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Syventävien opintojen kirjallinen työ

Syyslukukausi 2023

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Abstract

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Objectives: The objective of this study was to assess the scPCP model by (1) reviewing published findings of scPCP-induced neurochemical changes and effects on cognitive tasks in adult rats and (2) comparing findings from a multi-site study to determine scPCP effects on standard and touchscreen cognitive tasks.

Methods: Across four research sites, the effects of scPCP (typically 5 mg/kg twice daily for 7 days, followed by at least 7-day washout) in adult male Lister Hooded rats were studied on novel object recognition (NOR) with 1-h delay, acquisition and reversal learning in Morris water maze and touchscreen-based visual discrimination.

Results: Literature findings showed that scPCP impaired attentional set-shifting (ASST) and NOR in several labs and induced a variety of neurochemical changes across different labs. In the multi-site study, scPCP impaired NOR, but not acquisition or reversal learning in touchscreen or water maze. Yet, this treatment regimen induced locomotor hypersensitivity to acute PCP until 13-week post-cessation.

Conclusions: The multi-site study confirmed that scPCP impaired NOR and ASST only and demonstrated the reproducibility and usefulness of the touchscreen approach. Our recommendation, prior to testing novel therapeutics in the scPCP model, is to be aware that further work is required to understand the neurochemical changes and specificity of the cognitive deficits.

Keywords: Adult rat; Cognition; Schizophrenia; Subchronic phencyclidine; Touchscreen; Visual discrimination; Water maze.

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REVIEW

The subchronic phencyclidine rat model: relevance for the assessment of novel therapeutics for cognitive impairment associated with schizophrenia

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Keywords Subchronic phencyclidine · Cognition · Water maze · Touchscreen · Visual discrimination · Schizophrenia · Adult rat

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Introduction

Schizophenia is characterized by positive symptoms (e.g. hallucinations, delusions, paranoia and disorganized thoughts), negative symptoms (e.g. deficits in social interaction, emotional expression and motivation) and cognitive dysfunction, including but not limited to impairment of attention and working memory (Goldberg et al. 1988; Goldman-Rakic 1994).

The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative described seven core cognitive domains commonly deficient in schizophrenia: attention/vigilance, working memory, reasoning and problem solving, processing speed, visual learning and memory, verbal learning and memory and social cognition (Nuechterlein et al. 2004). A second initiative, Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS), proposed translational cognitive paradigms relevant for schizophrenia that could be used across species, from rodents to non-human primates, and finally to humans, amongst those touchscreen-based operant tasks.

Currently approved treatments for schizophrenia, antipsychotics, have only limited, if any, efficacy for the cognitive symptoms associated with the disorder (Keefe et al. 2007). Cognitive dysfunction is present already before the onset of schizophrenia and has a negative impact in long-term functioning and quality of life (Addington and Barbato 2012). Thus, the lack of effective treatment for cognitive impairment is a high unmet need. Importantly, it is not only the use of translational cognitive tests during preclinical assessment of novel compounds, but also the development of predictive and reliable animal models for cognitive deficits associated with schizophrenia that must be improved to facilitate research into schizophrenia-associated cognitive impairment. This has been addressed by the Innovative Medicines Initiative (IMI) project Novel Methods leading to New Medications in Depression and Schizophrenia (NEWMEDS), which is one of the largest ever research academic-industry collaboration projects to find new methods for the development of drugs for schizophrenia. By reviewing the published data, and comparing published and unpublished in-house data from participants in NEWM EDS, we assessed a number of animal models that are commonly used to evaluate the efficacy of novel compounds (i.e. MAM, scPCP, neonatal PCP). The current manuscript provides an overview of the subchronic phencyclidine (scPCP) model in adult rats, with an assessment based on published and hitherto unpublished data (provided by Orion Pharma, Lundbeck, Janssen, Roche) (Table 1), as well as a conclusion on the future utility of the model for the development of cognition enhancing drugs to treat deficits seen in schizophrenia.

Cognitive dysfunction in schizophrenia is thought to result from frontostriatal dysfunction and abnormalities in circuitries that use dopamine, serotonin (5-HT), glutamate and GABA (γ-aminobutyric acid) (Carlsson and Carlsson 1990; Robbins 1990; Grace 1991; Barch and Ceaser 2012). One of the main explanatory hypotheses for the underlying pathogenesis of schizophrenia is glutamatergic neuronal dysfunction (Carlsson et al. 2001). A key observation was that intoxication with PCP, a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, induced a psychotomimetic state that closely resembled the disorder (Javitt and Zukin 1991). Acute PCP administration caused transient schizophreniform psychosis in normal volunteers and exacerbated symptoms in schizophrenia patients in clinical trials (Javitt and Zukin 1991). Repeated exposure to PCP induced robust and enduring cognitive deficits that diminished within weeks after withdrawal (Cosgrove and Newell 1991). Later, acute administration of another NMDA receptor antagonist, ketamine, was established as a psychosis model in healthy volunteers (e.g. Lahti et al. 2001). Moreover, postmortem studies in schizophrenia patients have revealed abnormalities of NMDA receptor expression in the prefrontal cortex (Akbarian et al. 1996), and single nucleotide or dinucleotide-repeated polymorphisms of the NMDA receptor subunit gene increase susceptibility to schizophrenia (Rice et al. 2001; Itokawa et al. 2003). Accordingly, these findings and many others suggest a strong link between the glutamate system and some symptoms of schizophrenia, and what is of particular interest is the finding that amongst PCP abusers, some effects may remain even after the drug has been eliminated from the body.

Efforts have been made to develop animal models of relevance to schizophrenia by acutely administering NMDA antagonists, such as PCP, ketamine and dizocilpine to rodents and monkeys. The effects of repeated treatment with PCP, followed by withdrawal or cessation of treatment (referred as scPCP treatment), were also suggested to mimic some of the facets of schizophrenia (Jentsch and Roth 1999). For example, subchronic treatment with PCP (10 mg/kg for 14 days, followed by 1- to 10-day withdrawal) to rats was found to impair performance in a spatial delayed alternation task, a task suggested to depend on intact working memory, and also to reduce dopamine utilization in the prefrontal cortex (Jentsch et al. 1997b). Most published studies reported impairments following cessation of scPCP administration in the attentional set-shifting task (ASST), where especially one stage of the task, the extradimensional (ED) shift stage was impaired (Table 1). Another task frequently used in the literature where performance deficits were detected following cessation of scPCP administration is the novel object recognition (NOR) task (Grayson et al. 2007; Idris et al. 2010; McLean et al. 2011) (Table 1). There are also reports that scPCP treatment disturbs reversal learning in an operant lever-pressing task in female rats (Abdul-Monim et al. 2006; Idris et al. 2010; McLean et al. 2011), while the reversal stage in the digging version of the ASST remained unaffected (Rodefer et al. 2005; Rodefer et al. 2008; Broberg et al. 2009; Goetghebeur and Dias 2009; Goetghebeur et al. 2010; Maeda et al. 2014). These data suggest that the cognitive domains affected by scPCP include visual learning and memory, and reasoning and problem solving, i.e. executive function. There are, however, several other pivotal cognitive domains that are implicated in schizophrenia (Nuechterlein et al. 2004), for which the effects of the scPCP treatment have not been reported. Presumably, this is due to a lack of studies or of positive and reliable findings. Therefore, in addition to a literature review,

Table 1 Consistent findings across several research sites for cognitive effects and hypersensitivity to stimulants in the subchronic PCP model in adult rats (published studies and NEWMEDS multi-site findings)

Behavioral assay	*scPCP regimen*	*Reference or Research site*
Hypersensitivity of locomotor activity to stimulants:		
Male SD rats: Acute amphetamine at 1-1.5 mg/kg Male SD rats: Acute PCP at 1 and 10 mg/kg	4.5 or 5 mg/kg, i.p., twice daily for 7 days, followed by 7-day washout	(Jentsch et al. 1998b, Beninger et al. 2010) (Shirayama et al. 2007)
Male LH rats: Acute PCP 2.5 mg/kg Male LH rats: Acute PCP 5 mg/kg	5 mg/kg, i.p., twice daily for 7 days, followed by 1 to 13 week washout	Janssen (Fellini et al. 2014) Roche, Orion Pharma, Lundbeck (Fig. 1)
Selective deficit in extra-dimensional (ED) shift in attentional set shifting task (ASST):		
Female LH rats	2 mg/kg i.p., twice daily for 7 days, followed by 7-day washout	(McLean et al. 2012) (Fig. 2)
Male LE rats	2.6 mg/kg i.p., once daily for 5 days, followed by 72-h washout	(Egerton et al. 2008, Dawson et al. 2012) (Fig. 2)
	5 mg/kg i.p., twice daily for 7 days, followed by at least 7-day washout	(Maeda et al. 2014) (Fig. 2)
Male LH rats	5 mg/kg, i.p., twice daily for 7 days, followed by at least 7-day washout	Lundbeck (Broberg et al. 2009, Goetghebeur and Dias 2009, Goetghebeur et al. 2010) (Fig. 2)
Impairment of object recognition test:		
Female LH rats	2 mg/kg i.p., twice daily for 7 days, followed by at least 7-day washout	(Grayson et al. 2007, McLean et al. 2009a, Arnt et al. 2010, Damgaard et al. 2010, Idris et al. 2010, Damgaard et al. 2011, McLean et al. 2011, Snigdha et al. 2011, Grayson et al. 2014)
Female LE rats		(Snigdha et al. 2010, Horiguchi et al. 2011a, b, Horiguchi et al. 2012, Horiguchi and Meltzer 2012, Horiguchi et al. 2013, Horiguchi and Meltzer 2013)
Male LH rats Ovariectomized female SD rats		(McKibben et al. 2010) (Roseman et al. 2012)
Male SD rats	5 mg/kg i.p., twice daily for 7 days, followed by at least 7-day washout	(Shirayama et al. 2007)
Male LH rats	5 mg/kg i.p. (2, 3, 5 mg/kg Roche), twice daily for 7 days, followed by at least 7-day washout	Lundbeck (Redrobe et al. 2010, Redrobe et al. 2012, Maeda et al. 2014) (Fig. 3) Roche (Fig. 3)
No cognitive impairment:		
Acquisition of spatial learning in the Morris water maze in male LH rats	5 mg/kg i.p. (2, 3, 5 mg/kg Roche), twice daily for 7 days, followed by at least 7-day washout	Orion Pharma, Roche, Lundbeck (Fig. 4)
Reversal learning in the Morris water maze in male LH rats	5 mg/kg i.p. (2, 3, 5 mg/kg Roche), twice daily for 7 days, followed by at least 7-day washout	Orion Pharma, Roche, Lundbeck (Fig. 4)
Acquisition of visual discrimination task in touchscreen system in male LH rats	5 mg/kg i.p., twice daily for 7 days, followed by at least 7-day washout	Janssen, Orion Pharma (Fig. 5)
Reversal learning of visual discrimination task in touchscreen system in male LH rats	5 mg/kg i.p. (3 mg/kg Roche), twice daily for 7 days, followed by at least 7-day washout	Janssen, Orion Pharma, Roche, Lundbeck (Fig. 5)

Data across the four NEWMEDS partners shaded grey

LE Long-Evans rats, *LH* Lister Hooded rats, *SD* Sprague-Dawley rats

we wanted to widen the characterization of behavioural deficits by scPCP and investigated at different research sites the ability of the scPCP treatment to consistently impair performance in other cognitive tasks than those previously reported. This cross-site investigation was conducted among IMI NEWMEDS Work Package 2 partners. The novel multi-site data include the effects of scPCP treatment on performance in a NOR task to ensure that published results could be reproduced, the Morris water maze spatial learning task and touchscreen-based tasks, such as visual discrimination (Table 1), paired associates learning (see McAllister et al. in this issue) and the continuous performance task (Mar et al., in preparation). The NEWMEDS project has provided a battery of these translational cognitive paradigms using the touchscreen, and we have shown in another multi-site study that we are able to replicate visual discrimination acquisition profiles across different sites, despite the use of different testing apparatus, rat suppliers etc. showing that this testing approach should improve reproducibility of studies between groups (see Talpos et al. in preparation).

Neurochemical effects underlying behavioural changes in the scPCP model

PCP is a non-competitive antagonist at the NMDA receptor (Roth et al. 2013), and its main pharmacological action is on glutamatergic transmission, although it also directly or indirectly affects other neurotransmitter systems, such as the dopamine system. PCP has high affinity, at nanomolar range for the NMDA and sigma$_2$ receptors, and low affinity, at micromolar range for the 5-HT transporter (Seeman et al. 2005; Roth et al. 2013). Recent cell-based binding assays showed no affinity for PCP at dopamine receptors or at dopamine or noradrenaline transporters (Roth et al. 2013), although findings from synaptosomes indicated that PCP activated the high-affinity state of dopamine D_2 receptor with high potency and inhibited uptake of dopamine and noradrenaline (Chaudieu et al. 1989; Rogers and Lemaire 1991; Seeman et al. 2005). Acute PCP was reported to increase in vivo synaptic levels of dopamine in the medial prefrontal cortex and nucleus accumbens, 5-HT in the prefrontal cortex and dorsal hippocampus and noradrenaline and glutamate in the prefrontal cortex (Jentsch et al. 1997a; Martin et al. 1998; Adams and Moghaddam 2001; Quarta and Large 2011) (for reviews see, e.g.Breese et al. 2002; Moghaddam and Krystal 2012). PCP exerts broader neurochemical effects than the other NMDA antagonist that has been frequently used to study the behavioural effects of acute NMDA receptor blockade, MK-801, and the two compounds have been reported to produce different behavioural effects on, e.g. reversal learning (de Bruin et al. 2013). This review focuses on the behavioural effects following cessation of scPCP.

