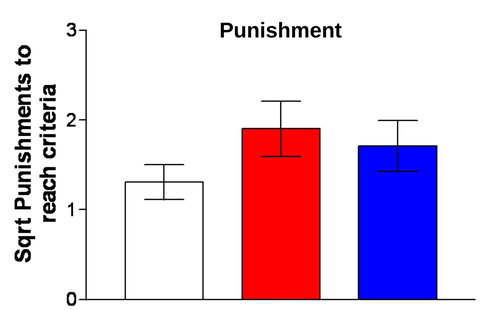
PCP produced deficits in attentional set-shifting as evidenced by an increase in the ED/ID ratio. This deficit was reversed by modafinil. + denotes p<0.05 significant difference from control (vehicle.vehicle) and * denotes p<0.05 significance from PCP treated animals given acute vehicle (PCP.vehicle). There was no significant difference between PCP treated animals given modafinil (PCP.Modafinil) and controls. Data analysed using Mann-Whitney U-test with Bonferroni correction.

Figure 3. PCP pre-treatment induced a deficit in reversal learning that specifically manifest in Rev3

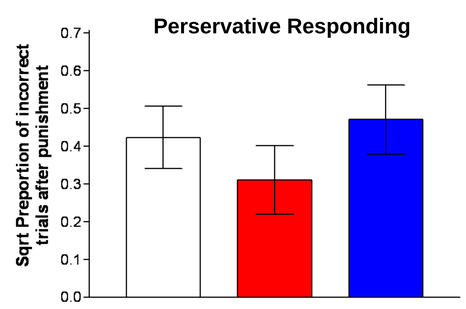


PCP-experienced animals show impaired 'reversal learning' in the third reversal (Rev3). This deficit is not normalised by treatment with modafinil. Data were analysed using t-test with Bonferroni post hoc correction. * denotes p<0.05 significant difference from control (vehicle.vehicle).

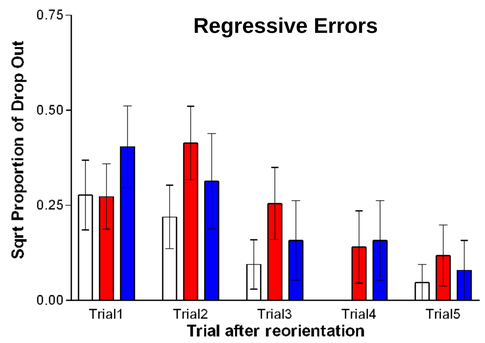
Figure 4. Regressive errors, rather than perservative responding, underlie the PCP-induced reversal learning deficit that manifest at reversal 3 (Rev3).



Punishment trials, where access to the baited bowl was blocked following an incorrect dig and animals are not allowed to retrieve the reward, were not significantly affected by PCP treatment. Data analysed using one-way ANOVA.



Perservative responding was measured as the proportion of trials following a punishment trial in which animals failed to appropriately re-orientate the digging behaviour to the correct (baited) bowl. Perservative responding was not significantly altered by PCP treatment. Data were analysed using one-way ANOVA with Tukey's post-hoc analysis.



PCP induces a significantly higher level of regressive errors, as evidenced by a higher proportion of drop out across all trial levels following punishment induced re-orientation of digging behaviour. Data analysed using two-way repeated measures ANOVA, main pre-treatment effect p=0.049

CONCLUSIONS

•The subchronic intermittent PCP treatment regime used in this study induces deficits in cognitive flexibility that model both the set-shifting impairment seen in schizophrenia and also the reversal learning deficits reported in this disorder.

•PCP-induced deficit in reversal 3 appeared to be due to regressive errors rather than perservative responding.

•Acute treatment with modafinil improves PCP-induced set-shifting deficits, similar to results observed in set-shifting tests in schizophrenic patients, but does not improve reversal learning deficits.

•These results show that modafinil modulates distinct cognitive domains in the ASST and further validates the subchronic PCP model as a translational model to identify compounds that target the unmet therapeutic need in schizophrenia.

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