Previously, the dopamine hypothesis was the primary line in schizophrenia research. Recent evidence suggests that rather than being the major defective system in schizophrenia, the dopamine system is abnormally regulated by brain regions such as hippocampus in which the primary deficit lies (Grace 2012). The hippocampus appears to be hyperactive, possibly due to a reduction of inhibitory parvalbumin-containing (GABAergic) interneurons. The hyperactivity of the ventral hippocampus-nucleus accumbens-ventral pallidum-loop then drives the dopamine system to an overly responsive state. The NMDA receptor blockade by scPCP is thought to decrease the excitatory drive on GABAergic neurons and to reduce GABAergic inhibition, which in turn, may disinhibit excitatory neurotransmission, possibly leading to increased drive on dopaminergic neurons (Carlsson et al. 2001). Recently, an elegant study using functional brain imaging and algorithms from network science described that repeated treatment with PCP induced compromised functional integration between distributed neural systems (e.g. the prefrontal cortex and hippocampus) and within brain subsystems (e.g. nigrostriatal pathway), thalamic disconnectivity and dysfunction of specific neurotansmitter systems such as dopamine and noradrenaline (Dawson et al. 2014).

Table 2 summarizes the neurochemical effects of repeated administration of PCP that have relevance to cognitive deficits and the underlying pathophysiology of schizophrenia. A cardinal and most consistently found neurochemical deficit by the scPCP treatment is the cortical hypofunction indicated by, e.g. reduced glucose utilization (Cochran et al. 2003; Dawson et al. 2012) and attenuated dopamine transmission (e.g. Jentsch et al. 1997b; Jentsch et al. 1998a) (Table 2). Multi-system changes in the prefrontal cortex and hippocampus have been reported, including reductions in 5-HT receptors (Steward et al. 2004; Hagiwara et al. 2008), glutamatergic NMDA, mGluR$_2$ and mGluR$_4$ receptors (Abe et al. 2001; Newell et al. 2007b; Bullock et al. 2009), α_{1A} and α_{1B} adrenoceptors (Tanibuchi et al. 2009) and α_7 nAChRs (Hashimoto et al. 2008c), as well as increases in GABA$_A$ receptors (Bullock et al. 2009; Beninger et al. 2010) (Table 2). Changes at the receptor level likely compensate for altered neurotransmission. As shown in Table 2, there is much variation in the scPCP dosing regimen and duration of the washout period (from 1 day to 6 weeks). This is important to recognize because the washout period may have a fundamental impact on neurochemical changes, e.g. hippocampal NMDA binding and cortical muscarinic $M_{1/4}$ receptor binding were increased at 24 h after scPCP, but reduced at 14 days post-scPCP (Newell et al. 2007a, b). An increase in muscarinic M_1 mRNA was found at 72 h post-scPCP (Steward et al. 2012) (Table 2). For comparative reasons, in Table 2, we have shaded in grey the studies which use an identical or similar treatment regimen to the NEWMEDS multi-site behavioural studies

Table 2 Neurochemical changes after repeated administration of PCP in rats and when available in non-human primates (some data from mice when no corresponding data available from rats)

PCP dose	Duration	Washout period	Animals	Outcome	Reference
Assessment of monoamines:					
10 mg/kg i.p.	once daily for 14 days	24 h	Adult male SD rats	Increased content of DA and 5-HT in NAc and increased ratio of homovanillic acid to DA in the striatum. No increases in the PFC.	(Nabeshima et al. 1987)
5 mg/kg i.p or: 10 mg/kg i.p.	twice daily for 7 days, or: once daily for 14 days	24 h	Adult male SD rats	Reduced basal and stress-evoked DA utilization in the PFC, but not in the NAc or dorsal striatum. No marked changes in DA content in the PFC, NAc or dorsal striatum.	(Jentsch et al. 1997b)
5 mg/kg i.p.	twice daily for 7 days	3 weeks	Adult male SD rats	Reduced DA utilization in PFC, but not NAc. No change in DA content in PFC.	(Jentsch et al. 1998b)
5 mg/kg i.p.	twice daily for 7 days	3 weeks	Adult male SD rats	Reduced basal and acute PCP-stimulated extracellular concentration of DA in the PFC. No changes in ACh transmission in the PFC.	(Jentsch et al. 1998a)
0.3 mg/kg i.m.	twice daily for 14 days	1-2 weeks	Young adult green monkeys	Marked and persistent reduction in DA transmission in the DLPFC and PLC.	(Jentsch et al. 1999)
0.3 mg/kg i.m.	twice daily for 14 days	4 weeks	Male and female adolescent green monkeys	Deficit in DA utilization in the DLPFC and amygdala, but not in the PLC, orbital frontal cortex or NAc; reduced 5-HT utilization in the orbital frontal cortex and NAc, with an increase in the amygdala.	(Elsworth et al. 2012)
Assessment of receptors and transporters:					
7.5 mg/kg i.p.	once daily for 14 days	24 h	Adult male Wistar rats	Increased affinity of 5-HT transporters, no change in number of binding sites.	(Hori et al. 2000)
2.6 mg/kg i.p.	once daily for 5 days, then 3 days per week for 3 weeks	72 h	Adult male LE rats	Decreased 5-HT_{2A} receptor binding in the PFC, no changes in striatal or hippocampal regions.	(Steward et al. 2004)
10 mg/kg s.c.	once daily for 10 days (days 1-5 and 8-12)	3 days	Adult male ICR mice	Reduced levels of 5-HT_{1A} receptors in the HC, but not in the frontal cortex.	(Hagiwara et al. 2008)
10 mg/kg s.c.	once daily for 14 days	24 h or 14 days	Female C57BL mice	Increased NMDA receptor binding in the HC after 24 h, but reduced binding after 14 days. Increased mAChR $M_{1/4}$ binding in the limbic system, caudate-putamen, cortex & thalamus after 24 h, but reduced binding after 14 days.	(Newell et al. 2007b, a)
7.5 mg/kg i.p.	once daily for 14 days	24 h	Adult male Wistar rats	Decrease in $mGluR_2$ mRNA expression in the ACC and $mGluR_4$ mRNA expression in cortical regions (parietal, temporal and entorhinal), caudate putamen, thalamus and subiculum.	(Abe et al. 2001)
7.5 mg/kg i.p.	once daily for 14 days	24 h	Adult male Wistar rats	Reduced expression of $GABA_A$ β2 mRNA in the cerebellum and β3 mRNA in the cerebral cortices, caudate putamen, inferior colliculus and cerebellum. No change in benzodiazepine complex.	(Abe et al. 2000, Abe et al. 2005)
4.5 mg/kg i.p.	twice daily for 7 days	7 days	Adult male LH rats	Increased density of $GABA_A$ binding sites in the striatum, PFC and HC. No alterations in markers for GABAergic neurons (GAT-1 and GAD-67 protein expression).	(Beninger et al. 2010)
2.6 mg/kg i.p.	once daily for 5 days then 3 days per week for 3 weeks	72 h	Adult male LE rats	Decreased expression of GAD-67, GAD-65 and the presynaptic GABA transporter GAT-1. Increased expression of $GABA_A$ receptor subunits α6, β3 and δ. Decreased expression of the mRNA levels of two Golgi cell selective NMDA subunits, NR_{2B} and NR_{2D}. No changes in NR_1, NR_{2A} or NR_{2C}. Decreased mRNA level of kainate receptor subunit $GluR_6$, increased level of KA_2 subunit and $mGluR_2$, and unaltered $mGluR_3$ and nNOS.	(Bullock et al. 2009)
10 mg/kg s.c.	once daily for 10 days (days 1-5 and 8-12)	3 days or 4 days for microdial-ysis study	Adult male ICR mice	Increased glycine transporter 1 protein and decreased extracellular levels of glycine in the HC, but not in frontal cortex. Decreased tissue content of glutamate in the HC, but not in frontal cortex. No changes in tissue content of glutamine, glycine, D-serine or L-serine in the frontal cortex or HC, or in extracellular levels or D-serine, L-serine or glutamine in the frontal cortex or HC.	(Hashimoto et al. 2008a)
10 mg/kg s.c.	once daily for 10 days (days 1-5 and 8-12)	3 days	Adult male ICR mice	Reduced protein content of α_{1A} and α_{1B} adrenoceptor subtypes.	(Tanibuchi et al. 2009)
10 mg/kg s.c.	once daily for 10 days (days 1-5 and 8-12)	3 days	Adult male ICR mice	Reduction of $sigma_1$ receptors in the HC.	(Kunitachi et al. 2009)
10 mg/kg s.c.	once daily for 10 days (days 1-5 and 8-12)	3 days	Adult male ICR mice	Decreased density of α_7 nAChRs in the frontal cortex and HC.	(Hashimoto et al. 2008b)
0.3 mg/kg i.m	twice a day for 13 days	24 h	Young adult male rhesus monkeys	Reduced binding of a PET ligand highly selective for α_7 nAChRs.	(Hashimoto et al. 2008c)

Table 2 (Continued)

10 mg/kg	twice daily for 10 days	36 h	Adult male SD rats	Reduced mAChR binding in the HC, striatum and cortex.	(Ward and Trevor 1981)
2.6 mg/kg i.p.	once daily for 5 days then 3 days per week for 3 weeks	72 h	Adult male LE rats	Increased mAChR M_1 mRNA in the PFC and a modest increase in the NAc core.	(Steward et al. 2012)
5 mg/kg	once daily for 5 days or: continuous s.c. implant for 5 days	24 h	Adult male LH rats	*Both treatments:* Reduced D_2 binding sites in the striatum and NAc; increased glutamate binding in the striatum. *Continuous PCP:* Increased D_2 binding in the HC; increased glutamate binding in the NAc.	(Schroeder et al. 2000)
Assessment of parvalbumin:					
5 mg/kg	once daily or: s.c. implant for 5 days	24 h	Adult male LH rats	*Both treatments:* Reduced parvalbumin-IR neurons within the CA3 of the HC, but no change in the DG.	(Schroeder et al. 2000)
2 mg/kg i.p.	twice daily for 7 days	6 weeks	Adult female LH rats	Reduced parvalbumin-IR neurons within the CA2/3 and DG of the HC. Reduced parvalbumin expression in the motor area 1 and increased parvalbumin expression in the cingulate cortex 1 and motor area 2 of the frontal cortex.	(Abdul-Monim et al. 2007)
2 mg/kg i.p.	twice daily for 7 days	6 weeks	Adult male LH rats	Reduced expression of parvalbumin-IR neurons in the PFC, with specific deficits observed in the prelimbic region, but not infralimbic or cingulate cortices.	(McKibben et al. 2010)
2 mg/kg i.p.	twice daily for 7 days	6 weeks	Adult male LH rats	Reduced parvalbumin-IR neurons in the CA1 and DG regions of the HC.	(Jenkins et al. 2008)
2 mg/kg or 5 mg/kg i.p.	twice daily for 7 days	6 weeks	Adult male LH rats	Reduced parvalbumin-IR neurons in the CA1 and CA2/3 regions of the HC, with modest reduction in the DG.	(Jenkins et al. 2010)
0.9 or 2.6 mg/kg i.p.; or: 2.6 mg/kg i.p.	once daily for 5 days; or: once daily for 5 days then 3 days per week for 3 weeks	72 h	Adult male LE rats	Reduced parvalbumin and Kv3.1 mRNA expression in the PLC and the ventral reticular nucleus of the thalamus, but not in the DG or CA1/2/3 of the HC.	(Cochran et al. 2003, Pratt et al. 2008)
Assessment of neuronal function by c-fos, 2-deoxyglucose autoradiography, spine density etc.:					
15 mg/kg i.p.	for 4 days	1 day	Adult male SD rats	Reduced c-Fos-like immunoreactivity in the striatum, the PFC and ACC.	(Turgeon and Case 2001)
10 mg/kg i.p.	for 14 days	1 day	Adult male SD rats	Increased induction of c-Fos-like immunoreactivity in the striatum in unstressed and swim stressed animals.	(Turgeon et al. 2007)
0.9 or 2.6 mg/kg i.p.; or: 2.6 mg/kg i.p.	once daily for 5 days; or: once daily for 5 days then 3 days per week for 3 weeks	72 h	Adult male LE rats	Reduced glucose utilization in the PFC structures, subcortical structures of the auditory system and the reticular nucleus of the thalamus. No changes in the HC, ACC, basal ganglia, anterior and midline thalamic nuclei or structures of the visual system.	(Cochran et al. 2003, Pratt et al. 2008)
2.6 mg/kg i.p.	once daily for 5 days	72 h	Adult male LH rats	Reduced glucose utilization in the PFC, thalamic nuclei, cingulate cortex, dorsolateral striatum and mammillary body. Increased glucose utilization in bed nucleus of the stria terminalis. Altered functional connectivity signatures of prefrontal and retrosplenial cortices.	(Dawson et al. 2012)
2.6 mg/kg i.p.	once daily for 5 days	72 h	Adult male LH rats	Compromised functional integration between distributed brain subsystems like PFC–HC, functional disintegration of discrete brain subsystems, including the nigrostriatal pathway, thalamic disconnectivity as well as aberrant NA and DA neurotransmission.	(Dawson et al. 2014)
2.6 mg/kg i.p.	once daily for 5 days then 3 days per week for 3 weeks	72 h	Adult male LE rats	Markers of neuronal function: Deficit of N-acetylaspartate and its precursor N-acetylaspartylglutamate in the temporal cortex. Elevated N-acetylaspartylglutamate in the HC.	(Reynolds et al. 2005)
5 mg/kg i.p.	twice daily for 7 days	1, 2, 3 and 4 weeks	Adult male SD rats	Sustained decrease in number of asymmetric (excitatory) spine synapses in the PFC. Increase in astroglia process density, without change in the number of astroglia cells.	(Hajszan et al. 2006, Elsworth et al. 2011b)
0.3 mg/kg i.m.	twice daily for 14 days	7 days	Yound adult male green monkeys	Loss of asymmetric spine synapses in the DLPFC, with greater loss in layer II/III than layer V.	(Elsworth et al. 2011a)
5 mg/kg i.p.	twice daily for 7 days	7 days	Adult male LH rats	Reduced cortical thickness in lateral somatosensory cortex and insula cortex anteriorly and posteriorly bordering the ectorhinal cortex. Reduced grey matter density in ACC, ventral striatum, amygdaloid nucleus and HC formation.	(Barnes et al. 2014)
5 mg/kg i.p.	for 5 days	2 days	Adult male Wistar rats	Upregulation of synapsin-1, Dpysl3, Aco2, Fscn1, Tuba1c, and Mapk1 in the PFC. Downregulation of Bin1, Dpysl2, Sugt1, ApoE, Psme1, ERp29, Pgam1, Uchl1, Ndufv2, Pcmt1, and Vdac1 in the PFC.	(Pickering et al. 2013)
5 mg/kg	once daily for 15 days	2 h	Adult male SD rats	Proteomic alterations in glutamate-mediated Ca^{2+} signaling (Ca^{2+}/calmodulin-dependent protein kinase II, PPP3CA, and VISL1), mitochondrial function (GOT2 and PKLR) and cytoskeletal remodeling (ARP3). Metabonomic profiling revealed changes in the levels of glutamate, glutamine, glycine, pyruvate, and the Ca^{2+} regulator taurine.	(Wesseling et al. 2013)

Data from LH rat studies using similar subchronic PCP treament regimen as NEWMEDS multi-site studies shaded grey (i.e. 2–5 mg/kg i.p. twice daily for 7 days with 7-day washout)

ACh acetylcholine, *DA* dopamine, *5-HT* 5-hydroxytryptamine, serotonin, *NA* noradrenaline, *GABA* γ-aminobutyric acid, *ACC* anterior cingulate cortex, *PFC* prefrontal cortex, *PLC* prelimbic cortex, *DLPFC* dorsolateral prefrontal cortex, *NAc* nucleus accumbens, *HC* hippocampus, *DG* dentate gyrus, *NMDA N*-methyl-D-aspartate, *mAChR* muscarinic acetylcholine receptor, *nAChR* nicotinic acetylcholine receptor, *mGluR* metabotropic glutamate receptor, *IR* immunoreactive, *SD* Sprague–Dawley, *LE* Long-Evans, *LH* Lister Hooded

described in this manuscript, which are mostly limited to analysis of parvalbumin expression.

Reduced parvalbumin expression, a hallmark of schizophrenia, has been reported in the hippocampal regions at 6 weeks after the cessation of scPCP (Schroeder et al. 2000; Abdul-Monim et al. 2007; Jenkins et al. 2008; Jenkins et al. 2010), while Cochran et al. (2003) reported a parvalbumin loss in the prefrontal cortex at 72 h post-scPCP (Table 2). There is no clear evidence that the loss of parvalbumin expression and immunoreactivity after scPCP parallels to a loss of GABAergic neurons, and findings from the scPCP-induced changes in markers for GABAergic neurons vary. One study did not find any changes in the GABAergic markers in striatal or cortical regions (Beninger et al. 2010), while another study reported a reduction in the GABA transporter 1 and a marker for GABAergic neurons (GAD-67) in the cerebellum (Bullock et al. 2009). Hashimoto et al. (2008a, b) reported reduced glycine transmission and glutamate content in the hippocampus, but not in the frontal cortex in mice (Table 2). Similar to schizophrenia, scPCP can reduce cortical thickness and grey matter in cortical and hippocampal regions (Barnes et al. 2014) and reduce asymmetric spine synapses in the dorsolateral prefrontal cortex of monkeys (Elsworth et al. 2011a). At the cellular level, scPCP impaired markers for neuronal function (Reynolds et al. 2005), upregulated markers for synaptic transmission and downregulated markers for cellular energy production, repair mechanisms and antiapoptosis (Pickering et al. 2013) (Table 2).

The hypofrontality shown by reduced glucose and dopamine utility and altered parvalbumin-immunoreactive interneuron activity mimic some of the neuropathological changes reported in schizophrenia (for reviews see, e.g. Pratt et al. 2008; Grace 2012). Proteomic and metabonomic profiling revealed that scPCP-induced changes were similar, although not identical, and affected similar pathways in the prefrontal cortex to those affected in schizophrenia (Wesseling et al. 2013). Nevertheless, one could argue that the scPCP-induced neurochemical changes are not robust (most changes are between 10 and 30 %, few up to 50–60 %) and their reproducibility between studies or even more importantly between labs has not been investigated (Table 2). Consistency of neurochemical findings, particularly between labs, and their correlation to behavioural changes is difficult to establish from the current literature due to the low number of comparative studies, and variation in the PCP dosing regimen and in post-scPCP cessation periods which impacts the effect of scPCP on neurochemistry as shown by, e.g. Newell et al. (2007a, b) (Table 2). The group by Roth has reported a reproducible reduction in frontal dopamine transmission at 1 to 4 weeks post-scPCP in rats and monkeys (Table 2). The magnitude of dopaminergic reduction within the dorsolateral prefrontal cortex and prelimbic cortex was suggested to correlate with cognitive impairment in an object retrieval/detour task in rats and primates (Jentsch et al. 1997b; Jentsch et al. 1999). Some studies showed reduced parvalbumin expression in the hippocampus (Schroeder et al. 2000; Abdul-Monim et al. 2007; Jenkins et al. 2008; Jenkins et al. 2010), while others found it in the cortex (Cochran et al. 2003). The loss of parvalbumin has not always been associated with a cognitive deficit, and again, there are very few studies (Neill et al. 2010). This raises a question whether the modest cognitive impairment by scPCP is due to inadequate neurochemical changes, and so, further studies are needed to explore this correlation. Broader investigation of functional neurochemical deficits by scPCP, similar to the one by Dawson et al. (2014), could help to establish a correlation between relevant specific changes in the brain and behaviour.

While the results of individual studies would suggest that the scPCP model has a high construct validity for the disorder, a closer examination of existing findings suggests that inconsistencies within the neurochemical and behavioural findings would question this validity. This is further confounded by positive publication bias, in which behavioural changes were supported by subsequent neurochemical changes, and neurochemical changes were again supported by behavioural changes, resulting in a positive feedback publication loop. In order to give a more accurate reflection of the state of the scPCP model, we would propose that the construct validity of this model for cognitive deficits associated with schizophrenia is low to moderate, since there have been very few studies which have fully assessed the pathophysiological changes underlying scPCP-induced deficits. On the other hand, the construct validity might be difficult to achieve for a single model since schizophrenia has multi-faceted causes for which we so far have limited understanding.

The effects of subchronic PCP treatment on locomotor activity and cognitive tasks

Hypersensitivity of locomotor activity to acute stimulants

Published data show that there is a hypersensitive response to acute challenge with stimulants in the rats treated with scPCP (Table 1). Subchronic treatment with PCP (5 mg/kg i.p. twice a day for 7 days, followed by at least 7-day washout) was found to induce a hyper-responsive state in the mesolimbic dopamine system (Jentsch et al. 1998b). This was shown by higher basal locomotor activity and enhanced locomotor response following acute administration of amphetamine (Jentsch et al. 1998b).

Multi-site characterization of scPCP-induced hypersensitivity to acute stimulants

We investigated whether hypersensitivity to acute PCP could offer an easy, non-invasive method for confirming that the scPCP treatment was successful before starting the labourious

and often long-lasting cognitive testing. At four research sites, we studied the effects of acute PCP challenge on locomotor activity in adult male Lister Hooded rats subchronically treated with vehicle (saline) or PCP (5 mg/kg, at Roche also doses 2 and 3 mg/kg, i.p. twice a day for 7 days, followed by at least 7-day washout) (see Online Resource 1 for detailed methods). The rats were first given a saline injection i.p., and basal locomotor activity in a novel environment was measured for 30 min (Orion Pharma, Roche and Janssen) or 60 min (Lundbeck). Then, acute PCP 5 mg/kg i.p. was administered, and locomotor activity was measured for 90 min (Orion Pharma and Roche) or 120 min (Lundbeck). At Janssen, a lower dose of acute PCP (2.5 mg/kg i.p.) and 60-min observation period were used (Fellini et al. 2014). The acute PCP challenge was studied at 0.5, 1, 2, 7, 8, 13, and 17 weeks after the scPCP treatment.

As shown in Fig. 1, acute PCP stimulated locomotor activity significantly more in the scPCP-treated adult male Lister Hooded rats than in vehicle controls when measured at 1, 2, 7, 8, and 13 weeks after the scPCP treatment (ANOVA $P<0.05$ to $P<0.001$; see Online Resource 2 for detailed results). The hypersensitivity to acute PCP had diminished at 17 weeks after the scPCP administration such that the locomotor response to acute PCP no longer differed between the scPCP

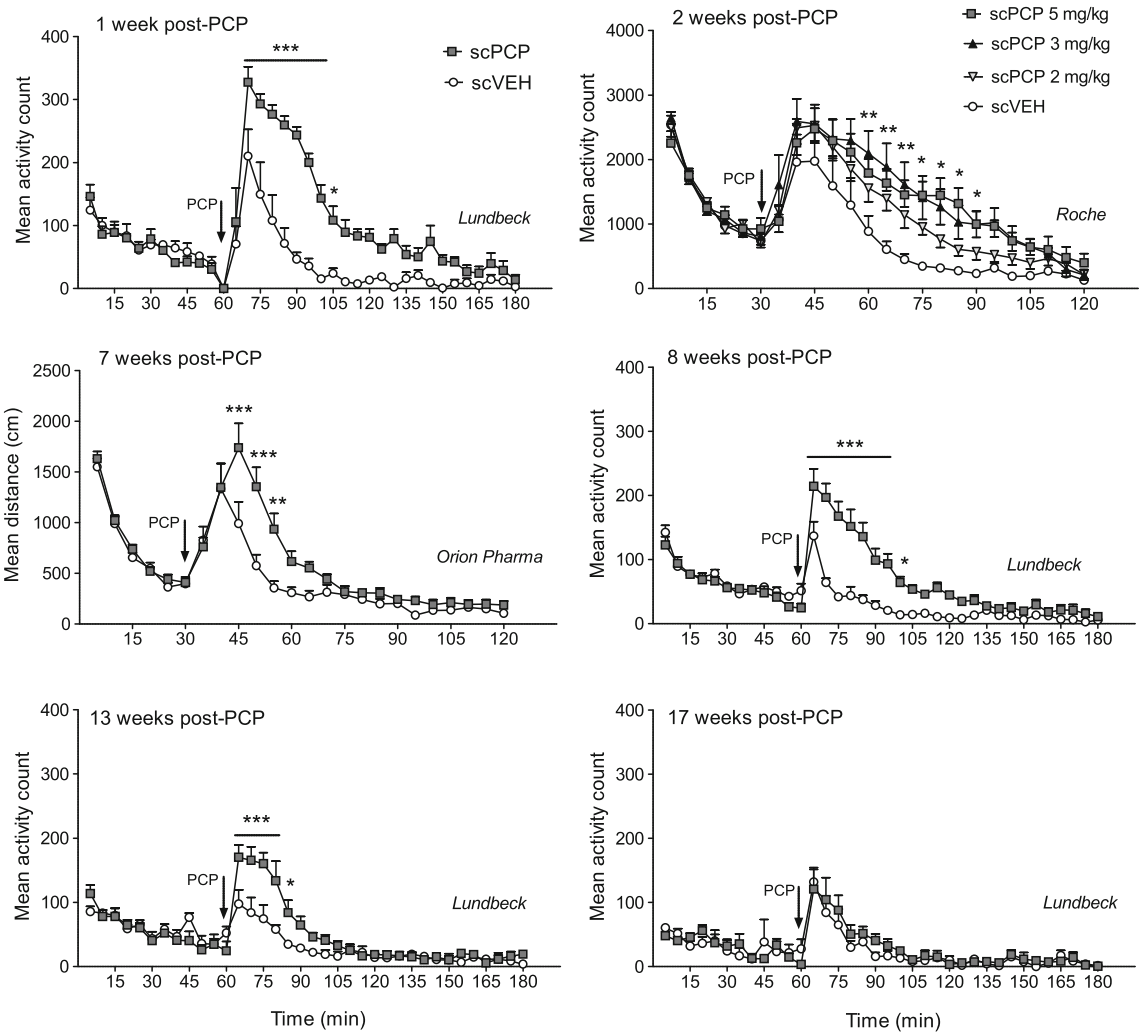

Fig. 1 The hypersensitivity of locomotor response to acute phencyclidine (*PCP*) after subchronic PCP treatment. Adult male Lister Hooded rats were treated with subchronic PCP (scPCP; 5 mg/kg, at Roche also 2 and 3 mg/kg, i.p., twice daily for 7 days) or vehicle (scVEH; 1 ml/kg, i.p.), and locomotor activity by acute PCP challenge (5 mg/kg, i.p.) was measured at 1, 2, 7, 8, 13 and 17 weeks after the scPCP treatment. During each experiment, the rats were first given saline i.p. and placed to the testing chambers for habituation period of 30 min (Roche and Orion Pharma) or 60 min (Lundbeck). The rats were then given an acute injection of PCP (5 mg/kg, i.p.), and locomotor activity was measured in 5-min intervals for 90 min (Roche and Orion Pharma) or 120 min (Lundbeck). At Lundbeck, the PCP challenge was done at 1, 8, 13 and 17 weeks post-scPCP (n=4–5, except n=10 at 8 weeks), at Roche at 2 weeks post-scPCP (n=10) and at Orion Pharma at 7 weeks post-scPCP (n=22–23) (See Online Resources 1 and 2 for detailed methods and results). Data presented as mean±S.E.M. The *arrow* depicts the time point when the acute PCP injection was given. Two-way ANOVA for repeated measures followed by Bonferroni's post hoc test for scPCP 5 mg/kg: *$P<0.05$, **$P<0.01$, ***$P<0.001$ vs scVEH group

and vehicle groups (Fig. 1; ANOVA P=0.48). The dose-response study by Roche showed that the hypersensitivity further enhanced from scPCP 2 to 3 mg/kg but not thereafter when the scPCP dose increased to 5 mg/kg, suggesting that scPCP 3 and 5 mg/kg may produce similar hypersensitivity of the mesolimbic dopamine system (Fig. 1). None of the studies showed differences between the scPCP and vehicle groups in basal exploratory activity measured after saline injection (Fig. 1; ANOVA P>0.25). At Janssen, a lower dose of acute PCP (2.5 mg/kg i.p.) significantly stimulated activity in the scPCP-treated rats, but not in vehicle controls at 3 days and 8 weeks post-scPCP (Fellini et al. 2014). Thus, we observed a qualitatively similar hypersensitivity of locomotor activity to acute PCP after the scPCP treatment at all four research sites (Orion Pharma, Roche, Lundbeck and Janssen), indicating an excellent reproducibility of these effects between research sites and studies.

Our present findings of hypersensitivity to acute PCP after the scPCP treatment are in line with previous reports (Table 1). Adult male Sprague-Dawley rats treated subchronically with PCP (4.5 or 5 mg/kg, i.p., twice a day for 7 days, followed by 7-day washout) displayed increased locomotor activity to acute PCP (1 and 10 mg/kg, i.p.) (Shirayama et al. 2007) or to acute amphetamine (1.0 or 1.5 mg/kg) (Jentsch et al. 1998b; Beninger et al. 2010). A challenge with a low dose of amphetamine (0.25 mg/kg) failed to show differences in locomotor responses of scPCP-treated rats and vehicle-treated rats, although in that study, the activity was overall higher in the animals treated with scPCP as compared to the scVEH-treated animals (Egerton et al. 2008). Our multi-site investigation did not show an enhanced locomotor response after saline injection in the scPCP group, whereas there was a small but significant increase in activity in the study by Jentsch et al. (1998b). However, in this study, the basal activity was also slightly higher in the scPCP group than the control group, in contrast to our findings. Difference to our studies could be explained by differences in rat strain and habituation of animals to handling and to mild stress.

To conclude, the locomotor response to acute PCP was reliably and qualitatively similarly sensitized after the scPCP treatment (Table 1, Fig. 1). In our scPCP protocol, the hypersensitivity was detected at 1 week post-scPCP, and it continued at least until 13 weeks post-scPCP in male Lister Hooded rats. The findings replicated well between studies and research sites, which further supports the use of acute PCP challenge as a tool for evaluation of successful scPCP treatment across studies and research sites if this is also associated with changes in behavioural measures of interest. Hypersensitivity to acute PCP might offer an easy, non-invasive method for confirming the imbalance between cortical and subcortical brain areas subsequent to the scPCP treatment (Jentsch et al. 1998b) before starting the labourious and often long-lasting cognitive testing.

Attentional set-shifting task

A core feature of schizophrenia is a selective impairment across several domains of cognition, including attention, executive functioning and working memory (Scheuerecker et al. 2008; Wobrock et al. 2009; Unschuld et al. 2014). Patients with schizophrenia demonstrate impaired set-shifting ability, typically characterized by an increase in perseverative responding (Elliott et al. 1995; Joyce et al. 2002; Pantelis et al. 2004). Patients with schizophrenia who fail at the ED shift stage may have also higher negative symptom scores compared with patients dropping out at previous learning stages (Pantelis et al. 1999). Schizophrenia patients exhibit deficits in performance in the Wisconsin Card-Sort Test (WCST), a test for executive function, and in task-related dopaminergic activation of the dorsolateral prefrontal cortex (Weinberger et al. 1986; Wobrock et al. 2009). These deficits inversely correlate with the level of dopamine metabolite homovanillic acid in the cerebrospinal fluid, implicating an involvement of a monoaminergic mechanism (Weinberger et al. 1988). Moreover, the specific deficits in a set-shifting task of executive function support the hypothesis that there is a dysfunction of frontostriatal brain areas in schizophrenia (Elliott et al. 1995; Wobrock et al. 2009). Excessive connectivity within brain networks coupled to the dorsolateral and medial prefrontal cortices accompany deficits in attention and working memory tasks in persons at risk for schizophrenia (Unschuld et al. 2014).

Preclinically, the intradimensional-extradimensional (ID-ED) task has been adapted for use with non-human primates, and performance in the task is impaired by lesions of the dorsolateral prefrontal cortex (Dias et al. 1996). Cessation of scPCP treatment has been found to produce impairments in the dorsolateral prefrontal cortex (Jentsch et al. 1999; Elsworth et al. 2011a), which could make it an ideal model of impaired cognition in schizophrenia when paired with a disease relevant paradigm like ID-ED. A version of the ID-ED task has been modified for use in rodents (Birrell and Brown 2000; Barense et al. 2002) (for a review see Tait et al. 2014). The task requires rats to solve a series of discrimination problems parallel to those presented in the ID-ED test by distinguishing which of two pots presented contains food rewards based on two or three nonspatial cue dimensions (odor, digging medium and/or texture). Lesions of the medial prefrontal cortex produce an impairment at ED shift but not at ID shift in rats, which is qualitatively similar to the deficits observed in first-episode schizophrenia (Birrell and Brown 2000; Barense et al. 2002).

Reports from several groups provide evidence for a consistent and reproducible impairment in the set-shifting of rats when appropriate administration and withdrawal regimens have been used (for a review see Tait et al. 2014). As

summarized in Table 1 and shown in Fig. 2, the '7+7 day' scPCP treatment (5 mg/kg i.p., twice a day for 7 days, followed by at least 7-day washout) selectively increased the number of trials to reach criterion at ED shift, but not at ID shift or any other parameter including reversal learning, in adult male Long-Evans rats (Maeda et al. 2014) and in adult male Lister Hooded rats at Lundbeck (Broberg et al. 2009; Goetghebeur and Dias 2009; Goetghebeur et al. 2010). Female rats appear more sensitive to PCP, and subchronic treatment with a lower dose of PCP (2 mg/kg i.p., twice a day for 7 days, followed by 7-day washout) produced a selective impairment of the ED shift in adult female Lister Hooded rats (Fig. 2) (McLean et al. 2012). Lower dosing and shorter withdrawal from PCP (2.6 mg/kg, once daily for 5 days, followed by 72-h washout) impaired ED shift in adult male Long-Evans rats (Fig. 2) (Egerton et al. 2008; Dawson et al. 2012). There are also others reporting the scPCP-induced increase in number of trials to reach criterion at ED shift in male Long-Evans rats at 5 mg/kg of scPCP (Rodefer et al. 2005; Rodefer et al. 2008) and in female Lister Hooded rats at 2 mg/kg of scPCP (McLean et al. 2008). These studies, however, did not show a significant increase in ED shift as compared to ID shift in the vehicle group, suggesting that the rats have not learnt the attentional set towards the relevant dimension at the stages before the ED shift, which is the key feature of the task as developed by Birrell and Brown (2000). In such cases then, it is not possible to confirm selective deficits in attentional set with scPCP. A long-term chronic PCP treatment without a sufficient withdrawal period or an intermittent treatment with PCP failed to impair set-shifting, which suggests that these treatments may fail to produce severe enough deficits in the prefrontal cortex and thus a selective impairment at the ED shift (Fletcher et al. 2005; Deschenes et al. 2006). All in all, the data indicate that cessation of scPCP treatment can produce a selective deficit in attentional set-shifting ability in rats.

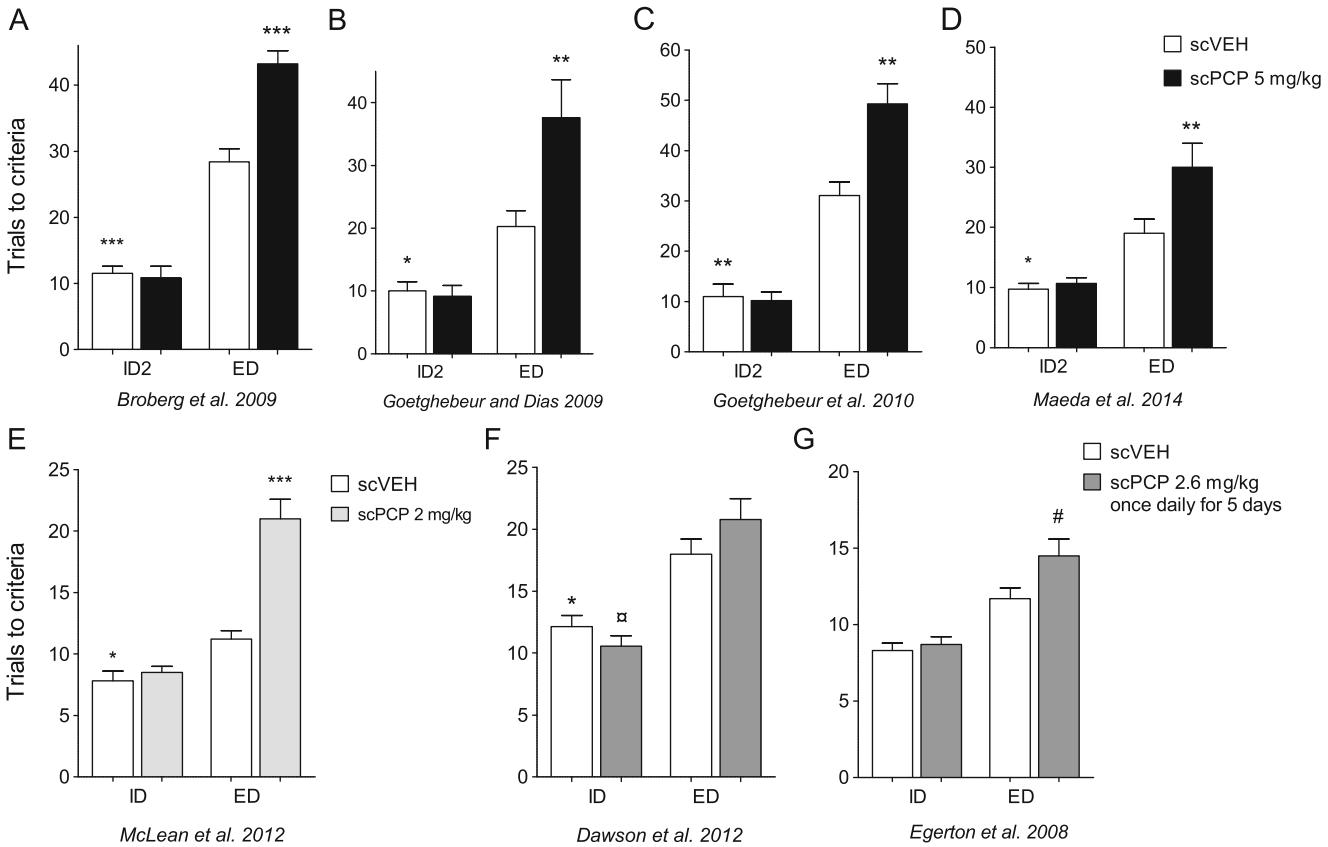

Fig. 2 Subchronic PCP treatment disrupts attentional set-shifting in rats. Graphs show number of total trials to reach criterion in intradimensional (ID or ID2) and extradimensional shift (ED) in the attentional set-shifting task. The scPCP treatment 5 mg/kg i.p. twice daily for 7 days, followed by 7-day washout, was given to male Lister Hooded rats (**a**–**c**) or to male Long-Evans rats (**d**). In **e**, female Lister Hooded rats received scPCP 2 mg/kg i.p. twice daily for 7 days, followed by 7-day washout. In **f** and **g**, male Long-Evans rats received scPCP 2.6 mg/kg once daily for 5 days, followed by 72-h washout. Data are expressed as mean±S.E.M. For methodological details and statistical analyses, see original publications. # P=0.055, *P<0.05, **P<0.01, ***P<0.001 vs scVEH group at ED shift; ¤P<0.05 vs scPCP group at ED shift. These data were previously published (Egerton et al. 2008; Broberg et al. 2009; Goetghebeur and Dias 2009; Goetghebeur et al. 2010; Dawson et al. 2012; McLean et al. 2012; Maeda et al. 2014), reproduced with permissions from Springer, SAGE Publications, ASPET and Oxford University Press

Pharmacological validation of scPCP impaired attentional set-shifting task

Second-generation antipsychotics such as clozapine and sertindole, but not olanzapine or aripiprazole or the typical antipsychotic haloperidol, have been reported to reverse the scPCP-induced impairment at ED shift (McLean et al. 2008; Rodefer et al. 2008; Broberg et al. 2009; Goetghebeur and Dias 2009; Maeda et al. 2014). Risperidone alleviated the scPCP-induced impairment at ED shift in female rats (McLean et al. 2008) but not in male rats (Goetghebeur and Dias 2009). The psychostimulant modafinil ameliorated the ED shift impairment subsequent to the scPCP treatment (Goetghebeur and Dias 2009; Goetghebeur et al. 2010; Dawson et al. 2012; Maeda et al. 2014). In addition, several putative and experimental compounds have shown efficacy against the scPCP-induced impairment at ED shift, including but not limited to an ampakine, a serotonin-dopamine activity modulator and a nicotinic alpha7 acetylcholine receptor agonist (e.g. Broberg et al. 2009; McLean et al. 2011; Maeda et al. 2014) (for a review see Tait et al. 2014).

In support of preclinical findings from the scPCP impaired ASST, there are few clinical studies which show that clozapine and risperidone may improve attention and executive function in schizophrenia, whereas evidence for olanzapine is inconsistent (for a comparative review see Meltzer and McGurk 1999). However, the general consensus in the field is that current antipsychotic treatments fail to normalize many of the cognitive deficits in schizophrenia (Keefe et al. 2007). Moreover, no treatment has yet been shown to have robust and reproducible effects on cognition in a clinically relevant manner, thus the need for novel treatments. When assessing novel mechanisms of action preclinically, it is important to use a model which has good predictive validity. For cognitive impairment in schizophrenia, we are limited in our assessment of this since there is no positive reference compound (i.e. active in the clinic) available, and so, the animal models are usually validated with negative reference compounds. In the rat ASST, impaired by scPCP, several studies have consistently shown that typical antipsychotics, like haloperidol as well as atypical antipsychotics, like olanzapine do not reverse the impairment in ED set-shifting which fits with the clinical findings. Yet, there are still conflicting findings regarding the effects of atypical antipsychotics between different research sites. These may be due to a number of differences between the procedures, such as duration of treatment, male vs female rats and whether dimension shifts are counterbalanced (e.g. for odour, media) or not. For instance, McLean et al. (2008) showed that subchronic administration of either risperidone or clozapine significantly reversed the ED impairment (without counterbalancing) in female rats, whereas acute administration of these compounds did not have an effect in male rats with counterbalancing of dimension shifts (Rodefer et al. 2008).

Phase 1 studies have shown improvements in attentional set-shifting in schizophrenia following sertindole (Gallhofer et al. 2007) and modafinil in patients with chronic schizophrenia (Turner et al. 2004), but not in first-episode psychosis (Scoriels et al. 2012). Although both sertindole and modafinil have been shown to improve ASST in the scPCP model providing back-translation of clinical findings, these findings have not been confirmed in larger, late-stage clinical trials, and neither treatment has been approved for the treatment of cognitive impairment in schizophrenia. Furthermore, activity with atypical antipsychotics such as sertindole, risperidone and clozapine has been observed in this rat model, but at doses which are below the antipsychotic concentrations required in both animal models and the clinic. This indicates that at doses which do not impair locomotor activity in rats, it is possible to see positive effects on cognition in this model. At higher doses, which are equivalent to antipsychotic doses resulting in D_2 receptor blockade, rats are unable to perform cognitive tasks such as ID-ED due to markedly reduced locomotor activity. There has been an attempt to understand the underlying pharmacological mechanism of action responsible for the positive effects of the atypical antipsychotics in some studies, and this has been attributed to lower D_2 blockade so that locomotor activity is not affected and procognitive effects possibly due to either 5-HT_6 and/or 5-HT_{2A} antagonism (McLean et al. 2008; Rodefer et al. 2008). However, since the positive effects of antipsychotics do not translate into clinical reality, the preclinical findings do not add confidence to the predictive validity of the model.

Preclinical data suggest that the scPCP treatment within the ID-ED test in rats produces a consistent, reproducible impairment in set-shifting across four independent research sites (Table 1, Fig. 2). The qualitative similarity in drug effects and neural correlates between clinical and preclinical studies may support the use of scPCP treatment within the rat ID-ED task as a preclinical model with relevance to the attentional set-shifting deficit in schizophrenia. However, the size of the scPCP-induced deficit in ED shift may vary as shown in Fig. 2, and for drug screening, validation of the model is needed to obtain an adequate deficit that can reliably detect dose-related effects of potential novel compounds. Preferably, deficits like those in, e.g. Broberg et al. (2009) and Goetghebeur and Dias (2009), would provide a suitable window for these studies. Furthermore, as mentioned previously, it should also be verified that the animals have formed an attentional set prior to the ED shift stage of the task in the vehicle-treated group, to confirm a selective attentional set-shifting deficit by scPCP. Regarding construct validity, in monkeys and rats, the scPCP treatment appears to impair the same cortical areas that play a pivotal role in set-shifting (Dias et al. 1996; Jentsch et al. 1999; Elsworth et al. 2011a; Dawson et al. 2012). However, in rats, it has recently been shown that scPCP treatment does not impair cognition in a test which is

sensitive to medial prefrontal cortex lesions, and vice versa, suggesting that the scPCP-induced deficits may not be directly mediated by the medial prefrontal cortex (see McAllister et al. in this issue). Accordingly, Dawson et al. (2012) identified functional prefrontal and subcortical connections that were altered by the scPCP treatment and suggested that these alterations and dysfunction of multiple brain regions, rather than a discrete dysfunction of the prefrontal cortex alone, underlie the cognitive inflexibility in scPCP-treated animals. Yet, care should be taken in interpreting the scPCP-induced behavioural impairments, since recent studies suggest certain perceptual deficits by scPCP, as shown by a decrease in the performance of the scPCP rats when challenged with low contrast stimuli in the touchscreen-based continous performance task (Mar et al., in preparation). Thus, further work is required to understand if the ED shift impairment induced by scPCP is similar to the deficit in schizophrenia or may instead be better attributed to changes in attention or perception that are also influencing performance of an ED shift.

Novel object recognition memory

Patients with schizophrenia show deficits in 2D object recognition tasks like the Brief Visual Memory Test (BVMT) or its revised version (BVMT-R) which are used to assess visual learning and memory (Nuechterlein et al. 2004; Aleman et al. 2005; Yoo et al. 2006; Schretlen et al. 2007). Object recognition memory in humans is considered as a classic test of declarative memory function that is mediated by distinctive parts of the medial frontal lobe (Murray et al. 2007). The perirhinal cortex plays an essential role in familiarity-based object recognition and perceptual processing of complex objects in humans, primates and rats (Aggleton et al. 1997; Pihlajamaki et al. 2004; Bussey et al. 2005; Bartko et al. 2007). The hippocampus is considered to contribute little, if at all, to this function (Ennaceur et al. 1996; Aggleton et al. 1997; Murray et al. 2007). Consistently, patients with schizophrenia show decreased volumes in the anterior ventromedial temporal lobe, including the perirhinal cortex (Turetsky et al. 2003).

The NOR test paradigm relies on the rodents' tendency to explore novel objects encountered in its environment (Ennaceur and Delacour 1988). During acquisition, a rat is exposed to two identical objects for a brief period of time (e.g. 3–10 min). After a delay (from minutes to days), the rat is exposed to the familiar object and to a novel object during a retention trial (Bevins and Besheer 2006). Rats typically spend more time exploring the novel object over the familiar object, which is interpreted as reflecting the rat's memory for the familiar object and its desire to explore a novel object. As described above, the perirhinal cortex, rather than the hippocampus, has been implicated in the NOR performance (Ennaceur et al. 1996; Aggleton et al. 1997; Winters et al. 2004). In rats, the role of the hippocampus seems to be irrelevant particularly when the spatial cues are eliminated (with, e.g. raised walls) (Forwood et al. 2005) or when a short intertrial interval (10 s or 1 min) is used between the acquisition and retention trial (Clark et al. 2000). Also, the prefrontal cortex might be less relevant with short intertrial intervals (e.g. 10 min) (Yee 2000), while at longer (24-h) delays, the prefrontal cortex might play a role (Nagai et al. 2007).

Multi-site characterization of scPCP impaired object recognition memory

There are a great number of studies from several groups reporting the effects of scPCP treatment on NOR performance (Table 1). However, the variety of dosing regimens, intertrial intervals, rat strains, apparatus and scheduling of the NOR study in relation to the scPCP treatment in these studies make it difficult to compare the findings between research sites and studies. Therefore, we focus on comparison of the effects of the scPCP treatment on NOR performance in separate studies at two research sites. At Roche, three doses of PCP (2, 3 and 5 mg/kg, i.p.) were injected twice a day for 7 days, followed by at least 7-day washout, and the NOR test was conducted on week 5 post-scPCP. At Lundbeck, PCP (5 mg/kg, i.p.) was given twice a day for 7 days, and NOR testing was conducted after the washout, on days 8 and 9 after the last scPCP injection (see Online Resource 1 for detailed methods). The data by Lundbeck has been previously published (Redrobe et al. 2010).

Detailed results can be found in Online Resource 2. As Fig. 3a shows, at Roche, the vehicle-treated adult male Lister Hooded rats spent significantly more time exploring the novel object over the familiar object during the 3-min retention trial (t test $P<0.001$). The preference for the novel object was diminished when the rats had been previously treated with scPCP at 2, 3 or 5 mg/kg and withdrawn from it (Fig. 3a). The scPCP treatment with 2, 3 or 5 mg/kg significantly decreased the discrimination index, a measure that corrects the difference between novel/familiar object exploration for total exploration activity (Fig. 3a; post hoc test $P<0.05$). The scPCP treatment had no effect on exploration activity (data not shown). Similarly to the findings by Roche, the scPCP treatment attenuated the preference for the novel object during the retention trial and significantly decreased the discrimination index at Lundbeck (Fig. 3b reproduced from Redrobe et al. (2010); $P<0.001$). These studies at two research sites comparably show that scPCP impaired the preference for the novel object in the recognition memory task when a longer intertrial interval of 1 h was used.

As summarized in Table 1, several previous studies have used similar subchronic PCP treatment (2 mg/kg i.p., twice daily for 7 days, followed by at least 7-day washout) and report that the scPCP treatment impaired the NOR

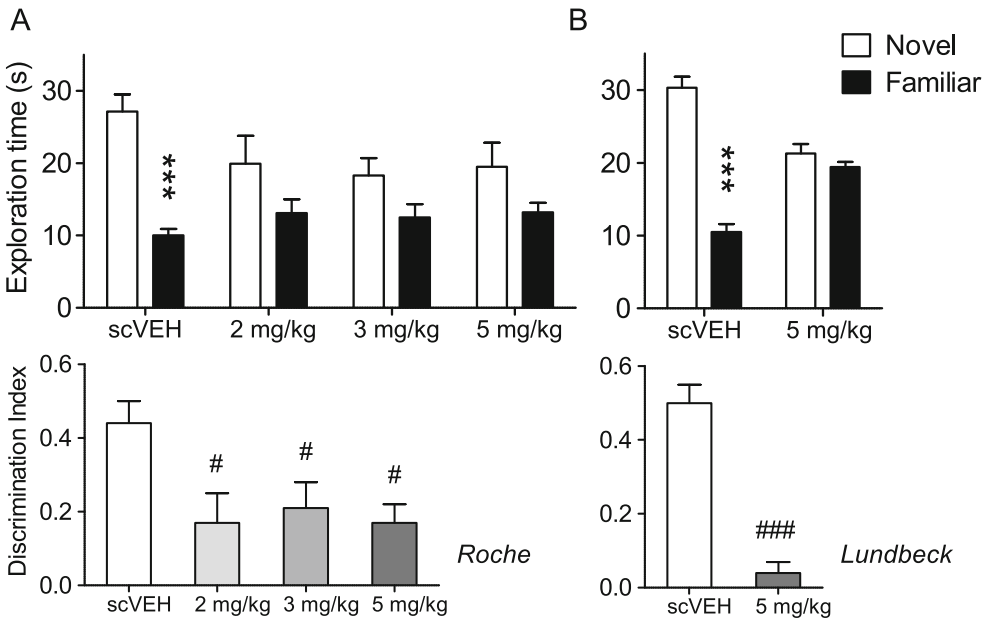

Fig. 3 The impairment of object recognition after subchronic PCP treatment. Adult male Lister Hooded rats were treated with subchronic PCP (2, 3 or 5 mg/kg i.p. in **a**, and 5 mg/kg i.p. in **b**, twice daily for 7 days) or vehicle (scVEH, 1 ml/kg, i.p.), and the novel object recognition test was conducted at 5 weeks (**a**) or at 8 to 9 days (**b**) after the scPCP treatment. An experiment consisted of two 3-min trials separated by an 1-h intertrial interval. In the first trial, the two objects were identical, and in the retention trial, one object was familiar (*closed bar*) and the other was novel to rats (*clear bar*). Exploration times (s) for each object during the retention trial are presented. Discrimination index: (novel-familiar)/(novel + familiar). Data presented as mean±S.E.M. (See Online Resources 1 and 2 for detailed methods and results). **a** n=10, Roche **b** n=31–33, Lundbeck. Student's t test: ***P<0.001 vs novel; one-way ANOVA followed by Dunnett's post hoc test: # P<0.05 vs scVEH, or by Tukey's post hoc test ### P<0.001 vs scVEH. Figure **b** is part of two figures originally published in Redrobe et al. (2010), reproduced with permission from Frontiers in Psychiatry

performance during the retention trial, leaving the acquisition phase intact in female Lister Hooded rats (Grayson et al. 2007; McLean et al. 2009a; Arnt et al. 2010; Damgaard et al. 2010; Idris et al. 2010; Damgaard et al. 2011; McLean et al. 2011; Snigdha et al. 2011; Grayson et al. 2014), in female Long-Evans rats (Snigdha et al. 2010; Horiguchi et al. 2011a, b; Horiguchi et al. 2012; Horiguchi and Meltzer 2012; Horiguchi et al. 2013; Horiguchi and Meltzer 2013), in male Lister Hooded rats (McKibben et al. 2010) and in ovariectomized female Sprague-Dawley rats (Roseman et al. 2012). Subchronic dosing of a higher dose of PCP (5 mg/kg i.p., twice daily for 7 days, followed by at least 7-day washout) reproducibly impaired the NOR performance in male Lister Hooded rats at Lundbeck (Redrobe et al. 2010; Redrobe et al. 2012; Maeda et al. 2014) and in male Sprague-Dawley rats (Shirayama et al. 2007). Although the majority of these studies have used an intertrial interval of 1 min between the acquisition and retention trial, there are also studies that have used a longer intertrial interval and report a robust impairment in the NOR performance after scPCP when the intertrial interval was 1 h (Fig. 3) (Idris et al. 2010; McKibben et al. 2010; Redrobe et al. 2010; Redrobe et al. 2012; Maeda et al. 2014) or 24 h (Shirayama et al. 2007). These reports are significant since a longer intertrial interval may help to exclude some of the confounding drug effects in this model (see discussion below).

Pharmacological validation of scPCP impaired object recognition memory

The majority of atypical antipsychotics tested, such as clozapine, sertindole, asenapine, olanzapine, melperone, lurasidone and amisulpiride, but not sulpiride, aripiprazole or the typical antipsychotic haloperidol, reversed the impairment in the retention phase of the NOR test subsequent to cessation of the scPCP treatment (Grayson et al. 2007; Idris et al. 2010; Redrobe et al. 2010; Snigdha et al. 2010; Horiguchi et al. 2011a, b; Snigdha et al. 2011; Horiguchi et al. 2012; Horiguchi and Meltzer 2012, 2013; Maeda et al. 2014). Findings from risperidone were less consistent: it was found to reverse the scPCP-induced deficit in the NOR task in female rats (Grayson et al. 2007; Snigdha et al. 2010; Horiguchi and Meltzer 2013), but failed to reverse it in male rats after acute or repeated administration when a longer intertrial interval (1 h) was used (McKibben et al. 2010; Redrobe et al. 2010). The psychostimulant modafinil ameliorated the scPCP-induced deficit in novel object exploration utilizing a 1-h intertrial interval, while the acetylcholinesterase inhibitor donepezil was without a significant effect (Redrobe et al. 2010). In addition, several putative compounds have shown efficacy against the scPCP-induced NOR impairment, including but not limited to a negative modulator of $GABA_A$ α5

receptor (Redrobe et al. 2012), a nicotinic α_7 acetylcholine receptor agonist (McLean et al. 2011), a choline uptake enhancer (Shirayama et al. 2007) and a 5-HT_6 receptor antagonist (Arnt et al. 2010) (for a review see Meltzer et al. 2013). Several 5-HT receptor mechanisms, like 5-HT_{1A} agonism and 5-HT_7 antagonism, have been implicated in reversal of the scPCP-induced deficit in the NOR test (Horiguchi et al. 2011b; Horiguchi and Meltzer 2012). Data from the studies using intertrial interval of 1 min should, however, be carefully evaluated. Drug-induced improvements in performance of the NOR test may be affected by non-specific effects of compounds on processes such as perception, attention and motivation, and not directly on memory, particularly when the intertrial interval used is very short, i.e. 1 min, as used in the majority of the studies mentioned above. This may explain why so many compounds with different pharmacological effects modulating dopaminergic, cholinergic, serotonergic and glutamatergic systems are all active in this paradigm, since they are likely to be acting on different processes. Furthermore, the effect of scPCP in this assay should be assessed across a range of intertrial intervals, since if this is a memory deficit then it should be possible to show a delay-dependent effect on performance.

There are consistent, reproducible findings from several research sites that the scPCP treatment impairs NOR performance in rats (Table 1), and that this deficit can be reversed by a great number of compounds, including most antipsychotics. On the other hand, the fact that antipsychotics improve cognitive performance in schizophrenia only at low doses and modestly, if any (Keefe et al. 2007), raises a concern for the predictive validity of the scPCP-impaired NOR test. For the NOR test in general, an observation was made that most of the published studies have indicated that almost all targets tested to date have shown efficacy in the NOR (Young et al. 2009). Yet, not all targets replicated positively later in patients. Despite this, some support for the translational value of the NOR exists as well. In line with the lack of improvement in the NOR, donepezil had no effect on cognition in schizophrenia patients in blinded, placebo-controlled studies (reviewed by, e.g. Friedman 2004). However, the effects in the clinic may also vary. A study reported a modest effect for modafinil on visual memory in schizophrenia (Turner et al. 2004), while findings in other studies vary from no effect to improved visual memory by modafinil (reviewed by, e.g. Wittkampf et al. 2012).

The NOR test has been suggested to model human declarative memory, although some have questioned this because it has not been shown that a rat can remember features of objects comparable to humans in this test (Sarter 2004). It is also not possible to determine what type of cognitive process the task is measuring, i.e. attention, motivation, encoding and retrieval. Interestingly, scPCP treatment failed to impair performance in Morris water maze which is a visuo-spatial learning and memory task (see below; Fig. 4). Thus, the scPCP treatment impairs visual memory in the NOR task but does not impair visuo-spatial memory in hippocampal-dependent Morris water maze (see below; Fig. 4), raising a question whether the impairment in NOR is really a selective impairment of visual memory. Also of note, and as discussed in more detail below, the scPCP treatment failed to impair visual discrimination memory and reversal learning in the touchscreen-based visual discrimination task (see below; Fig. 5). Interestingly, recent studies showed a decrease in the performance of scPCP rats in the touchscreen-based continous performance task when challenged with low contrast stimuli, suggesting that scPCP may cause certain perceptual deficits (Mar et al., in preparation). These visual perceptual alterations might explain the consistent findings of NOR deficits in these animals.

To conclude, the NOR test is a relatively fast- and high-throughput assay for studies of visual memory. Although the NOR task in general is sensitive to changes in protocol, environment and experimenter and thus requires thorough validation, the scPCP treatment appears to consistently impair NOR performance across several sites. However, our review of the literature raises concern for the predictive validity of the model, and our new data suggest that the scPCP-induced impairment might not be selective to visual memory.

Morris water maze

The Morris water maze (Morris 1984) is one of the most frequently used tools in behavioural neuroscience and in the evaluation of rodent models and novel procognitive therapies. It is a visual learning and memory task, but it also involves a visuo-spatial component (for a review see D'Hooge and De Deyn 2001; Young et al. 2009). There are supportive data for the validity of the water maze assay for assessing cognitive deficits associated with schizophrenia. The classical Morris water maze task is thought to probe hippocampal dependent spatial recognition memory similar to the revised version of the Brief Visual Memory Test (BVMT-R) in humans, and schizophrenia patients show deficits in the BVMT-R (Nuechterlein et al. 2004; Yoo et al. 2006; Schretlen et al. 2007). Importantly, patients with schizophrenia have difficulty in the hippocampus-dependent (i.e. hidden platform) version of the virtual water maze task which is very similar task to the rodent Morris water maze (Hanlon et al. 2006). Water maze performance depends upon the coordinated action of several brain regions and neurotransmitter systems, including hippocampus, striatum, basal forebrain, cerebellum and cerebral cortex (for a review see D'Hooge and De Deyn 2001). The dorsal hippocampus rather than ventral hippocampus is important for spatial learning in the water maze in rats (Moser et al. 1993), and selective CA1 and CA3 lesions impair acquisition in the water maze (Stubley-Weatherly et al. 1996). Performance in the water maze is disturbed by lesions of the

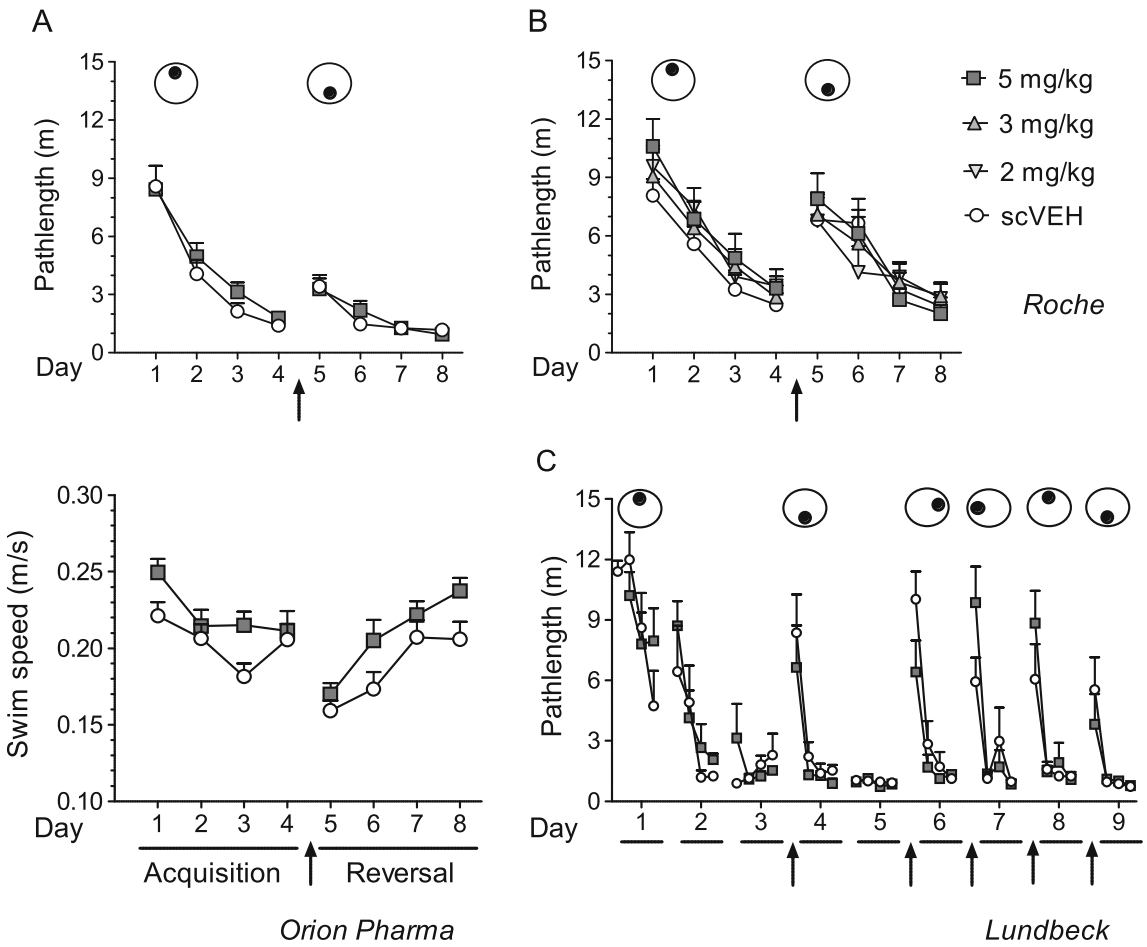

Fig. 4 The subchronic PCP treatment did not impair spatial acquisition or reversal learning in the Morris water maze. Adult male Lister Hooded rats were treated with subchronic PCP (scPCP; 5 mg/kg, at Roche also 2 and 3 mg/kg, i.p., twice daily for 7 days, followed by at least 7-day washout) or vehicle (scVEH, 1 ml/kg, i.p.), and the acquisition and reversal learning of a water maze task with hidden platform were examined. **a** Pathlength and swim speed, **b** pathlength to the platform during the acquisition phase in week 1 (days 1–4) and the reversal phase in week 2 (days 5–8), with each day containing the mean of three consecutive trials (**a** n=8, Orion Pharma; **b** n=10, Roche). **c** Pathlength to the platform during four daily trials in the acquisition phase (days 1–3), in the first reversal (days 4–5) and in the second to fifth reversal (days 6–9) (n=6, Lundbeck) (see Online Resources 1 and 2 for detailed methods and results). Data presented as mean±S.E.M. The *arrow* indicates the time point when the platform was positioned to another location (*shown by the dot in the circle*)

habenula, the dysfunction of which may contribute to the cognitive deficits in schizophrenia (Lecourtier et al. 2004).

The Morris water maze involves a rodent learning to spatially locate a hidden escape platform from various starting positions within the maze (Morris 1984). The task consists of trials (typically 2 to 4 trials per day for a 4- or 5-day period) in which the rodent is placed in an arena filled with water and containing a small hidden platform available for the animal to escape the water. To assess spatial memory and perseveration, probe trials with no platform can be conducted after completion of normal trials with a hidden platform. The task can also be modified to assay reversal learning where once trained to a location, the platform moves randomly to a different location either each week, each day or even each trial. In this way, the amount of time spent circling the former correct location can be used as a measure of perseveration.

Multi-site characterization of the effects of scPCP on spatial reversal learning in the Morris water maze

We conducted a cross-site investigation on the effects of the scPCP treatment on acquisition and reversal learning in a spatial reference memory task of the Morris water maze. Before testing in the water maze, the rats were subchronically treated with PCP (2, 3 or 5 mg/kg at Roche, or 5 mg/kg at Lundbeck and Orion Pharma; twice a day for 7 days, followed by a 7-day washout period) (see Online Resource 1 for detailed methods). At Roche and Orion Pharma, a 4-day acquisition phase was performed in week 1 (first platform location) and a 4-day reversal phase, with a new platform location, followed in week 2. Detailed results are presented in Online Resource 2. At both research sites, investigation of the pathlength to the platfrom revealed that the scPCP treatment had no effect on acquisition or reversal of a spatial learning at any dose studied

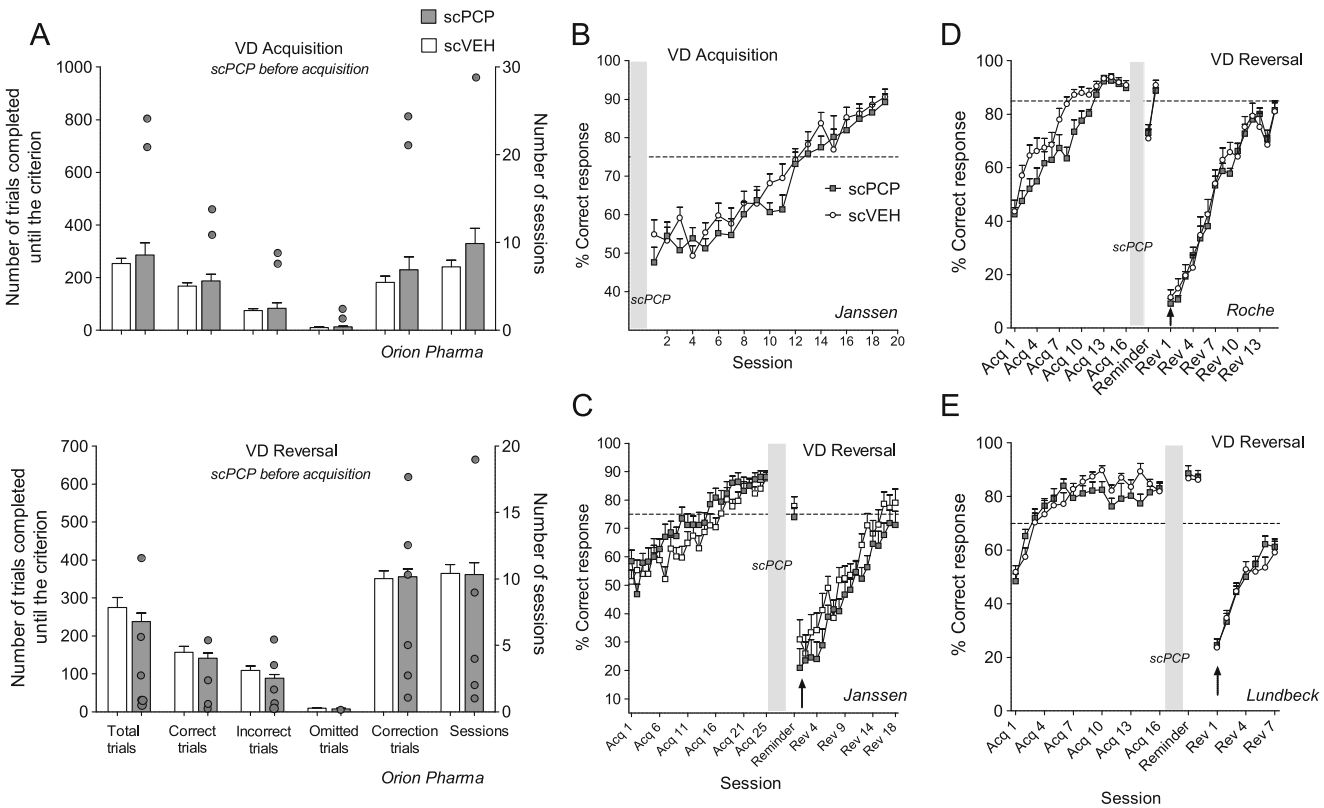

Fig. 5 The subchronic PCP treatment did not impair acquisition or reversal of visual discrimination (*VD*) task in touchscreen system. Adult male Lister Hooded rats were treated with subchronic PCP (scPCP; 5 mg/kg in **a**, **b**, **c** and **e**, or 3 mg/kg in **d**, i.p., twice daily for 7 days) or vehicle (scVEH; 1 ml/kg, i.p.) either before acquisition (**a**, **b**) or before reversal phase (**c**, **d**, **e**), and learning of the VD task was evaluated by calculating the % correct response. **a** Number of total, correct, incorrect, omitted and correction trials and test sessions completed to reach the criterion (80 % correct response). The scPCP treatment was given before acquisition and reversal (n=21–22, Orion Pharma). **b** The % correct response during acquisition of the VD task when scPCP was given prior to the acquisition (n=12, Janssen). **c**–**e** The % correct response during reversal learning of the VD task when scPCP was given between acquisition and reversal (**c** n=12, Janssen; **d** n=8, Roche; **e** n=12–16, Lundbeck) (see Online Resources 1 and 2 for detailed methods and results). Data presented as mean±S.E.M. In **a**, the *grey dots* represent outliers that failed to reach the criterion during the experiment. In **b**–**e**, the *grey shading* indicates the time point when scPCP was given and the *dotted line* represent the level of criterion. In **c**–**e**, the *arrow* depicts the time point when the task was reversed. The data by Janssen (**b** and **c**) has been recently published (Fellini et al. 2014), reproduced with permission from Elsevier

(Fig. 4a, b; ANOVA P>0.3). There was a clear effect by the test day on pathlength (Fig. 4a, b; ANOVA P<0.001 for acquisition and reversal), indicating that the animals learnt to navigate to the platform during the acquisition and reversal phase. The scPCP treatment increased swim speed only modestly (Fig. 4a; ANOVA P>0.2), indicating that it did not markedly disturb motor performance. At Roche, the probe trials on the fifth day of each test week did not show a difference between scPCP and vehicle group (data not shown), suggesting no impairment in spatial memory or perseveration by the scPCP treatment.

At Lundbeck, the 3-day acquisition phase was performed in week 1 and thereafter series of reversals followed, with the platform location changing approximately each day. Investigation of pathlength to the platform revealed no differences between the scPCP and vehicle group in within or between test day performance during acquisition or repeated reversals (Fig. 4c; ANOVA P>0.3). The lack of impairment by scPCP in the performance during individual trials was confirmed at Orion Pharma (data not shown). The findings imply that the scPCP treatment did not impair spatial learning during acquisition or reversal phase when the location of the platform was reversed each week or even each day. The scPCP treatment did not impair working memory, shown by the normal within-day performance, nor long-term memory, shown by normal performance during the first trial of each day.

We are the first to report the effects of the scPCP treatment and withdrawal on the acquisition and reversal learning in Morris water maze in adult rats (Table 1, Fig. 4). Our data from three studies and research sites consistently show that the scPCP treatment did not impair acquisition or reversal of water maze performance, indicating no impairment in short- or long-term visuo-spatial learning and memory after the scPCP treatment. Probe trials did not show differences between the scPCP-treated and vehicle control rats, suggesting no deficits in spatial memory or perseveration by scPCP.

There was no impairment in a within-day performance after scPCP when platform location was repeatedly changed at Lundbeck, indicating no impairment in working memory. Yet, the scPCP treatment was confirmed successful in these rats, by using the acute PCP challenge locomotor activity test (Fig. 1). Previous water maze studies in rats (or mice) have used either neonatal administration of PCP or administration of PCP during the water maze testing without a cessation from PCP. Postnatal PCP impaired water maze performance of juvenile rats (Brooks et al. 1997; Sircar and Rudy 1998; Andersen and Pouzet 2004). In contrast to our findings from scPCP, neonatal PCP impaired particularly short-term reference memory, reversal learning and working memory (Secher et al. 2009). In adult male Wistar rats, repeated treatment with PCP (0.5–2.5 mg/kg, s.c., once a day), starting at 3 to 7 days before and continued throughout water maze testing, disrupted spatial learning and memory (Podhorna and Didriksen 2005; Didriksen et al. 2007).

From the literature, it appears that in order to impair spatial water maze performance, PCP has to be given either repeatedly to rats as young pups or to adult rats during the water maze test. Acute NMDA receptor blockade produces hyperfrontality, that is, an increase in glucose utilization and blood flow in the prefrontal cortex, indicating enhanced excitatory processing in the brain (Weissman et al. 1987; Gao et al. 1993). Perhaps, the hyperfrontality by acute PCP rather than hypofrontality by scPCP severely impairs visual learning and memory. The subchronic PCP treatment, discontinued prior to testing, may not sufficiently disturb function of the brain areas that are activated during water maze performance such as cortical areas, hippocampus and habenula. Yet, previous reports indicate that scPCP treatment impaired function of the prefrontal cortex and hippocampus. As discussed in Neurochemical effects underlying behavioural changes in the scPCP model section, scPCP treatment produced a reduction in glucose and dopamine utilization in the prefrontal cortex, and a reduction in parvalbumin expression in the CA1 and CA2/3 regions of the hippocampus or in the prefrontal cortex (Table 2). The reduction in dopamine turnover in the prefrontal cortex after scPCP was found to correlate with the impairment in the performance in spatial delayed alternation task, a task considered to probe working memory (Jentsch et al. 1997b). However, several paradigms which are thought to measure working memory, although most likely assess short-term spatial or visual-spatial memory, do not show robust impairment after scPCP. There were no deficits by scPCP in the performance in a spontaneous alternation in Y-maze (Roche, inhouse data), in a delayed alternation in T-maze (Stefani and Moghaddam 2002), in a radial arm maze reference memory task (Li et al. 2003) or in a temporal order task (Marquis et al. 2003). Modest deficits by scPCP were found in a combined spatial discrimination-alternation task in Y-maze (Beninger et al. 2010) and in a continuous alternation task in T-maze (Marquis et al. 2007), but the deficits were so small that reproducibility is questionnable and there would be no room for drug testing. Indeed, as discussed in Neurochemical effects underlying behavioural changes in the scPCP model section, the scPCP-induced neurochemical changes are not robust (most changes are between 10 and 30 %, few up to 50–60 %), and their reproducibility has not been broadly investigated. The association between neurochemical changes and cognitive disturbances in the scPCP model remains to be elucidated in future studies. Novel approaches such as broad investigation of the effects of scPCP on the functional brain connectivity (Dawson et al. 2012) might help to establish behavioural correlates that follow specific scPCP-induced neurochemical changes.

Nonetheless, our cross-site studies consistently found no impairment in short- or long-term reference memory, reversal learning or working memory in the Morris water maze after the scPCP treatment (Table 1, Fig. 4), despite the use of a scPCP treatment regimen which induced an impairment in NOR and hypersensitivity to acute PCP. This was found in three independent studies at different research sites, and we consider this as a valid finding. The inability of the scPCP treatment to impair reversal learning in both Morris water maze and touchscreen-based visual discrimination task (see below) indicates that the scPCP treatment fails to model schizophrenia-like deficits in reversal learning.

Acquisition and reversal of touchscreen-based visual discrimination

We wanted to expand the characterization of scPCP-induced cognitive deficits and investigated the effects of the scPCP treatment on reversal learning in other paradigms than those reported so far. Across four research sites, we designed a set of experiments to assess the effects of scPCP treatment on reversal learning in the Morris water maze and in a touchscreen-based visual discrimination (VD) paradigm. A reversal learning task involves two phases, an initial phase that requires memory of a previously learned rewarded response, followed by a reversal phase in which the previous rewarded response is reversed. Reversal learning includes an element of task switching which requires cognitive flexibility and readiness to engage new responses, attention to stimulus-reward relationships, motivational state and suppression of previously learned response (Jones et al. 1991). Patients with first-episode or chronic schizophrenia can learn and generalize rules but are inflexible when rules change, at least in part reflecting reduced responsiveness to negative feedback and difficulty in switching attention (Pantelis et al. 1999; Leeson et al. 2009). In rats, the effects of subchronic administration of PCP (generally 5–14 days, once or twice a day, followed by withdrawal) on reversal learning are not fully understood: the scPCP treatment has been shown to disrupt reversal learning

in an operant environment (Abdul-Monim et al. 2006; Abdul-Monim et al. 2007; McLean et al. 2009a; McLean et al. 2009b; Idris et al. 2010; McLean et al. 2010), but not in the attentional set-shifting (ID-ED) task (Rodefer et al. 2005; Rodefer et al. 2008; Broberg et al. 2009; Goetghebeur and Dias 2009; Goetghebeur et al. 2010; Maeda et al. 2014).

Multi-site characterization of the effects of scPCP on reversal learning of visual discrimination

The touchscreen approach allows the use of multiple stimuli within a single testing session, which is important when trying to link changes in reversal learning to cognitive flexibility. The touchscreen approach is suggested to separate true cognitive effects from non-specific effects better than a standard operant box does (Fellini et al. 2014). The VD task protocols were for the most part similar between sites but a few differences existed, including apparatus, origin of the Lister Hooded rats and few selected parameters in the VD task (e.g. completion criteria varied between 70 and 85 % of accuracy) (See Online Resource 1 for detailed methods). Adult male Lister Hooded rats were first pretrained to the touchscreen system for 2 weeks and then trained to nose-poke for the S+ stimuli in the acquisition phase (Table 1 in Online Resource 1). When the pre-set criterion for acquisition was reached, the reversal phase was introduced, and the previous S+ became S− and vice versa (Table 1 in Online Resource 1). The rats were then trained to the new condition until they reached the criterion. All four research sites subjected the rats to a subchronic administration of PCP (5 mg/kg, except at Roche 3 mg/kg, i.p., twice a day for 7 days) or saline vehicle, followed by a 7-day washout period. By administering scPCP at different stages of the VD testing, before acquisition or before reversal of the VD task, we ruled out the potentially transient nature of the scPCP treatment.

The Online Resource 2 presents detailed results. The data by Janssen was recently published (Fellini et al. 2014). At Janssen and Orion Pharma, the scPCP treatment was given in week 0 (once the rats had been pretrained to the system), and the acquisition phase was performed after washout from week 2 onwards. Both research sites similarly found that the scPCP treatment did not impair the acquisition of the VD task (Fig. 5a, b). There was no difference between the scPCP treatment and vehicle controls in the number of total trials, consisting of correct, incorrect and omitted trials, or correction trials completed to reach the criterion of 80 % accuracy (Fig. 5a; ANOVA P=0.13 to P=0.60, Orion Pharma). The scPCP-treated rats had to complete a few more test sessions to reach the criterion as compared to the vehicle controls, and there were two scPCP-treated rats that failed to reach the criterion despite 29 sessions of training (Fig. 5a; 'outliers'). When these two rats were excluded, the number of test sessions did not differ between treatment groups (ANOVA P=0.16). At Janssen, training improved the % correct responses similarly in the scPCP and scVEH groups (Fig. 5b; ANOVA P=0.14). More than 84 % of trials were completed in all sessions (data not shown).

At Orion Pharma, the acquisition and reversal phases were performed consecutively, such that each rat was individually trained and immediately moved to the reversal phase when the rat had reached the criterion at the acquisition. In this set-up, there was no impairment in the reversal learning after the scPCP treatment given approximately 3 to 4 weeks earlier (Fig. 5a; ANOVA P=0.06 to P=0.82). There were six rats in the scPCP group that were not able to reach the criterion of the reversal phase during the experiment (total of 55 sessions) (Fig. 5a). For a subgroup of 3 to 4 rats, this appeared to result from a low completion rate of the trials, suggesting that rather than an impairment of cognition, there was a lack of motivation in some rats treated with scPCP.

In another experiment by Janssen (Fellini et al. 2014) and in experiments at Roche and Lundbeck, the scPCP treatment was given once all rats had reached the criterion of the acquisition phase (75 % correct response at Janssen, 85 % at Roche and 70 % at Lundbeck). After the scPCP treatment and washout, the rats were returned to the first condition of the VD task for one or two more sessions ("reminder") before the task was reversed (S+ became S− and vice versa). The scPCP treatment did not impair performance during the "reminder" or reversal learning of the task at any of the three sites, and the % correct improved similarly between the scPCP and vehicle groups [Fig. 5c; ANOVA P>0.61, Janssen (Fellini et al. 2014); Fig. 5d; P>0.74, Roche; Fig. 5e; P>0.60, Lundbeck]. The number of completed trials dropped with few trials on the first day of the reversal, partly because of the use of correction trials, but thereafter, the rats completed more than 95 % of the trials in each session (data not shown).

We report here similar effects for the scPCP treatment on the VD performance across five individual studies conducted at four independent research sites (Table 1, Fig. 5). Although the scPCP regimen has been shown to induce an impairment in NOR and hypersensitivity to acute PCP, it did not impair acquisition or reversal of a VD task when given at 2 to 6 weeks before each phase. The scPCP treatment was confirmed as successful in all VD studies, shown by the hypersensitivity to the stimulatory effect of acute PCP, even up to 13 weeks, in the same animals (Fig. 1). Our data agrees with the previous findings from the ID-ED task that cessation of scPCP treatment did not impair reversal learning (Rodefer et al. 2005; Rodefer et al. 2008; Broberg et al. 2009; Goetghebeur and Dias 2009; Goetghebeur et al. 2010; Maeda et al. 2014).

In a cued reversal learning task, when the reversal was preceded by a cue (timeout) in an operant environment, the scPCP treatment with a lower dose (2 mg/kg i.p., twice a day for 7 days, followed by a 7-day washout) did impair the ability to reverse performance in adult female Lister Hooded rats (Abdul-

Monim et al. 2006; Abdul-Monim et al. 2007; McLean et al. 2009a; McLean et al. 2009b; Idris et al. 2010; McLean et al. 2010). In this paradigm by Neill's group, the timeout appears to cue the upcoming reversal and probably explains the very rapid nature of the reversal and the lack of a clear adaptation or re-learning phase in the data (Young et al. 2009). The cued-reversal task differs in this respect from the rather slow reversal learning in the VD task. As previously discussed (Fellini et al. 2014), one could argue that the slow nature of reversal learning in a VD task over days may somehow mask, or protect against, the abnormalities induced by scPCP. On the other hand, this is counterargued by the finding that the scPCP treatment failed to impair the reversal learning already in the first trial of the spatial Morris water maze (Fig. 4).

In another study, subchronic dosing of a higher PCP dose (5 mg/kg i.p., twice a day for 7 days, followed by a 7-day washout) to adult male Sprague-Dawley rats impaired the ability to reverse an already-learned stimulus reward association (Jentsch and Taylor 2001). However, the scPCP-treated rats produced more responses during extinction of instrumental responding and more responses for a conditioned reinforcer as compared to control rats. This suggests that the scPCP treatment may cause an inability to inhibit conditioned responding towards incentive stimuli, leading to an inability to modulate behavior based upon new information about stimulus-reward associations. The scPCP-treated rats may learn one rule and then "stick with it". Interestingly, lesions of orbitofrontal cortex impair reversal learning (Chudasama and Robbins 2003; Boulougouris et al. 2007; Finger et al. 2008) as well as outcome encoding in pavlovian conditioning (Ostlund and Balleine 2007). The conditioning aspect of a reversal learning task in an operant environment may make it a more vulnerable task to the scPCP treatment than the reversal of a VD task or spatial learning.

Despite the use of a scPCP treatment regimen in our experiments which induced an impairment in NOR and hypersensitivity to acute PCP, the scPCP treatment did not disturb the acquisition or reversal learning of a touchscreen-based VD task, suggesting intact cognitive flexibility for simple reversal rule learning in these animals. This was seen consistently in all studies at all research sites (Table 1, Fig. 5). It seems that the scPCP treatment did not sufficiently disturb functioning of those brain areas that are recruited during visual discrimination memory and reversal learning. All in all, the inability of the scPCP treatment to impair reversal learning in both touchscreen-based VD task (Fig. 5) and Morris water maze (Fig. 4) indicates that the scPCP treatment fails to model schizophrenia-like deficits in reversal learning.

Conclusions and implication for use

We have reported findings from several studies and research sites that the scPCP treatment did not impair acquisition or reversal learning in a touchscreen-based visual discrimination task or in a visuo-spatial Morris water maze test, although the scPCP treatment regimen (5 mg/kg i.p. twice a day for 7 days, followed by at least 7-day withdrawal) was identical to the procedure used to induce cognitive deficits in object recognition and attentional set-shifting and induce hypersensitivity to acute PCP. The scPCP treatment also did not impair short- or long-term spatial reference memory or working memory in the Morris water maze. The long-term effects of the scPCP treatment were confirmed by determining hypersensitivity to the stimulatory effect of acute PCP in these rats. The hypersensitivity began within 1 week and lasted at least 13 weeks post-scPCP.

All in all, the scPCP treatment seems to disturb only visual memory (as assessed by NOR) and extra-dimensional (ED) set-shifting, but not reversal learning assessed over several paradigms. The lack of impairment in reversal learning assessed using different paradigms in the multi-site study, also fits with previous findings observed in reversal learning during the ASST digging paradigm, but not with the impairment in reversal learning observed in a cue-based operant paradigm (see Attentional set-shifting task section for discussion). The data suggests that changes in conditioning may contribute to the impairment in cue-based learning, and as such, the assay may reflect also deficits in impulsivity control. Further studies could help to explain why scPCP impaired reversal learning only in a cue-based operant paradigm but not in any other paradigm.

We did replicate previously reported findings of impairments in NOR, and this observed deficit following scPCP is consistently reported in the literature. This task is widely used, likely due to the minimal equipment required and the ease of running the protocol. Moreover, the scPCP-induced deficit is large enough for drug screening and to assess dose-related effects. Yet, it is not clear how the behavioural impairment in NOR is linked to the brain regions impaired by scPCP treatment. The ASST task has higher face validity compared to the NOR, since in normal rats, the ED set-shifting deficit requires similar frontal cortical regions for performance as non-human primates and humans. Although recent data suggests that further work is required to understand if the ED shift impairment induced by scPCP is similar to the deficit in schizophrenia, since a comparison of scPCP and medial prefrontal cortex lesioned rats on a battery of touchscreen cognitive tests revealed very different effects (see McAllister et al. in this issue). However, Dawson et al. (2012) suggest that alterations and dysfunction of multiple brain regions, rather than a single brain region, may underlie the cognitive deficits in scPCP-treated animals. The behavioural effects of scPCP in both ASST and NOR may be a consequence of impaired sensory effects (Mar et al., in preparation); thus, further work would need to be done to understand the specificity of the behavioural effects of scPCP based on these recent findings.

For both paradigms impaired with scPCP, predictive validity is an issue because a clinically validated positive control is not available; yet, efficacy is observed in both NOR and ASST with several compounds, including antipsychotics (in some labs) which were tested at low doses. NOR appears to be more sensitive than ASST in detecting the positive effects of a broad range of compounds with different mechanisms of action. Therefore, care must be taken in assessing novel therapies, and we recommend to determine their effect not only in the scPCP model but also in other models relevant for schizophrenia, in order to gain confidence in their therapeutic potential.

We would encourage further assessment of the scPCP model to better understand the pathophysiological changes underlying the cognitive deficits. As mentioned previously, there are a variety of neurochemical changes reported to be associated with this model, but not all findings have been repeated to determine their robustness and reproducibility between labs. It should be noted that the scPCP treatment is administered in the adult rat and so does not reflect the neurodevelopmental aspect of schizophrenia. We realise that one model is unable to reflect the complexity of a disorder such as schizophrenia, but may be able to reflect aspects of the disorder. Based on the neurochemical analysis reported to date, this model appears to reflect a dysfunction of cortical and/or hippocampal regions and a reduction in expression and immunoreactivity of parvalbumin neurones which is thought to contribute to the aetiology of schizophrenia. However, considering the variability of effects reported in the literature, a similar cross-site approach would be useful to confirm and verify the neurochemical changes that occur as a result of scPCP, and which of these changes are responsible for driving observed behavioural effects.

The present findings strongly support the importance of replication of studies within and even between labs to confirm both positive and negative findings (Steckler 2015). One of the aims of NEWMEDS was to use the power of multi-site studies to help understand whether a model or a paradigm would have a robust and reproducible effect. Not only positive results, but also negative findings are necessary for the translational feedback and reliable estimation of the predictive validity of a model. Another important aim of NEWMEDS was to provide a battery of translational cognitive tasks using the touchscreen system to improve reproducibility between different labs. This approach is very promising since we have now shown reproducible effects regarding both baseline performance and drug effects in the current study and in another multi-site study (see Talpos et al. in preparation).

In conclusion, models of schizophrenia need to be well-characterized by behavioural analysis to understand the specificity of the behavioural impairment and which aspects of cognition are impaired or not. Furthermore, analysis of the underlying pathophysiology of the model is required to determine whether this correlates with relevant changes in schizophrenia. Better understanding of disease processes aids the development of predictive behavioural assays and animal models. Two-way comparison of pharmacological effects in preclinical and clinical assays, reflecting the same cognitive domain, will help to develop animal models with predictive validity which is important for assessing novel therapeutics.

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